Utility of Network Science and Intensive Longitudinal Data in the Study of Symptom Associations in Rheumatoid Arthritis

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Abstract

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune condition primarily affecting the small joints of the extremities. RA patients suffer physical symptoms and has a high comorbidity with depression, with a prevalence rate of around 17%. These symptoms fluctuate wildly; sometimes throughout a day, and cross-sectional data analysis will only allow for one time point to be evaluated. Thus, it is important to carry out intensive follow up to allow tracking through fluctuations. A scoping review carried out showed that there a lack of high frequency follow up studies to investigate the associations between multiple physical and/or psychological symptoms in the field of musculoskeletal disorders. These showed important gaps in literature in the field of RA that needs to be addressed.

The overarching aim of this thesis is to explore physical and psychological symptom associations using advanced quantitative methods on a longitudinal dataset in RA patients; and to explore the feasibility of network science in this field of research. This will be addressed via three main objectives: 1) to investigate the feasibility of collecting intensive longitudinal data with the help of a wearable device in the field of RA; 2) to explore associations between physical symptoms, psychological symptoms and other important variables in RA patients; and 3) to test the usability of the network approach in evaluating multiple symptoms. These objectives will be addressed through data collected from two studies involving intensively collected (multiple times per-day) symptoms ratings: IA-COVID and APPro. In addition, cross-sectional data from the TITRATE-US study and routinely collected data from the KCL Rheumatology IMPARTS Patient Reported Outcome system are used to evaluate the usefulness of symptoms network approaches prior to applying these methods to longitudinal data.

To address the feasibility of collecting intensive longitudinal data, the APPro study showed that there was a success rate of 33.8% when recruiting patients to the study and the APPro study showed that the average compliance rate was 88.75%. This is higher than the proposed recommended compliance rate of 80% by several studies, and higher than the 73% that was shown in a review on EMA studies that utilises wearables as well on youth.

Both longitudinal studies used mixed effects regression and provided novel insights into the bidirectional association between physical and psychological symptoms in RA

patients. In the IA-COVID study, it was discovered that there were significantly less social contact and higher loneliness level during period of lockdown during the COVID-19 pandemic, and during this state, increased social contact was significantly associated with lower physical symptoms in the next time period. It also showed that positive affect was the only symptom that influenced physical activity in the next time period, suggesting that high positive affect would increase physical activity in the next time period. The APPro study demonstrated that there were significantly lower physical symptoms and, surprisingly, lower positive affect after the initiation of a new biologic treatment. After a new treatment, psychological symptoms have a significant impact on physical symptoms in the next period.

When examining the relationship between multiple symptoms, it becomes complicated to separately fit and interpret many different models (i.e. at least one model per-outcome assessed). This limited the analyses described above to focusing on broad constructs of psychological well-being rather than individual symptoms. Network science approaches were utilised in every empirical chapter to provide an insight into the associations between specific physical and psychological symptoms. Distinct clusters of physical symptoms, psychological symptoms, and inflammatory markers in RA were identified using a network approach. Individual network plots also showed that fluctuant symptom plot differs from a stable symptom plot where fatigue is highly connected to psychological symptoms rather than physical symptoms. The influence of each symptom was also looked at in APPro using centrality values. The influence of joint stiffness dropped dramatically after a new treatment, showing the effects of the treatment on inflammation. Both before and after symptom plots also showed psychological symptoms to be the most influential nodes, further showing the importance of positive and negative affect in RA patients.

In conclusion, this thesis displayed a framework for the recruitment and assessment of intensive longitudinal data in the field of RA. It also discovered several novel associations between symptoms and quality of life variables, and also reinforced the importance of psychological symptoms in a RA patient, especially after a new treatment. Fatigue was also discovered to be the symptom that has the most influence on the activation of psychological symptoms, and were shown to be affected by psychological symptoms tremendously in different situations. Network science also proved to be a methodology that could reveal new information, but more work is required to discover its full potential.

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1. Background

1.1. Rheumatoid Arthritis

1.1.1. Background

Chronic diseases, or long-term conditions, contribute to almost 60% of deaths worldwide (WHO, 2005) with this number predicted to rise to almost 73% over the next decade, largely driven by population ageing . Arthritis is one of the most common long-term conditions, and is a leading cause of disability worldwide (Neogi, 2013). It incurs massive costs to patients and healthcare providers due to the number and severity of symptoms, and patients' loss of functioning (Messier et al., 2004). Arthritis is a condition in which one or more of the patients' joints are inflamed, which results in soreness, stiffness, and swelling. There are two main types of arthritis, inflammatory arthritis (IA) where the immune system is causing inflammation due to autoimmunity, and non-inflammatory arthritis which is mainly osteoarthritis (Sacks et al., 2010). Osteoarthritis is normally caused by damage affecting the cartilage lining of the joints either due to wear and tear or injury, resulting in a breakdown of cartilage which leads to bone rubbing on bone. Inflammatory arthritis on the other hand, is a diverse group of chronic autoimmune conditions characterised by joint inflammation including rheumatoid arthritis (RA), spondyloarthritis such as psoriatic arthritis (arthritis in patients with skin condition psoriasis) and juvenile idiopathic arthritis (arthritis in children). This means that the inflammation is not caused by wear and tear like osteoarthritis, but instead by the immune system targeting certain joints leading to pain and swelling (Scott et al., 2010).

The total cost of rheumatoid arthritis, including direct clinical costs and indirect costs are high for patients and increasing due to the rise in use of biologics. This cost leads to a significant burden on the patient, the patients' family, health services, and the society as a whole (D. L. Scott et al., 2020). This shows that besides the fluctuant physical and psychological symptoms, IA patients experience additional burdens as well. These burdens also translate to the partners and families of IA patients; a study on 88 patient-spouse couples (Rat et al., 2021) showed that satisfaction of the partner is strongly associated with the mental health of the patient. This shows the potential problems that IA poses, and the

need to understand and manage the conditions. In order to understand IA, it is important to note that even though inflammatory arthritis conditions are all characterised by the common denominator of inflammation, the clinical features and aetiology differ for each condition. Spondyloarthritis, comprising of ankylosing spondylitis, reactive arthritis, and psoriatic arthritis, is characterised by inflammatory back pain, peripheral arthritis and extra-articular features such as psoriasis (Stolwijk et al., 2012). Spondyloarthritis is also recognised by the Spondyloarthritis International Arthritis (ASAS) to be divided into axial spondyloarthritis and peripheral spondyloarthritis where axial spondyloarthritis mainly affects the spine (Rudwaleit et al., 2011). Most importantly, all of these conditions are heavily associated with HLA-B27, which is a protein located on the surface of the white blood cell. Testing positive for HLA-B27 is the strongest known genetic risk factor for spondyloarthritis (Sieper et al., 2006). Even though around 90% of patients with ankylosing spondylitis (AS) are discovered to possess this protein (Hammer et al., 1990), it was discovered that HLA-B27 is only able to explain 20-40% of the genetic susceptibility to AS (Dougados & Baeten, 2011), suggesting that this disease is not entirely explained by hereditary or genetic factors. This shows the complexity and the lack of complete understanding of these disorders.

The symptom profiles for spondyloarthritis also differs among the different disorders. For ankylosing spondylitis, it mainly affects the axial skeleton; in particular the cranium, backbone and ribs, causing inflammatory backpain and asymmetrical limbs (Braun & Sieper, 2007). It also affects twice as many men as women, with 80% of the patients suffering the first symptom before age 30 (Feldtkeller et al., 2003). Psoriatic arthritis on the other hand, only affects patients with psoriasis, which is a skin condition that causes red and dry patches of skin. 30% of patients with psoriasis develops psoriatic arthritis, and this disease affects women and men equally (Ritchlin et al., 2017). The symptom profile for psoriatic arthritis includes nail pitting, tendon inflammation and the skin conditions for psoriasis (Stoll et al., 2006). Even though these different conditions that make up spondyloarthritis differs in both cause and symptom, they all share certain characteristics within the group. There have also been cases of overlaps between RA and spondyloarthritis, but the numbers remain small (Matei et al., 1992). There are differences in both aetiology and symptom profiles, and the main difference between symptoms in spondyloarthritis and

RA is that spondyloarthritis affects the spinal cords while rheumatoid arthritis is focused on peripheral inflammation and pain, in particular hands and feet (Akhondi & Varacallo, 2021).

Rheumatoid arthritis causes chronic synovial joints inflammation, which is the most common type of joints in the human body (Alamanos & Drosos, 2005). This can be seen in Figure 1.1 (Donvito, 2018) below, which shows the stages of RA. The constant inflammation causes the cartilage to wear down, leading to swollen and tender joints.

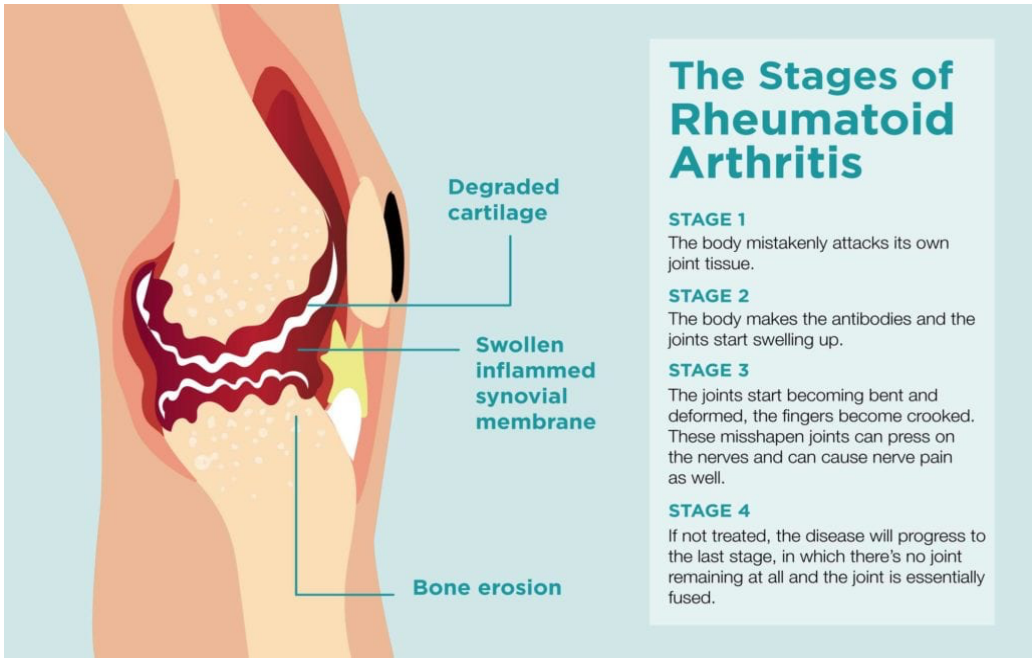


Figure 1.1: Stages of RA
Donvito (2018)

Rheumatoid arthritis has higher prevalence and incidence rate than spondyloarthritis in most countries (Akkoc & Khan, 2020). It is one of the most common form of IA worldwide (Majithia & Geraci, 2007) alongside gout (Roddy & Doherty, 2010), and the most common autoimmune inflammatory arthritis. Pain among IA patients has normally been attributed to peripheral pain, instead of non-inflammatory central pain (Lee, 2013). This pain has also been reported to be significantly associated with patient-reported arthritis disease activity as seen from different studies (Khan et al., 2012; Studenic et al., 2012). It was shown that pain is the most important determinant in scoring of patient global assessment (PGA) scores, and in Khan et al (2012)'s case, the only physical symptom that is correlated with PGA. With peripheral pain being the focus of pain for IA patients, and the characterization of RA being mostly peripheral pain, this shows the seriousness of RA and the importance of

understanding the condition. It is vital to first understand the aetiology and epidemiology of RA in order to better understand which area of RA should be worked on.

1.1.2. Pathophysiology, Aetiology and Epidemiology

Rheumatoid Arthritis can be characterised by the presence of several autoantibodies, most notably Rheumatoid Factor (RF) and anti-citrullinated protein antibodies (ACPA). RF is an autoantibody first discovered by Waaler (Natvig & Tonder, 1998) and is directed against the Fragment Crystallizable Region (the tail region of an antibody) portion of another immunoglobulin. In a prospective cohort study looking at elevated RF (Nielsen et al., 2012), it is discovered that those with an elevated level of RF in the general public has up to 26 times greater risk of developing RA in the long-term compared to those that don't. The testing of RF is the most widely used blood test for the classification of RA (Aletaha et al., 2010). ACPA is detectable in about 70% of RA patients and is highly specific for RA (Sokolove et al., 2014). ACPA is also a clinically utilised autoantibodies to diagnose RA because of the high specificity (Schellekens et al., 2000). The amount of these antibodies are elevated on average about 3.5 years prior to the onset of joint inflammation for RA patients (Demoruelle et al., 2014). This means that these antibodies would be present before any symptoms develop, which would enable clinicians to be able to identify and diagnose RA early. The mechanism of how inflammation in RA originates is not entirely clear, but there are arguments that initial inflammation starts outside of the joints (van de Sande et al., 2011). Several studies (Barra et al., 2013; Harvey et al., 2013; Mikuls et al., 2012) have stated that RA-related autoimmunity starts at a mucosal site, especially the oral mucosa which is the membrane lining the inside of the mouth. The uncertainty of the mechanisms behind RA contributes to the complexity of treatment for RA and its many serious symptoms that RA patients suffer from. Besides inflammation, patients suffer from a lack of function, pain, fatigue, poor sleep, stiffness and tenderness in joints, and also psychological symptoms such as low mood and increased ease of irritability (Bullock et al., 2018).

The spread of RA in ages and gender is quite similar around the world, as seen in studies in the UK (Symmons, 2005), US (Gabriel et al., 1999) and Norway (Uhlig et al., 1998). However, it is discovered by Alamanos, Voulgari & Drosos (2006) that there are significant differences ($p = 0.02$ for Kruskall-Wallis test) in prevalence worldwide, with North America

having the highest prevalence rate, followed by northern Europe, developing countries and lastly southern Europe. Prevalence means the total number of cases, pre-existing and new cases at that particular time point. The prevalence of RA in adults is about 1%, with females around two to three times more likely to suffer from this disorder than males. Incidence rates, which is the rate of new cases, increases overall until the age group of 65-74, whereafter it starts to decrease. This means that the older the age, the higher the rate of developing RA, and this has been reflected by evidence that the age of onset has been increasing over time (Silman, 2002). Baseline disease activity has also decreased, however functional disability has remained the same (Diffin et al., 2014) and comorbidity burden has actually been increasing (Nikiphorou et al., 2017). This suggests that even though modern treatment strategies succeed in reducing certain disease activity, RA still remains one of the most disabling diseases in the UK.

It is known that genetic and environmental factors are potential risk factors for the development of RA, however there is no single cause and these factors interact over time (Aho & Heliovaara, 2004). Twin studies carried out on two different populations from Finland and UK deduced that there are only concordance rates of 12% and 15% respectively in a RA cohort (Aho et al., 1986; Silman et al., 1993), which is fairly low, especially compared to an earlier study that calculated a rate of 30% from a smaller sample size of 30 twins (Lawrence, 1970). Heritability of RA was discovered to be around 60% (Kurko et al., 2013), however this result has to be interpreted cautiously because heritability estimates cannot be generalised into other populations easily (Cavalli-Sforza, 1974). In a study by van der Helm-van Mil, Wesoly & Huizinga (2005), it was stated that even with new genetic factors such as the PTPN22 and SLC22A4 discovered, more work is required to have complete clarification of the genetic risk factors of RA. Not all genetic risk factors and pathways have been discovered yet, which shows that this heritability estimate is not confirmed. It has also been shown that genetic factors could interact with environmental factors to influence the extent of the risk factors, for example smoking has a significant interaction with HLA-DR which is active only when smoking is present. These complex genetic factors and interactions display why there is a discrepancy between the concordance rate between twins and heritability, and that genetic factors alone cannot determine if there is a high possibility of the development of RA in an individual.

There are some evidence of hormonal involvement in RA as we can see an increased incidence rate of RA in women who recently gave birth (Symmons, 2005). The postpartum period is characterised by a drastic drop in oestrogen levels, which could be linked to RA. This theory is further affirmed by studies looking at how the Oral Contraceptive Pill (OCP) both lower the risk of developing RA (Spector & Hochberg, 1990) and also decreases disease severity (Amini et al., 2018). It is theorised that sex hormones will apply some immunological changes that will affect the prognosis and development of RA (Kanik & Wilder, 2000) but the possibility of OCP being a marker of some other protective effect cannot be dismissed. There are no concrete results on the effect of OCP and RA (Colangelo et al., 2011) and the mechanism of hormonal involvements in RA is not clear.

There are also many associations found between lifestyle and the development of RA, particularly smoking and diet. A case-control study by Carette et al (2000) discovered that people who smoke are significantly more likely to develop RA, with the risk even higher for men. It is also found that ex-smokers still have this increased association, suggesting that quitting smoking does not lessen the risk (Heliovaara et al., 2000). There is evidence that smoking is a risk factor for only Rheumatoid Factor (RF) positive RA, and not for RF negative RA (Criswell et al., 2002). This is significant because it means that for those who are RF positive, a change in lifestyle regarding smoking needs to be made because of the significant risk factor that it may become. However, there is limited research that can explain the mechanisms of how this association happens, and thus contributing to the lack of clarity of the aetiology of RA. There has been conflicting information about how diet affects the development of RA. Coffee, even decaffeinated coffee is associated with the onset of RA (Mikuls et al., 2002) but another study by Karlson et al (2003) showed that there are no significant association at all between coffee and the development of RA. Both studies are carried out on a women only cohort, and the difference between them could be due to individual differences. Research has also been carried out to show associations between the consumption of red meat and RA (Pattison et al., 2004), no association between consumption of alcohol and RA (Carette et al., 2000), and how n-3 fatty acids of fish and oleic acid from olive oil could be a protective effect on RA (Linos et al., 1999; Shapiro et al., 1996). However, research on diet is easily confounded because those food comprises of multiple nutrients, and thus it is hard to single out the specific nutrient that could be the leading risk factor or protective factor for RA. The effects from diet could also be influenced

by other lifestyle factors, and thus requiring more in-depth research to have a complete picture.

There are multiple potential risk factors, ranging from genetic to environmental. No research has been able to show any possible causation for RA, and the risk factors are just shown as strong associations. Risk factors could also be associated not just with the onset of RA, but with disease severity as well. An example in genetic risk factor, a variant of the tumor necrosis factor alpha (TNFA), TNFA -308G > A is associated with joint damage in RA, instead of the development of RA itself (Toonen et al., 2012). This means that the presence of this TNFA will signify a significant risk of developing RA with severe joint damage, instead of the development of RA itself. The aetiology of RA is thus still unclear, but the known risk factors can still be implemented by clinicians as a preventative, or treatment measure.

1.1.3. Diagnosis and Treatment

Diagnosis of RA is based on the classification criteria that is set by the American College of Rheumatology and European league against rheumatism (Aletaha et al., 2010) in Table 1.1 below. The classification criteria is based on the sum of the scores that are given for each of the sections A, B, C and D. A score above six will classify the patient as diagnosed with RA. This criteria did not include any X-ray findings in order to include early stage disease since X-ray findings are harder to be discovered in patients that have just developed RA (Pisetsky & Ward, 2012). This classification criteria must be interpreted together with a clinical context, because one of the sections looks at ACPA, which could be present several years before the development of RA (Majka et al., 2008). This means that patients could potentially score higher than six due to the presence of ACPA before the development of RA.

Table 1.1: Classification criteria for Rheumatoid Arthritis (RA)

Classification criteria for RA	Score
A. Joint Involvement	
1 Large joint	0
2–10 Large joints	1
1–3 Small joints (with or without involvement of large joints)	2
4–10 Small joints (with or without involvement of large joints)	3
>10 Joints (at least 1 small joint)	5
B. Serology	
Negative RF and negative ACPA	0
Low-positive RF or low-positive ACPA	2
High-positive RF or high-positive ACPA	3
C. Acute-phase reactants	
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1
D. Duration of symptoms	
<6 Weeks	0
>6 Weeks	1

The risk factors of RA are known, however the cause and the ways to prevent RA from developing is still unknown (Combe, 2007), so a large part of the research and treatment focus for RA is how to manage disease activity and the associated symptoms to reduce the impact of the condition on the lives of those with RA. The current standard approach to disease management is referred to as 'treat-to-target' (T2T), where the target is typically remission or at least low disease activity as indicated by the Disease Activity Score in 28 joints (DAS28). DAS28 will be discussed further in the Methods section. This is a clinical score that combines the number of swollen and tender joints, the patients' own rating of their own health, and a blood test for inflammation (Wells et al., 2009).

Steroids are one of the possible treatment plans for RA and can be taken as tablets, injected or by infusion (Society, 2021). However, steroids are used sparingly because of the dangerous side effects that they may produce for example fragile skin, fatigue, and weight gain. Thus, it is recommended that steroids are used low dose for a short time, and only in times of symptom flare ups, or in between other treatments. A study by Buttgereit et al (2013) showed that using low dosage of steroids together with other treatments resulted in a rapid improvement in symptom severity. This highlights the conditions in which steroids should be used, in conjunction with other treatments and in very low dosage to reduce any possible side effects. The development of non-steroidal anti-inflammatory drugs (NSAIDS) meant that the reduction of steroid usage is possible. NSAIDS work by reducing inflammation in the joint, however they do not stop RA from getting worse over time (Service, 2021). NSAIDS are the most commonly used drug for targeted symptom treatment (Crofford, 2013), and thus are still a very useful treatment for RA.

The most common pharmacological treatment method for RA is the use of disease modifying anti rheumatic drugs (DMARD) (NICE, 2018). There are two types of DMARD, conventional synthetic (csDMARD) and targeted (tDMARD), which includes both biologics and the synthetic JAK-inhibitors biological (known as biologics) that have been shown to reduce disease activity and delay joint deformity (Guo et al., 2018). A csDMARD (typically Methotrexate) is used as a first-line treatment while a tDMARD is reserved for those with inadequate response. In the UK, according to the NICE guidelines, tDMARDs are only used if a patient still has high disease activity score after at least six months on a combination of at least two different types of csDMARDs on a standard dosage. Even though biologics are regarded as the more effective option (Guo et al., 2018), NICE guidelines stated that they

can only be used after conventional DMARDs showed inadequate response. This is because tDMARDs are significantly more expensive than conventional DMARDs which are still effective for many individuals (Dalal et al., 2020). Therefore, patients generally undergo several different treatment processes before achieving some level of disease remission (indicated by a DAS28 score of < 2.6). The use of tDMARDs have consistently shown to be an effective treatment, even for those that did not start with a csDMARD (Emery et al., 2018). Multiple studies (Fleischmann et al., 2017; Kameda et al., 2010) have also discovered that using combination therapy (combining drugs with different mechanisms), for example using both targeted and conventional synthetic drugs will result in better treatment outcomes compared to just using csDMARD or tDMARD.

1.1.4. Symptom and Impact

Inflammation of the synovial membrane lining the joints is the main cause of RA, and this leads to swollen and tender joints which are the main symptoms associated with RA. Over time, this could lead to deformity of the joint (Niki et al., 2010) which will impact on the range of movements the joints enable, resulting in a problem with daily functioning. Pain, which results from an interaction between joint swelling and nerve processing of pain, is also one of the main symptoms of RA, even in cases where inflammation is controlled (Walsh & McWilliams, 2014). Fatigue is another main symptom, and has been attributed to both inflammation and pain (Crosby, 1991; Pollard et al., 2006). It is known that symptom severity for RA patients follow a circadian rhythm, with worse pain, functional disability and joint stiffness in the morning (Straub & Cutolo, 2007). Morning stiffness in particular is a symptom that could still be discovered in one out of six RA patients that are in remission and with low disease activity (Sierakowski & Cutolo, 2011).

These symptoms lead to a heavy burden on the patients, resulting in work disability, reduced productivity and early retirement (Kvien, 2004). It is discovered that at least 75% of the total costs is due to the indirect cost of work disability (Yelin & Wanke, 1999). Further burdens also include the societal and participation limitations where patients are unable to participate in activities due to functional disability and physical symptoms (Fransen et al., 2002). These burdens are only expected to grow, as there has been a trend of increasing burden in musculoskeletal disorders from 2004 to 2010 (Uhlig et al., 2014). In order to

properly define the functional disabilities and quality of life of RA patients, the International Classification of Functioning, Disability and Health (ICF) created by the World Health Organization (2001) was used to create a comprehensive list of factors. 17 experts from around the world went through 530 categories to choose 96 categories derived from main components of body structure (18), body functions (25), activities and participation (32), and environmental factors (21) to form the Comprehensive ICF Core Set (Stucki et al., 2004). This ICF Core set for RA has also been validated from the clinicians' (Gebhardt et al., 2010) and patients' perspectives (Coenen et al., 2006). This shows that quality of life and disability in RA is not just caused by inflammation's effect on body structure and function, but also by participation in activities and other environmental factors.

These common symptoms of RA, in particular pain and fatigue are often referred to as physical symptoms and will be labelled as such in the rest of this thesis. However, it is important to note the complexity and the multi-faceted dimensions of these symptoms, and how the inclusion of the possibility of physical symptoms being influenced psychologically, lend credit to the network model that will be discussed in future chapters. Fatigue has been described as a construct that is influenced by physical, psychological, and social factors that interact with each other in the biopsychosocial model (Hewlett et al., 2011). A systematic review on fatigue in rheumatoid arthritis was carried out (Geenen & Dures, 2019) and it showed that psychological functioning is one of the main categories for fatigue, and other factors such as physical activity and sleep also has a moderate correlation with fatigue. The biopsychosocial model can also be applied to pain, accounting for the influence that psychological and social factors have on the physical symptom of pain (Gatchel et al., 2007). As with fatigue, pain has been demonstrated to correlate not only with inflammation and synovitis but also with psychosocial factors (Walsh & McWilliams, 2014). Furthermore, a systematic review carried out on 15 studies showed that a positive clinician-patient relationship that includes understanding and support plays a major role in the treatment outcomes related to pain (Lion et al., 2014), suggesting that psychological and social factors play a role in pain alleviation. Psychological distress is also one of the key factors that can lead to progression of pain to long-term disability and pain (Booth et al., 2017), further exhibiting the link between psychological factors and pain. These showed how even though pain and fatigue can be interpreted as a physical phenomenon, there are psychological and social factors that plays a role in the development and the experience in RA patients.

Pain has been described as the main problem by a RA patients (Heiberg & Kvien, 2002), and this is due to RA patients suffering from not just chronic joint pain, but also neuropathic pain that is associated with the nervous system that is often described as a 'burning pain' (Perrot et al., 2013). This emphasis on pain by RA patients mean that it is vital to understand the multiple aspects of pain. As described above, pain is not just a physical construct but also includes psychological and social factors. Stress exacerbates pain and is also known to potentially sensitise pain pathways, thus stressful events tend to lead to patients suffering from more pain (Johnson & Greenwood-Van Meerveld, 2014). A systematic review carried out on 16 studies concerning RA patients showed that RA patients suffer from more stress than osteoarthritis patients, and that more disability and pain plays a role in increasing stress levels in patients (De Cock et al., 2022). The inclusion of inflammation in RA compared to other types of musculoskeletal disorders is important, particularly for pain because a key element of pain described by RA patients is due to joint inflammation, and suppression of inflammation shows an improvement in pain levels as well (Walsh & McWilliams, 2012). These show how inter-linked different symptoms are in RA, and the multiple elements that pain consists of that suggest that pain is not purely a physical construct. These physical symptoms can thus be considered as somatic symptoms which means that it has an emotional aspect that needs to be considered.

A study by Cadena et al (2003) shows that disease activity in RA is significantly associated with symptoms of depression and anxiety, such as low mood and anhedonia. This finding is reaffirmed by a systematic review (Lwin et al., 2020) that shows depression as twice as common in RA patients than in the general population. It also discovered that even with reduced inflammation, mental health symptoms do not improve. A systematic review on 72 total studies (Matcham et al., 2013) revealed that the lifetime prevalence of depression in RA patients is about 38.8%, and that it is significantly influenced by age, where a lower age means a higher likelihood of developing depression. The prevalence of depression in RA is also significantly higher than osteoarthritis (OA), with a recent study on 122 participants showing the prevalence of depression in RA patients to be around 24.9% higher than in OA patients (Mella et al., 2010). This shows that there is a heavy burden on mental health in RA patients, which is even greater than other forms of arthritis. With this

comorbidity between mental health and RA, it is important to look further into all possible comorbidities and extra-articular processes to see the extent of damage RA provokes.

1.1.5 Comorbidities and extra-articular processes

Co-morbidity of RA and other illnesses are a major concern for patients, as they leads to higher mortality rate (Gabriel & Michaud, 2009; Norton et al., 2013) and greater functional impairment (Gullick & Scott, 2011). Typically, co-occurring conditions are grouped into conditions that are considered to be extra-articular manifestations of RA itself, such as nodules and vasculitis, versus other comorbid conditions that are not directly caused by the underlying autoimmune mechanisms (Norton et al., 2013; Young & Koduri, 2007). These co-morbidities may be co-incidental, complications as a result of the medication consumed by the patients (e.g. steroids increases risk of osteoporosis), or caused by the chronic inflammation that RA patients experience (e.g. generalised inflammation is associated with ischemic heart disease) (Dougados et al., 2014). In the study carried out by Dougados et al (2014) that included 3920 participants, it is shown that possible co-morbidity include depression (15%), cardiovascular disease (6%), skin cancer (4.5%), hepatitis B (2.8%), and pulmonary diseases (3%). These percentages vary across geographical locations, with cardiovascular disease at a low of 1% in Morocco and a high of 17% in Hungary, and pulmonary disease being rare in Asian countries (around 1%), and much more common in Western countries (about 7.5%). This study confirmed that the monitoring of co-morbidities in RA is lacking, especially those of cardiovascular disease (which increases the mortality rate of RA patients twofold (Gossec et al., 2013). This points to a need to raise the awareness of the prevalence and dangers of co-morbidity in RA, and this thesis focus on the most common co-morbidity.

The comorbidity between RA and mental health disorders extend to more than depression, with anxiety and bipolar disorder all elevated in the RA population (Marrie et al., 2018). However, out of all these, the most common type of co-morbidity in RA is depression (Dougados et al., 2014). RA patients experience abnormally high rate of depression, about 16.8% (Matcham et al., 2013) which is around three times higher than the depression rate in the general population. This is an alarming statistic; a study (Ang et al., 2005) on 1290 RA patients showed that depression is an independent risk factor for

mortality in RA patients, disregarding suicide. This is reinforced by another longitudinal study carried out on 882 participants (van den Hoek et al., 2016) that showed comorbidity of depression in RA patients leads to a 2.25 times increased mortality risk. These show how serious the problem of depression is in RA patients, and the need for this comorbidity to be studied. Dickens et al. (2002) showed in their systematic review that even after controlling for gender, age, and socioeconomic status, the rate of depression in RA is significantly higher than the general population, meaning that there is a possibility of the presence of arthritis having a direct association with depression. This finding is also reflected in a newer study that matches RA patients with non RA patients by age and gender (Lin et al., 2015), which showed that the incidence of depression is 1.74 times higher in RA cohort. There is no doubt a strong association between RA and the development of depression. However, this only illustrates that depression and arthritis may be associated, but does not provide any clarity on how – such as whether depression worsens arthritis, or vice versa, or whether other factors than the ones included in the review might be having a confounding or mediating impact on the association. This is likely to be due to factors such as the high levels of pain, fatigue and physical disability, difficulties coping with the impact from arthritis, and also the limited support available to help patients (El-Miedany & El-Rasheed, 2002). The lack of support could also affect other lifestyle behaviours of RA, such as smoking and physical activity which play a part in the development of comorbidities and increased mortality rate (Gwinnutt et al., 2020).

Besides lifestyle and social factors, the higher depression rate in RA could also be attributed to factors associated with increased inflammation, which other types of arthritis do not normally contain (Margaretten et al., 2011). Systematic inflammation has been shown to be associated with the development of depression (Al-shair et al., 2011; Capuron & Dantzer, 2003), and could also contribute to depression symptoms in those with chronic inflammation (Dantzer et al., 2008). The role of inflammation, both peripheral and central in depression and other mental health disorders is growing as a field of study (Miller et al., 2017), but it does not completely explain the high depression rate. Research has also shown that physical symptoms of RA, such as pain is also a key factor in depression in arthritis, with pain levels being one of the main symptoms that could predict the incidence rate of depression (Walsh & McWilliams, 2014). It is discovered using brain imaging that the part of the brain that processes rheumatic pain overlaps with the part that is associated with

depression (Jones et al., 2012). The association between pain and depression is bidirection in nature (Kroenke et al., 2011), with a change in levels for both pain and depression being a predictor of one another for the next time period. However, a recent paper that looks at neurological function and brain regions (Sheng et al., 2017) supports the idea that pain leads to depression but requires further investigation. This shows a clear association between pain and depression, but an unclear direction. This could be mainly due to the lack of full understanding of the mechanics behind how pain may cause depression, with theories from biological to psychosocial. Pain is a stressor which means that corticotropin-releasing factor (CRF) is released when the brain detects pain (Hummel et al., 2010). CRF also interacts with other brain systems which influences the response to stress, which in turn makes it a factor for depression (Waters et al., 2015). Pain is known to cause maladaptive coping responses, for example perceived helplessness and catastrophising and these are risk factors for physical disability and heightened sensitivity to pain (Edwards et al., 2011). Coping strategies in RA influence quality of life and both physical and psychological symptoms in patients and is considered as an important factor in determining patient health state (Englbrecht et al., 2012).This means that maladaptive coping responses to pain will affect psychological health in patients, and plays a role in depression.

Besides pain, fatigue could also explain the link between RA and depression, as reduced quality of life is associated with fatigue, and quality of life is a common link to depression (Lyon et al., 2014). Furthermore, the presence of fatigue and depression is highly correlated, and fatigue is also a significant predictor of depression (Corfield et al., 2016). The mechanics between fatigue and depression is unclear again, however there are a few theories that may explain their connection. Inflammation, which is a key symptom in RA, is a shared factor for both fatigue and depression (Lee & Giuliani, 2019) as both share a significant association with higher inflammation levels. Antidepressants are also found to decrease inflammation, which suggests another hint at how fatigue and depression are linked. The direction of the association is unclear as there has been no research that shows a clear direction in a RA sample. However, it still shows a distinct association and the possibility of fatigue as a causation of depression. This link between fatigue and depression is also reflected by research in other fields as well, like cancer (Brown & Kroenke, 2009) which discovered that a massive amount of studies on fatigue (58 out of 59) showed that there is a significant association between fatigue and depression. This suggests that there

are various possible pathways for depression to develop as a comorbidity to RA, with inflammation and symptoms of RA as possible factors. Even though the mechanism behind this comorbidity is unclear, it shows that there is a significant interaction between the physical and psychological aspects of RA.

It is important to investigate these interactions because patients with comorbid depression and RA are less likely to be compliant with treatment, and negatively impacts physical and mental function, mortality, symptom severity, and quality of life in RA patients (Li et al., 2019). Patients are also more likely to participate in unhealthy behaviours such as smoking, excessive drinking, and lack of exercise (Lin et al., 2003). These factors all lead to poorer clinical outcomes (Ang et al., 2005) and a 2.2 times higher mortality rate (Culpepper, 2008). These show how depression negatively impacts RA patients and shows the importance in identifying and treating depression. Furthermore, treatment for depression has also shown to have some connection for better outcomes for RA. Lin et al. (2003) found that collaboratively caring for depression and arthritis leads to lower pain intensity, lower interference with daily activities, and improved health and quality of life, compared to treatment that only focuses on arthritis. Culpepper et al. (2008) agrees that disease activity of arthritis is influenced by the comorbidity of depression or anxiety, and that psychiatric care will help with arthritis outcomes like pain reduction. These show that the treatment of depression and alleviation of depressive symptoms is likely to bring benefits to the physical symptoms in RA, further providing the evidence of the interaction between physical and psychological symptoms. It was also discovered that experiencing depression symptoms at the start of a biologics treatment may lead to a 30% reduced odds of having good treatment response, as well as a reduced improvement in disease activity after the new treatment (Matcham et al., 2018). All these studies show the important interaction that exists between mental and physical health in RA, and that taking into account patients' mood and mental health needs while deciding treatment for the patients is likely to result in improved mental health as well as improved physical health and RA symptoms.

Even though RA patients suffer from increased likelihood of psychological distress and negative psychological impact, it is also important to note positive psychological growth can be derived from RA. The onset of RA is likely to be a period with high levels of stress and worry for most people who experience new symptoms of uncertain origin, needing to engage with the healthcare system, and manage the impacts of this on their work and social

functioning. Despite experiencing high levels of stress, the onset of RA may lead to positive changes in people's lives with many people describing benefits such as improved interpersonal relationships (Danoff-Burg & Revenson, 2005). Furthermore, with the increased stress that RA patients experience, primarily due to the symptoms experienced, the ability to cope with, recover from and adapt to these stressful situations may build up resilience through a mixture of emotional and cognitive strategies that include perseverance, social support, and control (Shaw et al., 2020). Furthermore, positive affect also plays a role in building up resilience, and helps in desensitizing towards pain fluctuations (Strand et al., 2006). The development of resilience is important, because there are evidence that increased life satisfaction is correlated with resilience (Ziarko et al., 2020). Resilience can be viewed as the culmination of coping strategies using optimism, benefit finding, gratitude, and self-compassion which will aid patients' well-being and even reduce stress (Sirois, 2014). This improved psychological well-being can be attributed to the positive social interactions and positive affect that these coping strategies provide (Smith & Zautra, 2008b).

Depression is the most common comorbidity of RA, and the negative impact that it brings to RA patients were discussed above. The cause of depression is unclear, however the importance of identifying and treating it in RA patients is evident, especially in how depression affects the treatment for RA. In order to study the comorbidity clearly, it is important to first have a full understanding of depression and models of depression. This will enable the researcher to be able to extend that understanding into the study of the comorbidity.

1.2 Depression

1.2.1. Background and Diagnosis

Depression has a lifetime prevalence ranging from 1% to 16.9% and a midpoint of about 7%, with the difference due to the geographical location and difference in study design (Kessler & Bromet, 2013). This is a substantial difference from the 16.8% prevalence in RA patients. Depression is also ranked as the leading cause of disability in high income countries (Friedrich, 2017) and is the most detrimental condition to health when compared with other chronic conditions such as angina, arthritis, asthma and diabetes (Moussavi et al., 2007)

There are many symptoms to depression, including negative mood, loss of pleasure, lack of motivation, inability to concentrate, loss of appetite and thoughts of suicide (DSM-V). Depression can be classified as a long-term condition because of continuous relapses throughout a patients' lifetime, and the frequency that it appears alongside physical chronic illnesses (Haddad & Tylee, 2011). Eaton et al. (2008) found that 50% of patients who suffer from a first depressive episode will experience further occurrences, and 80% of those with two episodes will suffer from another episode (Noteboom et al., 2016). As described above, there is a high occurrence of comorbidity of depression and RA which leads to a decreased quality of life for patients (Bruce, 2008), and additional burdens such as significant increases in hospitalization due to RA and increased healthcare costs (Joyce et al., 2009). This shows that depression exacerbates other conditions and can be a negative impact to patients throughout a lifetime.

The DSM-V criteria (Association, 2013) for depression states that for the list of symptoms below, the individual must be experiencing five or more symptoms during the same 2-week period, and that one of the symptoms must be either the first or second option of depressed mood or anhedonia.

1) Depressed mood most of the day, nearly every day.
2) Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day.
3) Significant weight loss when not dieting or weight gain, or decrease or increase in appetite nearly every day.
4) A slowing down of thought and a reduction of physical movement (observable by others, not merely subjective feelings of restlessness or being slowed down).
5) Fatigue or loss of energy nearly every day.
6) Feelings of worthlessness or excessive or inappropriate guilt nearly every day.
7) Diminished ability to think or concentrate, or indecisiveness, nearly every day.
8) Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

This diagnosis criteria also allows for further diagnoses of depression with maniac symptoms, and also depression with anxiety symptoms. It is shown that around 85% of

patients with depression have significant anxiety, and that comorbidity of depression and anxiety occurs in 25% of general practice patients (Tiller, 2013). This showed that there is a significant overlap between depression and anxiety, and that understanding of depression will need a consideration of anxiety as well.

DSM-V criteria tests for the presence of depression in an unidimensional fashion and is unable to account for the severity of depression. This means that this criterion is only able to detect severe depression. However, there are other subtypes of depression, such as mild and moderate, not just severe (Zimmerman et al., 2013). This showed that the DSM-V criteria is only able to screen for depression, but unable to detect the severity. In order for depression to be fully covered, the DSM-V criteria is commonly used with severity scales such as the Hamilton Depression Rating Scale (HAMD) (Tolentino & Schmidt, 2018). The PHQ-9 is also commonly used as a depression severity scale, by scoring nine DSM-IV criteria from 0 to 3, and is validated for primary care (Cameron et al., 2008). The nine DSM-IV symptoms were asked in relation to the occurrence of said symptom over the past two weeks, and the score corresponds to a range from not at all, several days, more than half the days to nearly every day. Both the HAMD and PHQ-9 provides a score to which the patient is screened for depression, but also stratifies the severity of depression according to the scores. The development of these two scales in conjunction with the DSM-V criteria test shows the importance for clinicians to measure the severity of depression instead of just the presence of depression.

1.2.2. Aetiology and Epidemiology

The aetiology of depression is dependent on both genetic and environmental factors, and the interaction between them. It is discovered that genetic factors account for around 40% of the variance in depression (Goldberg, 2006). The heritability of depression is around 37% (Flint & Kendler, 2014) however genetic factors change according to the gender. A study by Kendler et al (2001) on male-female twins and same-sex twins showed that the genetic factors that influence risk of depression in male and female are different, and that heritability of depression is significantly greater in female than male. This finding was reaffirmed by another sample of 7500 adult twins in Virginia which showed that there are significant differences in sex concerning genetic factors (Kendler et al., 2013). This

difference in genetic factors in gender leads to a significantly higher prevalence of depression in female compared to male across all age groups (Salk et al., 2017). Even though there is an evident genetic factor, there is still insufficient evidence for which genome it is that causes depression, and the current evidence is that it is a joint effect of multiple genomes (Ripke et al., 2013). Furthermore, the underactivity in monoamines in the brain, such as dopamine and serotonin could also cause depression, in a theory called the monoamine hypothesis (Lee et al., 2010).

Besides genetics, depression is also influenced by the environment. The earliest environmental influence on future depressive symptom is the quality of maternal attachment that is affected by postpartum depression (Sliwerski et al., 2020). This impact is not just due to postpartum depression, but a high level of depressive symptoms in the mother will also have an adverse effect on the newborn (Tronick & Reck, 2009). Infants at nine months are affected by maternal attachment through both social engagement and negative emotionality, which are both depressive symptoms (Granat et al., 2017). There are also other environmental risk factors, such as stressful life events during the stages of development during childhood that plays a role in the development of depression (Nyman et al., 2011). However, the environmental factors are not sufficient in explaining the aetiology of depression as well.

The last explanation for the aetiology of depression is the gene-environment interaction (GxE). Because of the inability for either genetic or environmental reasons to fully explain the cause of depression, the interaction had to be considered as well. The monoamine hypothesis makes up part of the interaction. One of the major genetic pathways to depression is the 5-HT transporter gene (5-HTT), specifically the 5-HTTLPR (serotonin transporter-linked polymorphic region) and this gene is heavily dependent on the interaction with the environmental factor of stressful life event to determine its risk factor towards depression (Yohn et al., 2017). This interaction was also shown in another study carried out on 234 children between the age of 3 and 5 (Bogdan et al., 2014), where it was shown that children with the short allele of 5-HTTLPR is significantly more susceptible to depression when exposed to stressful life events when compared to those with the long allele. This shows how the environmental stressors could affect depression through the specific genetics that a person has. The aetiology of depression is thus unclear, but is

evident that genetics, the environment and the joint interaction between them are all contributors.

There is geographical variability in the prevalence of major depressive disorder (MDD) worldwide according to a study carried out by Andrade et al (2003) where the lifetime prevalence of MDD according to the DSM-IV varies from 1% in Czech Republic to 16.9% in USA, with the median prevalenceof 8.3% and 9% belonging to Canada and Chile respectively. This huge variability could be due to the different cultures of the country leading to different interpretations of depression, and also different study design factors. A health survey conducted across 60 countries from the WHO recorded an average of 3.2% one-year prevalence of MDD in those without a comorbid physical condition. In those with one or more comorbid long term physical condition, the rate increases to 23%, and also shows a significant likelihood to develop depression over those without (Moussavi et al., 2007). It is also shown that the lifetime prevalence depression is higher in high-income countries compared to low-income countries, with the top 4 scoring countries being the Netherlands, USA, Brazil and France. The age of onset for depression in most countries is found to be similar, during the early to mid 20s (Bromet et al., 2011; Kessler et al., 2007), and it also remains similar in genders (Bogren et al., 2018).

Gender, age and marital status are found to be significantly associated with depression in most epidemiology studies (Kessler & Bromet, 2013). Women are twice more likely than men to develop major depression according to a study on 23 European countries (Van de Velde et al., 2010).The gender difference in depression extends to more than just the prevalence, as the symptom profiles of genders differ as well (Karger, 2014). The effect of depression on genders differ, with depression affecting men's ability to work while depression affecting women on the quality of sleep and general health (Angst et al., 2002). The coping methodology for depression also varies between gender with men turning to increased physical activity and consumption of alcohol to cope while women using religion and emotional release such as crying. It is also shown that married people are less likely to develop depression than those who are single, widowed or divorced in both Western and Asian population (Bulloch et al., 2009; Jang et al., 2009). However, married couples also affect each other significantly, as it is shown that if a partner has high depressive symptoms, the other partner will exhibit higher depressive symptoms as well within a year (Johnson et al., 2017). A systematic review also showed that in populations above 55 years old, being

unmarried is a significant risk factor for depression (Yan et al., 2011). Marital status is also influenced by gender, as it is shown that the odds for unmarried men to develop depression is higher than unmarried women. This shows the possible interactions between these environmental factors that could affect prevalence (Bulloch et al., 2017).

1.2.3. Models of Depression

As mentioned above, depression is usually diagnosed using the DSM-V criteria which includes many factors such as mood, fatigue, anhedonia, and suicidal ideation. It even takes into account the possibility of anxiety symptoms, suggesting the close relationship between depression and anxiety. However, it was also stated that using only DSM-V criteria was not ideal because of the inability to detect the severity of depression. Depression and anxiety are known as affective disorders, where they are part of the Axis 1 disorders which are mainly mood disorders (Beach & Whisman, 2012). Axis 1 disorders include depression, anxiety, PTSD, and bipolar, and depression is the most common. These mood disorders all share a degree of comorbidity and overlaps in symptoms, which means that that it is difficult to differentiate at times. The aetiology of depression is also unclear, with both nature and nurture playing a part in how depression is caused in individuals. In order to fully understand depression, a clear picture of the underlying disease process is required. There are many different models of depression, ranging from biological, cognitive and stress-related, and they all contribute differently to the understanding of depression (Duman, 2010). The below paragraphs will discuss the theories behind depression, and then choose an appropriate model for this thesis to continue with the understanding of depression in RA.

1.2.3.1. Chemical Imbalance (Disease-Pill)

In the 1960s, the psychodynamic approach by Freud dominated psychology and psychiatry. During this time, one of the most prominent models of depression looks at the biological processes behind depression; that chemical imbalance is the cause of depression. This has ties to the genetic aetiology of depression, where the monoamine hypothesis was described earlier. The disease-pill theory is developed around the same time the first antidepressant

were put through clinical trials (Hillhouse & Porter, 2015). The biological theory behind this model is logical, as the use of Selective Serotonin Reuptake Inhibitor (SSRI) is proven to effectively treat depression in a study by Burke, Gergel & Bose (2002) which tested 3 different SSRI and all has proved to be significantly more effective than placebos in decreasing depressive symptoms. The use of antidepressants such as the mentioned SSRI is still rampant today, as a recent study (Hieronymus et al., 2016), showed that out of 32 studies that compares the use of SSRI with a placebo, 29 showed a consistent reduction in depressive mood in those with depression. The theory of chemical imbalance was first proposed in the late 1950s because of the observation of changes in mood after the intake of certain pharmaceutical products (Leo & Lacasse, 2007).

The focus shifted to serotonin, after it was discovered that the drug reserpine depletes monoamine (of which serotonin is a type of) and could also lead to a depressed state (Nemeroff, 1998). This finding in the 1960s inspired a lot of studies that investigates how the use of reserpine could lead to a drop in serotonin which could lead to depression. However, it was discovered In a review by Baumeister, Hawkins & Uzelac (2003) that the median prevalence for depression in studies that includes patients using reserpine is only 10%, which is close to what the general population's prevalence is. It is also shown that more than two-thirds of the cases reserpine caused depression in the studies actually involve patients who already had pre-existing mental disorders. It was also shown that the few studies which showed a significantly higher rate of depression during reserpine treatment all had study design flaws which means that their conclusions were biased. This discounted the idea that the use of reserpine could cause depression, however the chemical imbalance theory based on serotonin continued on. The perpetuation of this idea is extended to other disorders as well, such as ADHD and the idea has been pushed by the Food and Drug Administration (FDA) and National Institute of Mental Health (Baughman, 2006).

This leads to the 'disease pill' treatment model where mental disorders are regarded as illnesses that could be treated by pharmaceutical products, which explains the continued sponsorship of this theory to facilitate pharmacotherapy. This biological theory is still one of the most common theories these days and does hold some truth as a systematic review (Jakubovski et al., 2016) showed that using a high dose of SSRIs is more effective in reducing depressive symptoms than a low-dose. Continued research in this field has also developed

new drugs, such as the glutamatergic medication which is aimed at the N-methyl-D-aspartate (NMDA) receptors in the glutamatergic system and is shown in a literature review to have significant antidepressant effects in clinical studies (Serafini et al., 2013).

Besides the facilitation of pharmacotherapy, the chemical imbalance theory is also supposed to help reduce stigma and self-blame through the attribution theory. According to the attribution theory, attributing a mental disorder to an uncontrollable factor should alleviate stigma and self blame (Muschetto & Siegel, 2019). However, a study by Kemp, Lickel & Deacon (2014) showed that in cases where patients are shown a bogus credible biological test that proves chemical imbalance to be the cause of depression, the patients suffered from pessimism regarding the disease course and worse negative mood regulation. This showed that the attribution to depression to the chemical imbalance theory is actually unhelpful to the individual and may be harmful. Even though the use of SSRI and antidepressants do have some effect in treating depressive symptoms, there is a growing trend of research that states that the chemical imbalance theory is primarily the work of pharmaceutical companies and the evidence base of it is weak and conflicted (Probst, 2015). This meant that in order to fully understand how depression works, other aspects of depression need to be explored.

1.2.3.2. Cognitive Approaches

In the 1970s, the dominant approach towards psychology was the cognitive theory. Beck's Cognitive Theory of Depression (Beck, 1964) is one of the dominant theories of depression in the late 20th Century and it suggests that negative thoughts are central to how depression is caused, and that these cognitive symptoms occur before mood symptoms. It is believed that dysfunctional beliefs generate negative thoughts and perception of the patient which result in depression for the patients. These dysfunctional beliefs are formed through early experiences, and a critical event is likely to trigger the start of negative thoughts later in life. Individuals will then interpret experiences negatively which limits their focus to only the negative aspects of situation, thus causing hopelessness and helplessness about the future. These depressive symptoms will then generate more negative thoughts, and a vicious cycle is formed which will develop depression for the individuals. Depression as described by Beck is made up of negative biased view of oneself, negative view of the world in general and

also a negative view of the future. There are also backings for this theory through neural mechanisms, as it was shown that there is an association between hyperactivity of the amygdala and hippocampus with the rumination and recollection of depressive thoughts, and the dysfunctional attitudes due to the depressive thoughts is also associated with decreased connectivity between the dorsal anterior cingulate cortex and the limbic system (Disner et al., 2011). Another study carried out on 40 students (Boury et al., 2001) looked at how the Beck Depression Inventory (BDI-II) scores change with regard to thoughts written down by the students, and it showed that there is a direct relationship between negative thoughts and severity of depressive symptoms, and that the effects of negative cognitive processes will prolong depression.

Beck's Cognitive Theory is still one of the dominant theories today and is one of the fundamental influences on Cognitive Behavioural Therapy (CBT), alongside Behavioural Therapy which was developed by Wolpe in 1958 (Westbrook et al., 2011). Behavioural Therapy is based on looking at reproducible associations between a stimuli and response, thus recognising unwanted behavioural and emotional reactions and tries to form new associations between stimuli and response. Negative automatic thoughts, or negative interpretations from events is fundamental to CBT and exert a direct influence over mood (Westbrook et al., 2011). This means that the purpose of CBT is to help patients understand the current way of thinking and behaviour, and to change the negative patterns (Fenn & Bryrne, 2013). A meta-analysis on 29 papers (Beltman et al., 2010) showed that when comparing depressed patients undergoing CBT to depressed patients with no treatment, CBT significantly reduces depression symptoms. However, comparing CBT to other active treatments such as psychodynamic treatment and problem-solving therapy showed mixed results (Hofmann et al., 2012). CBT reducing depressive symptoms shows the validity of the cognitive theory, but the comparable treatment rate compared to other therapies showed that the cognitive theory is insufficient to fully explain depression. CBT is also the recommended therapy for NHS patients, particularly in the Improving Access to Psychological Therapy (IAPT) service where patients are referred to from the General Practice (GP). The use and effectiveness of CBT showed how Beck's Cognitive Theory is still in use today, and contributes to the understanding of depression. However, CBT when compared to other psychological therapy methods are not always the most effective, as it was not more efficient than interpersonal or supportive therapy (Tolin, 2010). This showed

that the cognitive theory may not be able to be generalised to all depression patients. Beck's cognitive theory also presents a simplified look at how depression is formed, as negative thoughts is not always the only trigger for depression. A study on college students and the views about future (Abela & D'Alessandro, 2002) showed that individuals who have negative thoughts about the future does not always have depressive symptoms. This is an example of the possibility that the feedback loop between depressive thoughts and beliefs does not always result in depression, and that more factors could be involved in the theory of depression.

1.2.3.3. Environmental Stress Models

Besides Beck's cognitive theory, other environmental factors may also play a role in depression. Stress can be referred to as part of psychological well-being, and exposure to stress is a major risk factor associated with depression (Keller et al., 2007). Stress may even have interactions with generic risk factors to increase the possibility of depranession among the general public (Caspi et al., 2003). The inclusion of a stress in a model of depression is stated to strengthen the validity of the model because it takes into account the association between stress and depression (Duman, 2010). Stress has also been shown to have negative effects on cognition, leading to an inability to focus properly, as stress acts as a cognitive load (Stawski et al., 2006). This diversion of cognitive processes to deal with the load, coupled with stress responses like difficulty with coping and catastrophizing (Van Loey et al., 2018) will contribute to the higher likelihood of negative thoughts, which links back to the Beck's Cognitive Theory of Depression and adding to its validity.

One of the possible stress models of depression is Learned Helplessness, in which individuals exposed to uncontrollable events will exhibit disrupted behaviour (Seligman, 1972). This means that individuals who are exposed to events that are out of their control eventually give up trying to change it. This theory was initially applied on animals, but is also applicable to humans, where the first human study was carried out in 1974 (Hiroto, 1974) which is based on college students and the attempts to stop an uncontrollable loud noise. The students in the first group that is faced with a loud noise that could not be stopped gradually lost motivation even when changed to a new situation, which is a major symptom of depression. This model is part of the environmental stress models of depression, and also

has its basis on cognition where it is the cognitive appraisal of the event that causes depression. However, it has also been shown that learned helplessness does not always generalise to new situations in humans, and thus will not be able to explain all the factors of depression (Vollmayr & Gass, 2013). Another theory under the environmental stress model is the Chronic Mild Stress Model of depression. It describes a major symptom named anhedonia which is the decreased response to pleasure and reward, as being caused by constant and unpredictable stressors (Willner, 2017). It is mostly based on the psychological and neurological basis, in which constant stressors result in the behavioural change of anhedonia, or the neurological part where the threshold for brain stimulation rewards is increased, and thus there will be a decreased response to pleasure from normal (Moreau et al., 1992). This presents a different look at how situations could lead to depression, without the same cognitive basis as Beck's cognitive theory. Stressful life events were regarded as an important aetiology for depression, and thus it is logical for stressors to be one of the theories of depression as well. Both the cognitive and stress models of depression represent depression as a result of environmental factors, but without taking into account the possibility of biological factors. With the effectiveness of certain antidepressants, this environmental perspective is not inclusive enough of other factors.

1.2.3.4. Tripartite Model

The Tripartite Model of Anxiety and Depression (Clark & Watson, 1991) states that anxiety manifests through physical hyperarousal and an increased sensitivity towards pain, while depression from an absence of pleasure and low positive affect. The Tripartite Model was developed in order to explain the comorbidity that exists between anxiety and depression, and the common symptoms that exist between these two disorders. Previous models described in this section did not explain the presence of comorbidity, and with this thesis focusing on the comorbidity between depression and RA, meant that it is important to get an understanding of comorbidities of depression. Anxiety is also a critical psychological symptom in RA, with a prevalence of around 50% (Uguz et al., 2009), and 16% for mixed anxiety and depression disorder (Isik et al., 2007).

This model coincides with the Chronic Mild Stress Model (Willner, 2017) in which one of the major symptoms of depression is the lack of pleasure derived from activities. The

Tripartite model maintain that both depression and anxiety share elements of general affective distress, and thus in order to distinguish properly, the three part structure consist of general distress, physiological hyperarousal and anhedonia. The moods and emotions associated with depression and anxiety are different as well, with depression being linked to sadness, and anxiety motivated by fear (Watson et al., 1995). Depression and anxiety both have an influence on exposure and sensitivity to stress (Bolger & Zuckerman, 1995), but all three symptoms are actually distinct (Covic et al., 2012) and require separate measurements. There is a high comorbidity rate and similarity between depression and anxiety as stated by the Tripartite Model (Clark & Watson, 1991),but it is vital to be able to distinguish between depression and anxiety clearly to help make accurate diagnosis (Gaylord-Harden et al., 2011).

The Tripartite Model (Clark & Watson, 1991) divides the symptoms of anxiety and depression into negative affect, positive affect and physical arousal. These symptoms are considered latent variables. Negative affect is shared by both disorders, which contributes to the negative mood that patients with either disorders experience. Physical arousal on the other hand, can be used to distinguish anxiety from depression. Those suffering from physical arousal experience shortness of breath, sweaty palms and trembling, and these will not be found in depression patients. For those with depression, low positive affect is what separates them from anxiety patients. Low positive affect results in patients losing interest and pleasure in activities that are normally pleasurable, which is a critical depression symptom that is mentioned before in other models. It is also found that negative mood such as sadness, and fatigue is also part of low positive affect (Watson et al., 1995).

The understanding of the Tripartite Model led to a more transdiagnostic approach which emphasises a single common pathology that underlies different disorders instead of utilizing the distinct DSM-IV definitions of individual disorders (Norton et al., 2004). This meant that the focus is more on symptoms rather than the conditions, and prompted the transdiagnostic focus on treatment, for example giving people with depression or anxiety the same treatment, such as CBT (Ali et al., 2017) because of the overlap in symptoms. This model thus provides a good template for the understanding of comorbidity with depression, and also the framework of working with symptoms instead of conditions.

On

1.2.3.5. Network Models

All the models that were described above, ranging from the biological to the environmental models all attempted to explain depression as a single condition, besides the Tripartite model. In this respect, depression can be considered as a latent variable; a construct that cannot be directly observed but is indicated by the symptoms it causes. In this tradition, depression is either considered to be a latent categorical variable (a latent class) representing a distinct condition, or alternatively the extreme end of a latent continua, as in the Tripartite model. Importantly, the symptoms of depression, such as low mood or low energy, were not regarded as a significant factor into the causation of depression but a key characteristic of the condition. The interactions of depressive symptoms were also not considered, and the same explanation (i.e. theoretical model) is assumed to apply to each individual case. The lack of ability of the models to be able explain differences in development and presentation of depression is an important limitation that has been noted. For example, in recent publications relating to Beck's cognitive theory (Beck & Bredemeier, 2016), it was stated that one of the main aspects of cognitive theory that needed to be improved was the generalisability of the model to account for all clinical cases. One explanation for the weakness of existing models is that different subtypes of depression may exist, and the models are not sufficiently well specified to account for this heterogeneity. It is also possible that the pathways to depression could also differ across individuals. This is a key focus of recent research regarding the network theory of depression, which has used ideas from physics and complex systems theory in order to understand the pathway of depression to for each individual, and for the biological, social, and psychological aspects of depression to all be considered.

The network theory of depression, first proposed by Borsboom (2008a) combines the biological, psychological and societal mechanisms of mental illness into a causal network with strongly connected symptoms to form a common explanatory model. This theory was proposed because for mental disorders, symptoms are not necessarily all effects of a common cause and there is no central disease mechanism that causes all the symptoms (Borsboom, 2008a). Instead, the symptoms interact with one another, and sometimes with themselves, resulting in a vicious cycle and the formation of a mental disorder (Cramer et al., 2010). Using network theory will thus place symptoms as nodes, and associations

between each other as a link, creating a structure that will allow researchers to look at the mental disorder as a whole.

Network theory is part of the science of complex systems, which is a new field of science without a concise definition but is aimed at understanding causality (Ladyman et al., 2013). Complex systems theory allows for the study of how mental disorders change, for example how symptoms of depression change after CBT, by not just looking at a single outcome capturing overall symptoms severity but taking into account changes in multiple components simultaneously (Hoffart & Johnson, 2020). Furthermore, existing theories for depression that consider depression to be a latent variable also looked at changes in severity in a linear manner, for example between pre and post treatment. However, in reality symptom changes are dynamic and fluctuate. New studies have promoted the change from a linear to non-linear and dynamic models in order to fully capture the patterns of change (Nelson et al., 2017; Pincus, 2019). This means that complex systems, in particular network science, which looks at mental disorders as a study of interacting symptoms and feedback loops that fluctuate in non-linear manners, is well-equipped to handle the modern requirements (Hayes & Andrews, 2020).

One of the main differences between the network approach to depression with previous theories is the thinking that symptoms are not just effects of the disorder, but that symptoms actually interact with each other bidirectionally. This causes the aforementioned feedback loop, which is when one symptom causes another symptom to worsen, which in turn caused the original symptom to be affected as well. This loop will continue until a state of prolonged symptom activation which is referred to as a mental disorder (Borsboom, 2017). This means that every symptom, and every symptom interaction is vital to the network of depression because any could cause this feedback loop. This theory is then modelled into a network, where nodes are the symptoms, and links are the possible interactions between the symptoms. This means that each node could have multiple links, and that every node will be affected by each other, even if there are no direct links between them because of the indirect effects from any shared symptom nodes. The network approach to depression also takes into account any external events, such as an adverse life event activating one of the symptom nodes, which will then have a ripple effect through the network. This can be seen in Figure 1.2 below.

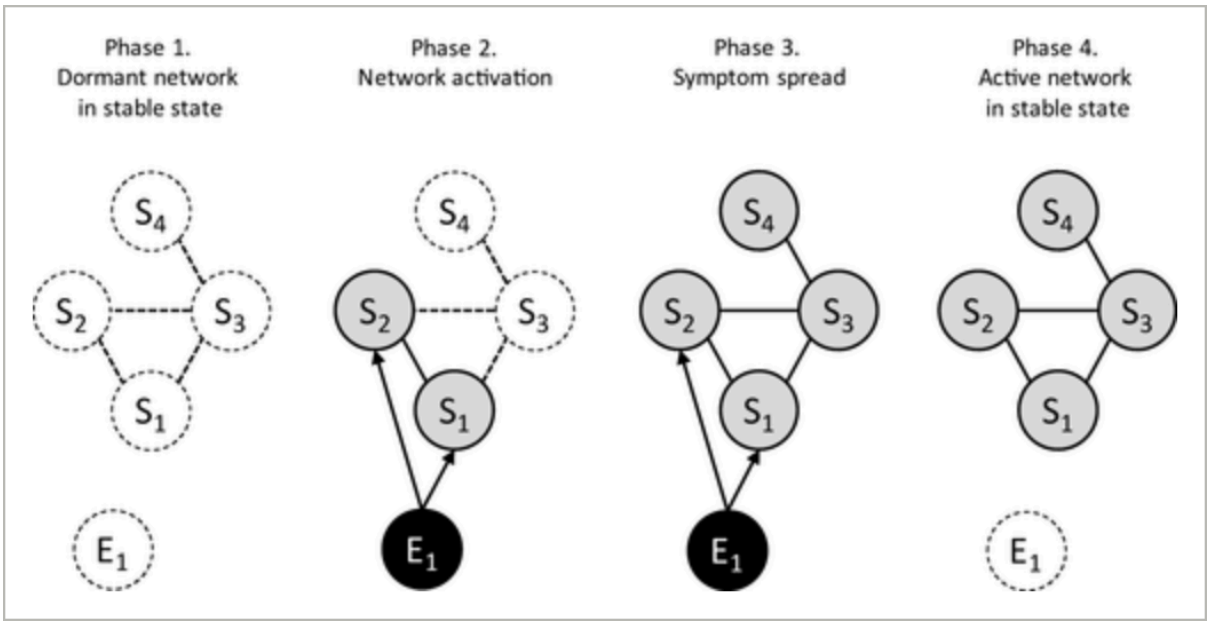


Figure 1.2: Spread of Activation from External Event in Network Science
Borsboom, D. (2017). "A network theory of mental disorders." World Psychiatry **16**(1): 5-13.

Figure 1.2 shows how the network gets activated when an external event, E_1 leads to the activation (i.e. experience of) two symptom nodes, S_1 and S_2 in Phase 2. E_1 activates the two nodes, which then lead to a spread in activation onto two further symptoms, S_3 and S_4 , in phase 3; even though there was no direct link with E_1. Phase 4 shows the symptom network still being activated even after the disconnection of E_1, which is what would be observed for someone with a mental disorder. This shows that in the case of a strongly connected symptom network, even the removal of the trigger is not enough to reducing depressive symptoms because there is a feedback loop within the network itself that causes ongoing activation in the network, and those maintenance of symptoms experienced. It is important to bear in mind, that this model does not rely on there being an underlying latent variable that causes these symptoms.

The network approach to psychopathology has become more popular in recent years, and a systematic review by Contreras et al (2019) showed that network approach has been used in various different mental disorders, including anxious disorders, psychosis, comorbidity between disorders and mood disorders. There were 16 studies on depression between 2010 and 2017 that utilised a network approach. All of these studies managed to identify important aspects in depression. For example, Lee Pe et al (2015) found out that in a seven day longitudinal study, patients with major depressive disorder had a much denser negative affect network than controls. This suggests that previous negative emotion have a

greater influence on the next time period's negative emotion, which was not found in the positive affect network. This indicates that negative emotions are more resistant to change and more likely to remain activated.

It was also found by Madhoo & Levine (2016) that symptoms are significantly more connected before therapy than after therapy, affirming the theory of a strongly connected symptom network indicating a feedback loop for depression. These network papers on depression also utilized centrality, which is a quantifiable method to calculate influence in a network plot. It is discovered that DSM-V symptoms are not more central than non DSM-V symptoms, and that both groups have symptoms (e.g. sad mood and anxiety) that are among the highest in centrality, and thus influence in the network(Fried et al., 2016). This means that focus cannot be just on DSM-V symptoms, but that centrality should be applied to each patient to find out the central symptom for each respective symptom network to better understanding the course of disease. These studies show novel findings through a new understanding of depression, and establishes the network approach as a model for depression that might help further our understanding of this condition.

A literature review by Robinaugh et al (2020) that looked at progress of network theory in psychopathology since the development of the theory in 2008, showed that there is still a need to develop guidelines for specific disorders instead of a general framework for mental disorders. This provides an excellent opportunity for this thesis to develop a network science model of the development of depression specifically in RA patients. Having established the theory of depression that this thesis will be based on, it is important to explore the presence of depression in RA. It was touched on previously regarding the comorbidity of depression in RA, but the following section will explain the aetiology of depression in RA, and also the utility of network model in the comorbidity.

1.2.4. Depression in Long Term Conditions

1.2.4.1. Background and Epidemiology

Depression is a common comorbidity for long term physical conditions, as it is revealed that 38% of prostate cancer patients report a comorbidity of depression (Rice et al., 2018), 8.33% of patients in breast cancer suffered major depressive disorder (Su et al., 2017) 10-15% in

diabetes (Anderson et al., 2001) and 19.8% in coronary heart disease (Carney & Freedland, 2017). It is discovered that patients with a long term condition is twice as likely than the general population to develop depression (Aragones et al., 2007). Comorbidity of depression in long term conditions could lead to functional impairment, higher treatment costs, lower treatment adherence and a higher mortality rate (Scott et al., 2007). In Chapter 1.1.5, it was also shown the high prevalence of depression in Rheumatoid Arthritis, and that a systematic review on 12 independent studies showed that patients with rheumatoid arthritis are significantly more likely to develop depression than in the general public, after controlling for any sociodemographic differences. Depression in RA is particularly dangerous, as it reduces chance of remission of RA (Michelsen et al., 2017) and increases disability (Lowe et al., 2004).

1.2.4.2. Causal Explanations of Depression in RA

To better understand the comorbidity between depression and RA, it is important to know the causal explanations behind the association. Increased levels of inflammatory cytokines have been detected in the brain and blood of patients with depression (Miller et al., 2009). It has also been shown that CRP is one of the main biomarkers of depression, which is also one of the main inflammatory biomarkers for RA. It is shown by Kohler et al (2014) that the blockade of cytokines will reduce depressive symptoms in those with RA. Combining this with targeted immune therapy for RA has not only helped with reducing inflammation, but also reduced depressive symptoms (Nerurkar et al., 2019) and this shows the possible association between inflammation and depression. However, a systematic review by Eyre et al (2015) showed that Non-Steriodal Anti-Inflammatory Drugs (NSAIDs) which is a common treatment for RA, have an inconsistent and negligible impact on depressive symptoms. This conflicting information showed that there are more factors at playing when discussing the association of depression and RA.

This inflammatory pathway may also mean that the association between depression and RA is bidirectional, in that depression is a major risk factor for RA (Vallerand et al., 2019). The mechanism by which inflammation in depressed patients could lead to autoimmune diseases like RA is not yet clear (Belleau et al., 2019) but a study based on a British population comparing a MDD group with the general population showed that those

with MDD are 38% more likely to develop RA. It is also shown that MDD patients that used antidepressants are significantly less likely than MDD patients that did not use antidepressants to develop RA (Vallerand et al., 2018).

1.2.4.3. Network theories approach on comorbidity of depression and RA.

The co-morbidity between depression and RA increases the complexity of treatment for both the physical and mental health conditions (Covic et al., 2012) and has negative side effects, such as lower recovery rate, higher suicide rate and higher relapse rates (Mineka et al., 1998). This pushes the agenda for psychological symptoms to be understood better in RA, along with the association with other physical symptoms. In order to do this, it is important to consider the dynamic and interacting nature of symptoms in both RA and depression. As mentioned in Chapter 1.1.5., the network approach can be used to study comorbidities as well. It has been shown in 1.2.3.5. to be the ideal model in which depression should be looked at because it allows individual symptoms and symptom interaction to be considered directly. This is important particularly for symptoms that are common to both RA and depression, such as fatigue.

Comorbidity network analysis studies symptom networks that are created from shared symptoms between larger groups of disorders (Capobianco & Lio, 2015) and aims to derive novel clinical associations between symptoms that could cause the comorbidity (Brunson & Laubenbacher, 2018). Using network analysis to study comorbidity has also been shown to be robust, in a study that examined seven different datasets (Brunson et al., 2020) tested for sensitivity and stability on summary statistics and centrality rankings in the field of comorbidity network analysis showed that the network structures created for comorbidity is robust and that the summary statistics are reliable, however the centrality rankings are highly sensitive to changes. This meant that the use of network analysis to investigate comorbidity is promising, however requires caution to ensure accurate results.

The network science approach focuses explicitly on symptoms and the causal interactions between symptoms, which could lead to a mental disorder. This is different to most other theories which thinks that symptoms are a product of the mental disorder. Symptoms commonly overlap between different conditions, for example as the Tripartite Model showed, anxiety and depression share similar symptoms such as negative affect. This

means that the symptoms of these conditions spread, and that having particular symptoms of one condition could put one at risk of developing the other condition. These particular symptoms are known as the bridge symptoms (Jones et al., 2021). In order to identify these bridge symptoms, one possible way is for researchers to visually inspect the created networks for symptoms that are connected to both conditions (Beard et al., 2016; Levinson et al., 2017). However, this method becomes too complicated when the conditions involve too many symptoms and there is also the possibility that visual inspections are misleading (Jones et al., 2018). Another method is to calculate the bridge centrality score using the bridge strength, bridge closeness and bridge betweenness scores. These scores were used with a sensitivity of 92.7% and a specificity of 84.9% in predicting bridge symptoms on different datasets. When the bridge symptom was removed from the networks, it is also shown to stop spreading of activation between the disorders, suggesting that the bridge symptom is vital to how comorbidity forms. This shows the applicability of network approach in studying both RA and depression.

Having decided to utilise the network approach as the framework of depression and the comorbidity of depression and RA, it is important to clarify the means by which depression will be measured for this thesis. This is because depression will be used as one of the major nodes in the network plot in RA, and with the discussion of different theories behind depression, it is clear that depression is a multifaceted disorder that requires enough nodes to fully capture depression. The inclusion of just one node for depression, such as a sum score for a patient reported outcome (e.g. PHQ9, BDI), is insufficient because it will not neither be able to fully capture the severity of depression nor the depth of symptoms that depression comprises of (Fried & Nesse, 2015). Thus, the tripartite model of depression and anxiety is utilised which showed that depression is affected by both positive and negative affect. A full discussion will be included in the Methodology section (Chapter 4) which will discuss in detail which positive and negative affect symptoms are used.

1.3. Rationale for Thesis

There is a shift in the behavioural and medical sciences towards non-linear systems and dynamic thinking, which encourages the application of network approaches. Utilizing the

network approach to depression and the comorbidity of RA and depression will allow researchers to be able to detect dynamic changes in symptoms, which is likely important because of the fluctuant nature of RA. It is also important to be able to study RA in terms of both physical and psychological symptoms because of the common comorbidity between depression and RA. In order to do this appropriately, longitudinal data of multiple symptoms are needed with sufficient intensity of follow-up assessments to allow for any dynamic changes in symptoms to be observed.

There is a paucity of studies using intensive longitudinal designs in the rheumatological literature. The majority of studies considering interrelations between physical and mental symptoms in RA are either cross-sectional or longitudinal with a limited number of follow-ups spread out over weeks or months. A review by Vriezekolk et al (2011) considered longitudinal studies in RA, focusing on psychological distress. A search yielded only 19 studies (of which only 14 are unique cohorts) that used longitudinal data in looking at psychological distress in RA. This review is dated however, and more studies could have been carried out in the last 10 years, suggesting the need for a new review to investigate longitudinal data collection in the field of RA. Conducting longitudinal studies are beneficial because longitudinal studies allow for cause and effect relationships to be examined, establish sequencing of events and also investigate how symptoms change over time (Caruana et al., 2015). Intensive longitudinal data also allows for more thorough estimation of relationships between symptoms, as a systematic review on the mechanism between sleep and pain showed that the collection of intensive longitudinal data would allow an improvement in analysis and more information to be revealed (Whibley et al., 2019).

RA symptoms can fluctuate wildly, even over a short period of time from day to day (Evers et al., 2014).These changes in symptom, or in other words, symptom variability plays a big part in the well-being and quality of life in RA patients as well. This was established by a qualitative study by Flurey et al (2014), which looks at RA patients' experiences of daily life. This study demonstrated the struggle that RA patients go through with fluctuating symptoms which is a constant unwelcomed reminder. In order to deal with their condition, patients have to micromanage the impact of RA on their daily lives which impacts on the overall quality of life. This shows just one aspect of how symptom variability affects RA patients, and there could be other effects that have not been investigated yet. This emphasises the importance of the dynamic changes that network science will be able to

provide further insights into. It also indicates that symptom variability needs to be assessed over very short intervals, suggesting the need for a study that measures symptoms at several points throughout a day; allowing for the study of within-day symptoms fluctuations as well as between day fluctuations. A systematic review carried out on chronic pain research showed that there were 105 papers from 62 studies that collected a type of intensive longitudinal data called ecological momentary assessment (EMA) data (May et al., 2018). It was shown that most of these papers could investigate within-person fluctuations and were flexible in design. This showed the potential of using these types of data collection method in RA. There has also been a push for network science to be applied to the individual level, for example creating symptom networks depending on each patients' symptom severity and interaction (Fried & Cramer, 2017). This is particularly useful for the fluctuant nature of RA. Having a personalized look at how symptoms change for each patient will be useful for the clinical team to understand the best way to manage the disease course. However, currently no studies have considered a network approach to the study of symptoms in RA.

This issue of symptom variability has been recognised in other conditions, most notably in chronic obstructive pulmonary disease (COPD) where there is considerably more research looking at this problem. A pan-European study by Kessler et al on COPD patients (2011) found that around 62.7% of patients reported their symptoms to vary daily or/and weekly. It is also discovered that previous exacerbations of symptom severity are associated with symptom variability and other factors that affect symptom variability include geographical location, symptom severity and age. A qualitative study by Lopez-Campos, Calero & Quintana-Gallego (2013) also found that COPD patients that are not experiencing exacerbations still perceives symptom variability throughout a day. It is further explained that this is a problem because of the effect that symptom variability has on both health-related quality of life and daily activities. A longitudinal study in Korea by Kim et al (2019) discovered that high symptom variability in COPD is significantly associated with exacerbation risk and also more severe disease activity such as respiratory problems.

To summarise, RA is a disorder that affects patients tremendously through both the physical and psychological aspects. The symptoms fluctuate throughout the day, and thus it is important to collect longitudinal data in order to track how fluctuations and symptoms vary with each other. The most common comorbidity of RA, depression, was also discussed

and the concept of network analysis was introduced to explain depression and the comorbidity. It was also shown that there was a lack of studies in the field of RA and depression that utilises intensive longitudinal data which is present in other fields. These gaps in research thus leads to Chapter 2, where the aims of this thesis are discussed.

2. Aims of this Thesis

Chapter 1 established how prevalent RA is, and the devastating effects that it can have on patients. The common comorbidities were discussed as well, and it could be seen how RA affected patients in multiple ways. In order to alleviate patient suffering and encourage disease remission, it is important to discover how RA symptoms interact and associate with each other. Current literature has revealed ample information on RA, but with the advancement in both technology and analytical methodology, novel information could be extracted from longitudinal data and other analysis methods. This means that the research question of this thesis is to explore physical and psychological symptom associations using advanced quantitative methods on a longitudinal dataset in RA patients; and to explore the feasibility of network science in this field of research. This will be achieved through three main aims.

1. The first aim is to investigate the feasibility of intensive data collection methods, including the use of a wearable device.

Aim 1 Objective 1: The first objective is to carry out a scoping review to reveal current literature in the field of musculoskeletal disorders that uses longitudinal data.

Aim 1 Objective 2: The second objective is to check for the feasibility of the recruitment methodology for a study that incorporates wearables and intensive data collection methodology.

Aim 1 Objective 3: The last objective is to investigate if this data collection method allows for enough data to be collected.

It was described in Chapter 1 that disease activity of RA fluctuates wildly and the risk of a flare is a pronounced problem. The symptomology of RA is also vast, varying from inflammation to pain to low mood. Most current research uses cross-sectional data or compare between a low number of time points instead of utilizing longitudinal data. This meant that information about the variability of symptoms in RA is lacking, and thus it is

necessary to investigate current literature to identify gaps. This will be used as a benchmark for the design of a study chapter that will collect and analyse longitudinal data.

2. The second aim is to investigate what associations exist between the different symptoms in RA and other relevant variables.

Aim 2 Objective 1: The first objective is to investigate how symptoms change throughout the day.

Aim 2 Objective 2: The second objective looks at how physical and psychological symptoms are related to physical activity.

Aim 2 Objective 3: The third objective examines how the COVID-19 induced lockdown has influenced associations between symptoms, physical activity and social contact.

Aim 2 Objective 4: The last objective is to find out how the commencement of a new Biologics treatment for RA patients change symptom associations.

After establishing the feasibility of the methodology and the usability of the data, the data will be used to evaluate the possible associations between the symptoms included. Chapter 1 demonstrated how prevalent and dangerous RA was and also showed how common the comorbidity of depression existed in RA patients. It was established that both physical and psychological symptoms affect patients greatly, and that the connections between the symptoms are unclear. This meant that it is important to investigate the associations between physical and psychological symptoms in RA. Furthermore, other important variables such as physical activity and social contact also play a role in influencing different symptoms in RA, and the connections between these variables and the symptoms need to be covered as well. Because of the COVID-19 pandemic, a study was also created to capitalise on the opportunity to look at how RA patients' symptoms behave differently during a lockdown. Chapter 1 also discussed the importance of different treatments for disease remission in patients, and thus in order to provide important clinical implications, the associations of RA symptoms before and after a new treatment are investigated to enable more understanding in how a new treatment works.

3. The last aim is to investigate the feasibility of using a new analysis method, the network approach in exploring cross-sectional and longitudinal data in the field of RA and depression.

Aim 3 Objective 1: The first objective is to utilise network analysis on a secondary cross-sectional dataset.

Aim 3 Objective 2: The second objective is to create individual network plots for patients with different symptom variabilities.

Aim 3 Objective 3: The last objective is to investigate how network plots differ before and after treatment for RA patients.

In Chapter 1, the comorbidity of depression in RA patients were explored thoroughly. It was established that in order to understand the comorbidity, the model of depression had to be covered first. The models of depression changed over time, and it was demonstrated that the modern approach looked at depression not as a latent variable, but as a construct that made every symptom significant. This change in model of depression pushed forward the network approach as the way to not only look at depression, but also the comorbidity that exists between RA and depression. There were no study in the field of RA that utilised longitudinal data and network analysis to look at individual symptoms and the interactions between each symptom. Thus, it is important to discover if the use of network analysis in this field is feasible, and what novel information could be revealed while using this method. With most current literature focused on cross-sectional data, network analysis will be carried out on cross-sectional data first to discover if there are similarities in findings. With the network approach suggesting that each patients' symptom network plot to be different from each other, a comparison could be made between different types of patients to distinguish if there were any particular differences in patients with high variability in symptom severity.

2.1 Structure of Thesis

Chapter 3 is a scoping review that is carried out to investigate current literature that is based on longitudinal data in the field of musculoskeletal disorders. This chapter will complete the first objective of the first aim, and also provide more rationale for why the empirical chapters are created. Chapter 5 utilised secondary cross-sectional datasets of TITRATE and IMPARTS to estimate the network structure of physical symptoms, psychological symptoms, and inflammatory markers in RA. This will aid in discovering a potential bridging symptom between physical and psychological symptoms. This chapter tests the feasibility of using network science in the analysis of symptoms in RA by seeing if findings reflect existing literature, and also the possibility of novel findings from using network science, thus fulfilling the first objective of the third aim. Chapter 5 could be considered as the preliminary chapter that tests for the feasibility of network analysis in the field of RA, and also what potential cross-sectional result could be derived from multiple physical, psychological, and inflammatory symptoms.

Chapters 6 and 7 were chapters added in because of the COVID-19 pandemic and resulting lockdown. It is part of the larger IA-COVID study and participants were recruited from the sample that participated in the IA-COVID study. Chapter 6 includes data collection during July 2020, a period of no governmental lockdown restrictions, and Chapter 7 includes data collection during November 2020, which is during a period of government implemented lockdown. Chapter 6 looked at the association of physical and psychological symptoms temporally and investigated any diurnal patterns. The use of network science was also more advanced here, where individual network plots were created for patients of different symptom variability and severity to compare differences. Chapter 7 compared data collected during lockdown with data collected during a period of no restrictions to identify how symptoms change between the two time periods, and if any temporal associations change as well because of the change in social contact and physical activity. This was a build-up of the temporal associations that were discovered in Chapter 6 and brought in further variables such as physical activity and social contact. Symptom network plots were also drawn to evaluate differences between the two time periods. These network plots consist of multiple subjects over a long period of time and could be considered as a feasibility test for Chapter 8. Chapter 8 also included an intensive data collection

methodology that utilises wearables and included periods of both before and after a new biologic treatment. Chapter 8 tests the feasibility of the study design of intensive data collection and wearables in a RA cohort starting a new treatment, and also the adherence to study protocol and drop-out rate to evaluate the quality of the data collected. This tested for the feasibility of the collection and analysis of such data. Associations between physical and psychological symptoms were then calculated before and after a biologic treatment, which provided clinically important information Symptom network plots for both before and after exposure to the new treatment were also created, thus allowing a complete look at how a new biologic treatment changes the symptom profile and interactions in RA patients. Table 2.1 below shows where each objective and aim are investigated in this thesis, and the corresponding study name and population associated with it.

Table 2.1: Objectives and Chapter Number

Aim and Objective Number	Thesis Chapter	Study Name	Study Design	Population
Aim 1 Objective 1	Chapter 3	Scoping Review	Scoping Review	Musculoskeletal Disorders
Aim 1 Objective 2	Chapter 8	APPro	EMA Study with wearables	RA
Aim 1 Objective 3	Chapter 8	APPro	EMA Study with wearables	RA
Aim 2 Objective 1	Chapter 6	IA-COVID	EMA Study	IA
Aim 2 Objective 2	Chapter 7	IA-COVID	EMA Study	IA
Aim 2 Objective 3	Chapter 7	IA-COVID	EMA Study	IA
Aim 2 Objective 4	Chapter 8	APPro	EMA Study with wearables	RA
Aim 3 Objective 1	Chapter 5	TITRATE	Secondary Data Analysis	RA
Aim 3 Objective 2	Chapter 6	IA-COVID	EMA Study	IA
Aim 3 Objective 3	Chapter 8	APPro	EMA Study with wearables	RA

3. Scoping Review

3.1 Overview of Scoping Review

This chapter directly addresses the first objective of the first aim and examines current literature in the field of longitudinal data analysis in musculoskeletal disorders. This chapter also shows the gap in literature in this field and helps to shape the design of both the IA-COVID and APPro studies in the following chapters. This scoping review was published in the *Rheumatology* Journal in 2021 (Tung et al., 2021) and the chapter is slightly adapted from the published manuscript. This means that there are some overlaps in information in the Introduction section. This review was designed to be a scoping review instead of a systematic review because the purpose of this chapter is to investigate current literature and to identify a gap in research that can help shape the future chapters (Munn et al., 2018). As the aim was to identify the range of previous studies published, the number of studies within certain categories was considered (e.g, monitoring method, symptoms assessed). This means that it is not important to perform a meta-analysis because there is no requirement for the review to answer a question or to provide evidence.

3.2 Introduction

Longitudinal studies of patient reported outcomes in musculoskeletal disorder research typically capture outcomes for a limited number of time points, often months or years apart (Bildt et al., 2001; Collins et al., 2010; Kennedy et al., 2005). They usually assess change from baseline, where baseline may be diagnosis, or treatment or research study initiation, and the level of a variable at baseline is typically used as a predictor of some longer-term outcome. However, for most outcome measures, such as pain, there is a dynamic component, which is not captured using this approach. The natural day-to-day fluctuations of symptoms(Stefan Schneider et al., 2012), that are a major aspect of living with a musculoskeletal condition, are treated as noise, and potentially important insights missed.

It is increasingly recognised that while understanding disorder trajectory is important, because symptoms behave dynamically, there will be missing insights if trajectory is the sole focus of a study (Hamaker et al., 2018). Contemporary longitudinal studies and clinical trials fail to collect data frequently enough to reveal diurnal variations and fluctuations of symptoms over-time. The majority of studies include further follow-ups only if specific events happen within the study, such as in Maradit-Kremers's study (Maradit-Kremers et al., 2005) where the event is death or migration, or follow-up only after months or years have elapsed (Ogdie et al., 2014; van Steenbergen et al., 2015). It has traditionally been difficult to collect more intensive measurements because of the burden of data collection, for example in a sample of 50 individuals, daily measurements for a month would mean 1500 separate datapoints, and 6 assessments per day would mean 9000 datapoints. However, technology is making high frequency assessments more feasible to collect (Bromberg et al., 2016; Fischer et al., 2016; Hacker & Ferrans, 2007).

High-frequency follow-up studies, often referred to as ecological momentary assessment (EMA), experience sampling, or ambulatory assessments, provide fast 'in-the-moment' assessment, reducing recall and desirability bias (Saul Shiffman et al., 2008). Furthermore, since EMA involves repeated sampling in participants' natural environments, ecological validity is maximised. This allows researchers to see how behaviours change in real life contexts (Saul Shiffman et al., 2008), and enhances establishment of causal relations between variables (Welsing et al., 2004).

EMA studies in other areas have demonstrated how examining within-person variability in symptoms can provide novel insights. For example, in general population samples, people with fluctuating mental health have been shown to have a greater mortality risk than those with a low stable mental health, even though less time is spent with low mental health in the fluctuating group (Boehm et al., 2015). This demonstrates the potential for novel insights using high-frequency assessments in musculoskeletal disorders, where symptoms such as pain and fatigue may vary dramatically even over short time periods.

Currently there has been no review specifically focused on studies with high-frequency assessment of psychological and physical symptoms using EMA approaches in musculoskeletal conditions. Therefore, our aims are: i) identify and describe the nature of studies in the field musculoskeletal disorder using high-frequency assessments using EMA

approaches, and ii) examine whether this research has considered whether symptom variability independently predicts worse disease outcomes, where symptom variability is defined as the change in the severity of symptoms over a short-period of time, which could be quantified using methods such as the within-person standard deviation, coefficient of variation, or difference between the persons highest and lowest level of repeated assessments of a symptom (e.g. pain) over a day or week..

3.3 Methods

This review was conducted following the method for scoping reviews outlined by Liberati (Liberati et al., 2009) and the PRISMA reporting statement (Moher et al., 2009). Determining the coverage of high frequency follow-ups in the musculoskeletal disorder field and identifying a gap in available literature was the priority here, therefore a scoping review was carried out instead of a full systematic review (Munn et al., 2018), thus some components differ from the PRISMA statement. Meta-analysis was not undertaken, and the scope of the narrative synthesis is broad and focused on describing the topics addressed, rather than summarizing findings of the studies.

OVID was used to conduct the search in health journals, using the Embase, Medline, and PsycInfo databases. The Institute of Electrical and Electronic Engineers (IEEE) database was also searched using the IEEE Xplore search engine to ensure that studies published in computer science would be included in this review. These searches were initially carried out in 2018, however an updated search was also completed in November 2020 before the publishing of this paper.

The inclusion and exclusion criteria can be seen in Table 3.1 below.

Table 3.1: Inclusion and Exclusion Criteria

Inclusion Criteria	**Exclusion Criteria**
1) Patients must have a musculoskeletal condition such as as osteoarthritis, fibromyalgia, rheumatoid arthritis, low back pain, or juvenile idiopathic arthritis 2) the design must be prospective observational 3) follow-up must be intensive and focus on at least one physical or psychological symptom. We defined 'intensive' as at least 10 assessments no less frequently than weekly*	1) Studies not involving human participants 2) Study focused on the genetic and biological side (on a cellular level) without looking at any physical or psychological symptoms

The following search strategy was used on OVID:

1. These musculoskeletal disorders terms combined with OR.
   "Arthritis" "Tendonitis" "Muscle Strain" "Tendon Strain" "Spondylitis" "Rheumatoid Arthritis" "Connective Tissue Disease" "Fibromyalgia" "Chronic Widespread Pain" "Low Back Pain" "Joint Pain".

2. These assessing symptoms terms combined with OR.
   "Pain" "Stiffness" "Fatigue" "Tenderness" "Mobility" "disability" "function" "tiredness" "swelling" "depression" "anxiety" "mental disorder" "disease activity" "inflammation" "distress" "adherence" "compliance".

3. These intensive follow up terms combined with OR
   "Diary Research" "Daily Diary" "Event-Contingent Recording" "Intensive Follow-up" "Passive Telemetric Monitoring" "Naturalistic Observation Sampling" "n-of-one" "ecological momentary assessment" "remote measurement" "remote monitoring" "home based assessments" "ambulatory assessment"

4. 1 AND 2 AND 3.

Additional musculoskeletal disorders were included in the search terms, instead of just arthritis related terms, because there were concerns that there were insufficient literature if only rheumatoid arthritis and inflammatory arthritis studies were included in the search. There are similarities between these musculoskeletal disorders in shared symptoms (i.e., pain is central to all) and fluctuations in symptoms, and thus the information derived from these studies will be helpful in identifying the gap in literature. Furthermore, this allowed for the identification of evidence in areas outside of inflammatory arthritis to identify evidence gaps in the inflammatory arthritis evidence base. The terms for assessing symptoms were chosen because they are the most common symptoms and terms that are associated with musculoskeletal disorders. There are many other possible symptoms but the terms that were selected should cover all aspects of symptoms.

A final total of 1504 records were returned after deduplication was performed. Screening the title and/or abstracts to determine if the study included the requirements of symptom assessments, intensive monitoring (defined as at least 10 assessments and no less than once per week), and appropriate musculoskeletal disorders led to a shortlist of 28 papers that required full text inspection. The final sample of papers included in this review involved 21 reports of 33 different cohorts, which can be seen in the PRISMA flow diagram in Figure 3.1. There are additional cohorts compared to studies because some studies used multiple cohorts in the analysis.

For searches on the IEEE database, the search strategy was modified to simply identify all available studies focused on musculoskeletal disorder. The search terms were: “Arthritis” OR “Tendonitis” OR "Muscle Strain" OR "Tendon Strain" OR Spondylitis OR "Rheumatoid Arthritis" OR "Connective Tissue Disease" OR Fibromyalgia OR "Chronic Widespread Pain" OR "Low Back Pain" OR "Joint Pain". This resulted in 759 papers, however, none of the papers found met our definition of intensive monitoring of symptom assessment (Figure 3.1).

Due to heterogeneity of the research questions addressed and study analytic approaches, no meta-analysis was conducted.

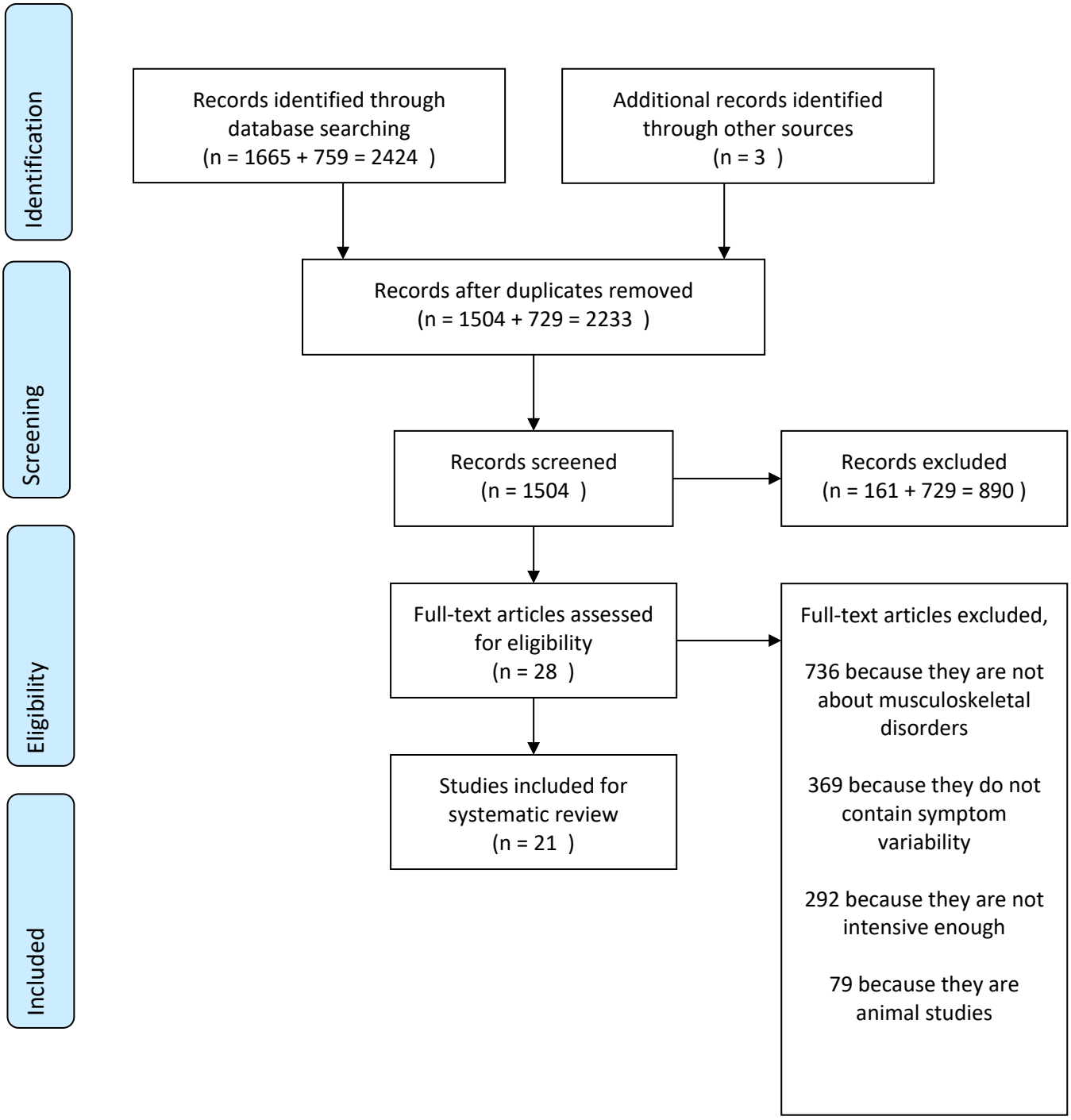


Figure 3.1: PRISMA Flow Chart

3.4 Results

The conditions, symptoms, monitoring methods, number of follow-ups completed, and a brief summary of each of the 21 included studies are shown in Figure 3.2.

Paper Title	Condition	Symptoms	No. of patients	Monitoring technique	Times collected	Brief Summary
Inflammatory & Osteo Arthritis						
Graham-Engeland et al. (2016) (Graham-Engeland et al., 2016)	RA	Depression/Mood/ Pain	31	EMA, palmtop computer with custom software	5 times a day for 7 days	31 patients with RA recorded pain and mood using EMA for 5 times a day for 7 days. It is found that greater momentary positive mood is associated with lower momentary pain, while greater depressive symptoms predicts more pain.
Hamilton, Catley, & Karlson (2007) (Hamilton et al., 2007)	RA/FMS	Sleep/Stress/Pain	49	EMA, has a watch to remind them to fill in 2 small booklets	7 times a day for 2 days	49 patient with RA or fibromyalgia were recruited to record levels of pain, occurrence of stressful event, sleep quality, as well as positive and negative affect 7 times a day for 2 days. It is found that sleep disruption does not influence affect, but plays a role in moderating the association between stress and affect, and pain and affect.
Keefe et al. (2001) (Keefe et al., 2001)	RA	Spiritual and religious coping/pain	35	Structured daily diary	1 time a day for 30 days	35 RA patients recorded structured daily diaries for 30 days looking at spiritual experiences, spiritual pain coping, pain and mood. Participants that recorded higher frequent daily spiritual experiences also had higher levels of mood, while lower pain is associated with those that has higher spiritual pain coping efficacy.
Stone et al. (1997) (Stone et al., 1997)	RA	Pain/Fatigue	35	EMA, alerted by wristwatch and fill in part of a small booklet	7 times a day for 7 days	This study included 35 patients with RA and utilized EMA (7 times a day for 7 days) to look at their levels of pain and fatigue. It was found that there were large individual variations in both, and low sleep quality is associated with both.
Cruise et al. (1996) (Cruise et al., 1996)	RA	Pain/Mood	35	EMA, alerted by watch and fill in questionnaire in booklet	7 times a day for 7 days	This study uses EMA on 35 RA patients for 7 times a day for 7 days to look at levels of pain and mood. Mood is separated into different aspects of positive and negative mood, and it is found that pain has a strong negative association with Alert and Energy, and a strong positive association with Fatigue
Smith and Zautra (2009) (Smith & Zautra, 2008a)	RA/OA	Anxiety/Depression	82/88	Interviewed by phone	1 time a week for 11 weeks	82 patients with RA and 88 patients with osteoarthritis are recruited to this study where they track depression, anxiety, pain, stress, and affect weekly for 11 weeks. It is found that anxiety and depression are associated with pain, with a much bigger association with anxiety. Depression also interacts with stress to predict current pain.
Zautra, Johnson, & Davis (2008) (Zautra et al., 2005)	RA/OA	Positive affect/pain	124	Interviewed by phone	1 time a week for 10/12 weeks	124 female patients with osteoarthritis or fibromyalgia recorded pain, stress and affect for 10-12 weeks through an interview. Higher affect scores weekly results in lower weekly negative affect scores. Increased negative affect scores are also associated with greater levels of pain in the subsequent week.
Robbins et al. (2012) (Robbins et al., 2011)	RA	Sighing/Depression	13	Using an Electronically Activated Recorder, an observational ambulatory assessment tool	50 seconds every 18 minutes for 2 weekends (fri-sun)	13 RA patients used an electronic device in their ear for 2 weekends (Friday-Sunday) one month apart to track the number of times they sighed. Depression and pain were measured as well during those assessment periods. It was found that sighing is associated to depression, but has no correlation with pain.
Bromberg et al. (2016) (Bromberg et al., 2016)	Arthritis	Sleep/Pain/Function	59	EMA, smartphone based diary	3 times a day for 1 month	This study included 59 children with Juvenile Idiopathic Arthritis (JIA) and recorded sleep quality daily for a month, and pain and functioning 3 times a day for a month. It is found that pain is a mediating factor in the association between function and sleep quality, which affirms their hypothesis.
Bromberg et al. (2014) (Bromberg et al., 2014)	JIA	Pain/disease symptoms	59	E-diary	3 times a day for 1 month	Bromberg et al looked at 59 children with JIA and collected ratings of pain, stiffness, fatigue and function 3 times a day for 1 month. It was found that no children were entirely pain-free, and high pain and high stiffness is associated with high functional limitations.
Bromberg, Gil, & Schanberg (2013) (Bromberg et al., 2012)	JPA	Sleep/Mood/Pain	51	Daily Diary	1 time a day for 2 months	51 children with polyarticular arthritis were recruited to track sleep quality, mood and pain over 2 months. It was concluded that poorer sleep quality is associated to higher next day pain ratings, however this relationship is weakened when the participant has high positive mood. Daily pain does not predict that day's sleep quality.
Fibromyalgia						

Doerr et al. (2017) (Doerr et al., 2017)	FMS	Stress/Fatigue	26	Using a pre-programmed iPod Touch.	6 times a day for 14 days	26 female fibromyalgia patients recorded general, mental and physical fatigue levels 6 times a day for 14 days, and stress were measured by salivary cortisol and alpha-amylase. Lower increases in cortisol after awakening predicted higher average general and physical fatigue levels for the day. Physical fatigue is also associated with concurrent cortisol levels. Alpha-amylase showed no associations with fatigue.
Fischer et al. (2016) (Fischer et al., 2016)	FMS	Stress/Pain	32	Using an iPod Touch	6 times a day for 14 days	32 female fibromyalgia patients participated in this study by providing diary entries on stress and pain levels 6 times a day for 14 days. Cortisol and alpha-amylase were analysed for those time points as well. Higher stress level is associated with a higher pain level for the subsequent diary entry, however cortisol and alpha-amylase plays no role in the association between stress and pain. Cortisol levels are however found to be independently associated with concurrent pain levels.
Linnemann et al. (2015) (Linnemann et al., 2015)	FMS	Pain/Stress	30	Using an iPod Touch	5 times a day for 14 days	30 females with fibromyalgia recorded pain intensity, perceived control over pain, stress level and music listening behavior 5 times a day for 14 days. Saliva samples were taken during each measurement too for cortisol and alpha amylase analysis. It is found that increased music learning helps with perceived control over pain, especially when it was listened for purpose of "relaxation". Stress plays no role in mediation between this association.
Hamilton et al. (2008) (Hamilton et al., 2008)	FMS	Sleep/Negative event recovery	89	Using paper and pencil diaries and hand held computers	3 times a day for 30 days	This paper uses daily diaries and EMA to look at 89 women with Fibromyalgia and how sleep influences affect and negative event reactivity. It is found that sleep quality is related to affect and fatigue, and low sleep quality will affect patients from recovering from negative events the next day.
Okifuji et al. (2011) (Okifuji et al., 2011)	FMS	Pain/Fatigue/Emotional Distress	81	Custom programmed palmtop computer	3 times a day for 30 days	81 females with fibromyalgia recorded pain, fatigue, and emotional distress for 3 times a day for 30 days. Controlling for previous fatigue ratings, previous pain and emotional distress scores are associated with subsequent fatigue score. It is suggested that emotional distress and pain increases fatigue, only fatigue increases pain and only pain increases emotional distress.
Tennen, Affleck, & Zautra (2006) (Tennen et al., 2006)	FMS	Depression/Pain	71	Daily Diary	3 times a day for 30 days	71 female fibromyalgia patients (30 previously depressed) recorded pain and mood for 3 times a day for 30 days. These two groups differed in how they cope with increased pain and how they appraised their pain coping efficacy.
Garcia-Palacios et al. (2014) (Garcia-Palacios et al., 2014)	FMS	Electronic Diary(smartphone)/ Pain	47	Comparing paper diary and smartphone diary (smartphone was superior)	3 times a day for 2 weeks	47 patients were assigned either one group that uses paper diary first, then smartphone diary, or the other group that does it opposite to track pain levels for one week with each method. It is found from both groups that the smartphone diary gives more accurate and complete ratings, and well accepted by patients, even those with low familiarity with technology.
Chronic Low Back Pain						
Burns et al. (2015) (Burns et al., 2015)	Low back pain	Anger/pain/function	105	Electronic Daily Diaries	5 times a day for 14 days	105 married couples (with one spouse having low back pain) is recruited to this study where they recorded their behavioral anger expression and inhibition, and pain related factors for 5 times a day for 14 days. The healthy spouse completed items on their observation of patient pain-related factors. It is found that increased anger is associated with increase in pain and pain interference, and also matches the observation of pain by spouse. Lower function is also related to chronic pain and anger arousal.
Bruehl et al. (2012) (Bruehl et al., 2012)	Low back pain	Pain/Anger	48/36	EMA, electronic diary	4 times a day for 7 days	This study looks at 48 patients with low back pain (LBP) and 36 healthy controls where electronic diary ratings of pain and behavioral anger expression is recorded 4 times a day for 7 days. LBP group shows higher levels of daily anger expressions, and a greater association between high pain intensity and high levels of anger expression.

Jamison et al. (2001) (Jamison et al., 2001)	Chronic Back Pain	Electronic Diary/Pain	36	Electronic Diary and paper diary (electronic diary seems superior)	1 time a day for 1 year	36 patients with LBP were recruited to this study for a year to monitor their pain. 20 used palmtop computers and paper diaries, while 16 used only paper diaries. Ratings of pain intensity were accurate for both methodology, but patients using both methods prefer palmtop computers over paper diaries and showed greater compliance and satisfaction at the end of the study.

Figure 3.2: Figure of conditions, symptoms, monitoring methods, number of follow-ups completed, and a brief summary of all 21 papers included.

Of the 21 papers included, 11 focus on arthritis, 7 on fibromyalgia, and 3 on chronic low back pain samples. There was a mean of 54 patients (standard deviation 27.7) and a mean of 3588 observations (SD 3271) per study. Five studies assessed symptoms once daily or less, and 16 studies assessed symptoms more than once per day. The most common symptoms examined were pain (n=16), stress (n=5), depression (n=4), and fatigue (n=3).

3.4.1 Monitoring Methods

The main data collection methods were daily diaries, phone interviews, and using portable electronic devices. Nine (43%) studies involved using technology for data collection, such as customized iPods or palmtop computers, and most of the data input required were numbers or short phrases. In a methodological study involving 36 patients with low back pain, Jamison (Jamison et al., 2001) found that portable electronic devices were preferred over paper diaries.

Studies involving wearable technology were typically shorter (about one to two weeks), but with higher frequency of five to seven times a day. Garcia-Palacios (Garcia-Palacios et al., 2014) studied 47 patients with Fibromyalgia and compared the use of paper diaries and smartphones. It was found that even among those unfamiliar with the technology, smartphone diaries are well-accepted and give more accurate and complete data. One study (Robbins et al., 2011) of 13 RA patients involved the use of a novel wearable, an electronically activated recorder that participants put into their ear to automatically register the number of sighs that the participants made. The number of sighs was found to be associated with depressive symptoms and may serve as an objective marker of mood. This demonstrates the use of wearable technology to automatically collect data, which may reduce assessment burden for those with severe symptoms and others who may have difficulties self-monitoring.

3.4.2 Symptoms assessed

Sixteen studies (76%) investigated interactions between pain and other symptoms, making pain the most highly researched symptom. The five studies not considering pain looked at depression, anxiety, stress, fatigue, and sleep. Pain was found to be independently linked to

psychological symptoms including depression (Graham-Engeland et al., 2016), mood (Cruise et al., 1996), and fatigue (Stone et al., 1997). In a study of 31 patients with RA, Graham-Engeland (Graham-Engeland et al., 2016) found higher levels of pain were associated with more severe depressive symptoms, and lower pain levels were associated with greater positive mood. An earlier study with 35 RA patients found that higher pain variability is associated with worse sleep quality and higher levels of fatigue for the next day (Stone et al., 1997). Finally, a study of 35 RA patients (Cruise et al., 1996) found a strong negative association between pain and two components of positive mood (alertness and energy), and a strong positive association between pain and one component of negative mood (fatigue). Pain was also found to be related to other physical symptoms. In two studies, based on the same sample of 59 children with Juvenile Idiopathic Arthritis (JIA), pain was found to be associated with higher levels of functional limitation (Bromberg et al., 2014), and to mediate the association between function and sleep quality (Bromberg et al., 2016).

It is also important to note that out of the 21 studies, none looked at more than three symptoms and the associations. Only 5 out of 21 (24%) looked at three symptoms, and the rest only compared associations between two symptoms. This is an important observation to make because musculoskeletal disorder patients suffer from a multitude of symptoms and comorbidities, and most of these symptoms have an association with each other. Looking at only two or three symptoms in a vacuum will mean that possible confounders of the symptoms are not included, and possible interactions with other symptoms will be missing as well.

3.4.3 Temporal associations

Table 3.2 below shows whether symptom severity is a predictor of outcome in the short or long term (i.e. subsequent days or weeks versus months later), and whether studies investigated symptom variability as an independent predictor of outcome. Out of the 21 studies, 7 studies only considered associations cross-sectionally, while 14 examined whether symptom severity was a predictor of outcomes in the short-term.

Table 3.2: Table of papers included in Chapter 3 and their temporal associations

Author	Predictor of outcome in short term (day/week)	Predictor of outcome in long term (month/year)	Symptoms investigated	Was symptom variability investigated as an independent predictor of outcome?
Graham-Engeland et al. (2016)	Yes	No	Depression/Mood/ Pain	No
Hamilton, Catley, & Karlson (2007)	Yes	No	Sleep/Stress/Pain	No
Keefe et al. (2001)	Yes	No	Religious coping/ Pain	No
Stone et al. (1997)	Yes	No	Pain/Fatigue	Yes
Cruise et al. (1996)	No	No	Pain/Mood	No
Zautra, Johnson, & Davis (2008)	Yes	No	Positive affect/Pain	No
Bromberg et al. (2016)	Yes	No	Sleep/Pain/Function	No
Bromberg et al. (2014)	No	No	Pain/Disease symptoms	No
Bromberg, Gil, & Schanberg (2013)	Yes	No	Sleep/Mood/Pain	No
Smith and Zautra (2009)	Yes	No	Anxiety/Depression	No
Robbins et al. (2012)	No	No	Sighing/Depression	No
Fischer et al. (2016)	Yes	No	Stress/Pain	No
Okifuji et al. (2011).	Yes	No	Pain/Fatigue/ Emotional Distress	No
Tennen, Affleck, & Zautra (2006)	Yes	No	Depression/Pain	No
Garcia-Palacios et al. (2014)	No	No	Electronic Diary/Pain	No
Burns et al. (2015)	No	No	Anger/Pain/Function	No
Bruehl et al. (2012)	Yes	No	Pain/Anger	No
Jamison et al. (2001)	No	No	Electronic Diary/Pain	No
Doerr et al. (2017)	Yes	No	Stress/Fatigue	No
Linnemann et al. (2015)	No	No	Pain/Stress	No
Hamilton et al. (2008)	Yes	No	Sleep/Negative Event Recovery	No

No studies examined whether symptom severity predicts outcome in the longer-term (e.g. weeks or months later). While examining whether the predictive ability of one symptom, such as stress, is associated with another, such as pain on the subsequent day, is useful, examining longer-term outcomes, in particular specific events, such as job loss, surgery and mortality are needed.

Only one study in Table 3.2 considered symptom variability, and none specifically considered symptom variability as a predictor of outcome. In that study (Stone et al., 1997), 35 RA patients recorded symptoms seven times a day for seven days, and it was found that higher average muscle pain, joint pain, swelling on awakening, and poorer sleep quality were observed to be related to greater variability in pain and fatigue over the same period.

3.5 Discussion

Musculoskeletal disorder symptoms are dynamic (Hamaker et al., 2018). However, this review has identified relatively few studies using EMA methods to investigate these dynamic processes. Furthermore, there is a dearth of studies examining how within-individual variability across symptoms is linked, and how this might influence outcomes in the longer-term outcomes. Pain was the most commonly researched symptom, which is unsurprising given it is a central feature of musculoskeletal conditions. This review demonstrated the advantages and disadvantages of each type of monitoring methods (daily diary providing lowest frequency each day and handheld technology providing highest frequency). Most importantly, the results from this review highlight a lack of understanding, particularly of symptom and outcome associations, and the lack of knowledge around predictive ability of symptom variability in addition to symptom severity. Pain and fatigue have a positive correlation with other major symptoms; therefore it would be useful to clarify whether fluctuations in these symptoms have an impact as well. No research investigated the interactions of more than three symptoms.

There were methodological changes as technology progressed: studies from mid 1990s and early 2000s used paper booklets and diaries for participants to fill in data, while recent years favor the use of electronic data capture (e.g. smartphones). As method of data collection changes, so did the frequency of data collection, with electronic data capture allowing participants to completing multiple assessments each day at a particular time with

more ease. It was surprising that no studies combined EMA with wearable technologies to objectively assess physical activity. The increasing availability of low cost wearable technology should lead to further and more in-depth research in this area. A key issue with research into symptoms and interactions within conditions such as RA and FMS is the need for accurate and easy monitoring of symptoms. In order to see how a symptom fluctuates within a day, or the trend that a symptom takes over a long time period, a large amount of data is needed. The methodology applied then, cannot be too complex due to constraints on time and resources, while the accuracy of the data needs to be maintained. Symptoms such as mood, pain, fatigue, and stress fluctuate greatly throughout a day, thus research that records only once a day could result in an inaccurate picture of variability. Rating symptoms only at one point per day has been shown to be prone to recall bias (McColl, 2004).

One method not employed in the sample of papers reviewed here, the day reconstruction method (Kahneman et al., 2004), has been demonstrated to have lower susceptibility to retrospective reporting biases, and may be useful in musculoskeletal populations. The day reconstruction method first involves participants completing a structured diary regarding the series of episodes that happened the previous day. Then, participants use this diary to answer questions regarding what happened and what they felt during those episodes which will then be analyzed by researchers. In comparison to the EMA method, there is far less burden on the participants because it only requires one assessment per day. However, it will be less accurate because assessment only happens the day after and thus will be difficult to recall symptom severity at a particular moment.

Daily diary methods are often used when the monitoring period lasts for at least a month and with at least one recording a day, while electronic methods are typically used for shorter periods but with multiple recordings per day. The studies in this review illustrate that most of the EMA studies are more recent, suggesting a shift in methodology in order to assess intra-individual variability, and perhaps also the technological advances that allow EMA studies to be carried out readily. One of the studies identified in the review compared paper and smartphone diaries assessing at pain (16) and another compared reports on pain using paper diary and e-diary on a palmtop computer (15). These both showed that electronic diaries have a distinct advantage in providing convenience to participants and more complete data sets. With the advance of technology and abundance of smartphone

use (85% of UK citizens use a smartphone (Henshaw, 2018)), electronic methods that can both alert the patient to the time of recording and provide a platform for them to input their data are surely the way forward in this area of research.

The use of EMA in high frequency follow-up studies is common, which means that data can be collected at home without researcher input and thus non-adherence may be reduced. However, constant reminders for participants to check their symptom severity might cause increased health anxiety issues for these participants as they are constantly reminded of the suffering that they are experiencing. The relative ease of collecting these data also means that there is a risk that clinicians and researchers assign too heavy a measurement burden for their patients and participants. Researchers need to be mindful of the burden expected of their participants, and involve patients in the design of their studies, and thus pilot testing the procedures and intensity of data collection are appropriate.

High frequency follow-up provides sufficient data for researchers to investigate the predictive ability of symptom variability. The lack of this in current research highlights the lack of focus on the potential importance of symptom variability and the repercussions of this for other symptoms and aspects of disease activity. The predictive ability of symptom variability has been utilized in other fields of research, such as in lung diseases where it was found that high symptom variability is associated with lower lung function and more severe respiratory symptoms (Kim et al., 2019). Variability of heart failure symptoms was found to be a predictor of higher risk for worse event-free survival (Moser et al., 2011). In cases of musculoskeletal disorders, where symptoms fluctuate wildly (Flurey et al., 2014). it is important to know whether the excessing symptom variability or unpredictable flares affect patients' symptom severity. For example, patients could be more affected by high pain variability than by a consistently high pain level, because of the uncertainty of when pain flare-ups will happen and interfere with daily life. Knowing the importance of symptom variability will help clinicians decide which symptom to prioritize treatment in patients with high disease activity. It is also clear that in current literature, no study has managed to look at more than three symptoms even though musculoskeletal disorder patients suffer from a huge number of physical and psychological symptoms. This means that when designing future study, it is important to include more symptoms that can cover different aspects of a patients' symptomology in order to have a more accurate picture of how patients are affected.

High frequency symptom assessment could prove to be more than just a research tool, potentially providing provide clinicians with useful insights into patients' symptom variations. An understanding of the effects of symptom variability may aid clinicians in predicting future symptom flares, which will be important in helping manage these and reduce patients' suffering. Clinicians can also use electronic, high frequency measurement to assess the level of intervention required, for example moving some consultations into a digital pathway when the symptom severity are particularly low. The potential knowledge of when during a day patients suffer symptom flares also means appointment scheduling can be improved and made more acceptable to patients.

The fluctuant nature of RA symptoms means that there will be high variability in symptom severity, which makes this kind of analysis even more important. This scoping review has illustrated that there is a lack of understanding around symptom variability in RA, and also a lack of data around which symptoms interact with each other. Some studies that do not fit the inclusion criteria for this review highlight the acceptability and feasibility of remotely collecting longitudinal data from RA patients, such as the Remote Monitoring of Rheumatoid Arthritis (REMORA) study, which uses smartphone apps to remotely collect longitudinal data from RA patients (Lynn et al., 2020).

Alongside the need for more research in high frequency follow up with numerous symptoms, there is a need to consider the acceptability of intensive measurements like several other studies in this field such as REMORA and Remote Assessment of Disease and Relapse – Central Nervous System (RADAR-CNS) (Matcham et al., 2019). Coupled with numerous symptoms, it may be a burden for patients to complete a long list of questions multiple times a day. High symptom variability will also mean that patients will have to input data when highly symptomatic, and thus could result in high drop-out rates. This is because higher pain intensity is a potential predictor for higher drop out rate (Carosella et al., 1994), and thus a sudden flare in pain might result in participants not able to complete the assessment.

Patients with musculoskeletal disorders generally have joint pain and stiffness that will prevent them using the electronic devices to complete the assessments. This can be addressed by keeping patient questionnaires as easy to complete as possible with Likert or numerical rating scales, and also on an easy to access app or website that will not take too much time. High frequency data input may also remind patients of their health care

problems, thus increasing health anxiety which could prove to be problematic. Mental health support must thus be provided for all patients. Even though electronic methods provide ease and accuracy in collecting data, it is important to consider the possible drawbacks that comes with these methods. The use of technology potentially poses a challenge to those that do not possess adequate technology literacy. This means that some patients who are willing to participate in these studies are not able to because of the inability to use the data collection methodology provided. This exclusion could lead to systematic bias where certain groups of people are not able to participate and thus not able to provide a complete picture of the population. However, with increasing access to technological devices, the improvement of electronic measurement methodology, and the need to collect intensive data, the use of these electronic data collection techniques is inevitably going to increase. It is important that future studies, considered issue of digital exclusion due to low digital health literacy or other factors that may drive health inequalities.

Another issue relates to the potential negative impact of symptom monitoring on symptom experience. For example, a randomized study of 58 patients with low back pain showed that those who were assigned to fill out daily pain diaries had a significantly lower rate of recovery than those assigned to not complete daily ratings (Ferrari, 2015). This exacerbation of symptoms is a concern as well for electronic data capture, which means that any future study based on the design of EMA needs to consider the possible negative effects that it has on the participants.

Analysis may also be challenging, including the analysis of multiple symptoms and the respective variability, thus using novel analysis techniques such as network analysis may be a solution. This is because network analysis can consider numerous symptoms, including variability and associations between each symptom simultaneously (Borsboom, 2017). Connections between groups of psychological symptoms (depression, mood), physical symptoms (pain, fatigue) and inflammatory markers (ESR/CRP) should be looked at to see if there is a particular symptom that links the different distinct groups together. This symptom is known as a ‘bridging’ symptom may be important for clinical use because the elimination of a bridging symptom in a network could mean collapse of the network (Goekoop & Goekoop, 2014). This means that targeting the symptom that links distinct groups together

could cause the connection between those groups to be diminished, and thus will have the potential to alleviate the symptom severity for the other group (Lee et al., 2009).

To summarise, this scoping review identified 21 studies in the field of musculoskeletal disorders that utilise high frequency follow up. Out of these, only 1 looked at whether symptom variability is an independent predictor for other outcomes, and none of these studies looked at more than 3 symptoms together. Symptom variability is especially important in disorders that have abilities that fluctuate throughout a day, and thus is a noticeable gap in available research that should be researched. New analysis techniques, and improvement in technology will make both the collection of data, and analysis of data possible. Alongside this, higher levels of pain were found to be associated with lower adherence to treatment (Brown et al., 2002), which is problematic as correct treatment for RA improves outcomes (Gibofsky & Yazici, 2010). However, bit is difficult to effectively and accurately measure pain because it is accompanied by other sensations. (Jakobsson & Hallberg, 2002) This means that making pain the focus of research could result in data not reflecting what participants actually wanted to express, which may adversely affect the conclusions drawn by putting additional emphasis on pain when it is not as important. Methodology and intensity of follow up in research has progressed over time, with EMA using electronic methods a popular study design which alleviates a lot of difficulty in getting an intensive data set. With the increase in technology and popularity in technological products, and also new analytical methods like network science available, there is a wealth of opportunities for research and clinical practice.

4. Methodology

4.1 Introduction and thesis design

This thesis includes four separate studies to address the aims that were set out in Chapter 2. The first is TITRATE-US, which is a cross-sectional study that recruit patients in clinics and provides detailed clinical phenotyping. The next study is the IMPARTS study, where data from routine care, and patient reported outcome measures (PROM) are combined with other information from the electronic healthcare record in the hospitals. These two studies are combined in the same chapter in Chapter 5. The third study is the IA-COVID study which is a 10-day intensive longitudinal study that recruited patients online. There were two waves of assessments, where the first was during a period of no governmental restrictions during the pandemic, and the second during a lockdown where clinical services were severely limited due to the pandemic. This study will make up Chapters 6 and 7, with Chapter 6 focusing on the first period of data and Chapter 7 focusing on the difference between waves of assessments. The last study is the APPRo study, which is a 30-day intensive longitudinal study that recruit patients via clinics at the time of initiating biologic therapy. This study will make up the final empirical chapter in Chapter 8. Chapter 5 utilises secondary data analysis using the TITRATE-US and IMPARTS datasets that were collected in the hospitals. The IA-COVID study for Chapters 6 and 7 is a primary research study that is a sub-study of a larger cross-sectional study. The researcher designed the sub-study personally, recruited participants from the larger study, and managed the data collection procedure for this study. It is useful to note that this study was set up due to the delayed start of the APPro study. The APPro study for Chapter 8 is wholly designed and carried out by the researcher.

As there are four different studies, the specific details of the methodologies of these studies will be described in each of the chapters that first includes those studies. This meant that the IMPARTS and TITRATE studies will be discussed in Chapter 5, IA-COVID study in Chapter 6 and 7, and APPro study in Chapter 8. This chapter will instead focus on the methods of assessment of clinical and psychological factors in rheumatological studies, and to provide additional information about the specific analytical methods used in this thesis.

This will include analysis of intensive longitudinal data using regression techniques, and also network analysis.

4.2 Ecological Momentary Assessment of symptoms

4.2.1 Introduction

IA-COVID and APPro studies both involve the collection of intensive longitudinal data, where assessments are gathered at least once a day throughout the study period. As mentioned, RA symptoms can fluctuate widely throughout a day, and these fluctuations may potentially impact on physical, mental, and social health of patients (Sanderson & Kirwan, 2009) and thus intensive longitudinal data is needed to investigate this. High-frequency data collection is referred to using numerous terms, one of the most common that will be used here is ecological momentary assessment (EMA). Other terms used are experience sampling, daily diaries, and ambulatory (psychophysiological) assessment. Although these describe specific types of studies with intensive longitudinal data collection, there are overlaps and the term EMA is used here. This is because self-reported outcomes are not limited to diaries or ambulatory methods and experience sampling is focused on the representativeness of experiences, while EMA is focused on the dynamic changes of behaviour.

There are multiple ways to develop an EMA study, as long as the underlying principles are met. These main features, as outlined by (Stone & Shiffman, 1994) are:

1) Data needs to be collected in a real-world environment, where the participants are going on with daily lives. This will allow the data to be generalisable to the participants' real lives and explains the ecological aspect of EMA.
2) The data collected needs to concern participants' current experience and symptoms, instead of a different time point. This is to ensure that there are no recall bias and to provide real-time data and explains the momentary aspect.
3) There needs to be multiple repeated sampling of the participants to allow for generalisable data across time and across environments.

EMA data is applicable in the field of RA because researchers are interested in how the experiences and symptoms of RA symptoms change throughout the day, and during their

day-to-day lives. Clinicians and researchers often use retrospective self-reports during clinical visits that require patients to describe the symptom levels and behaviours during a previous period of time, typically a week or more ago (S. Shiffman et al., 2008). This means that researchers potentially not only miss out on seeing the dynamic changes of behaviours and symptoms, but also restricts the ability to generalise findings to patients' day to day lives and invites the possibility of recall bias. It has been shown that when participants are asked quantitative information regarding the past, there are limits on the ability to accurately recall information which means that participants have to combine both inference and partial memory to give an answer (Bradburn et al., 1987). This means that different types of recall bias errors could happen, like omission, telescoping, and confusion (Öztaş Ayhan & Işiksal, 2005). Omission refers to forgotten events. Telescoping occurs when there are inaccurate perceptions regarding the period of time that the event is in, and can happen both backward and forward, where backward is interpreting a recent event as more remote, and forward is when a remote event is interpreted as more recent. Confusion is the mixing up previous events when trying to recall. Together these issues demonstrate that retrospective surveys could potentially result in missing or wrong information. The effect of recall bias is also present with mood and psychological symptoms, especially positive affect that has been found to often be overestimated in retrospect (Ottenstein & Lischetzke, 2020). This study also found that the accuracy of retrospective assessments of positive and negative affect varies both between and within persons, showing the importance of using EMA which eliminates recall bias and the possibility of inaccurate retrospective assessments.

Retrospective surveys often also require not just the recollection of experiences, but also the need to aggregate the recollected experiences into one overall score in order to record the experiences of an entire day. For example, some surveys would ask about the pain score for the past week, and with pain being a fluctuant symptom, it is difficult to give a total score for such a long period of time. This means that it is not just recall bias that could affect the accuracy of the data, but also the aggregation methods that participants use in order to have an overall score (Robinson & Clore, 2002). Not only does EMA allow there to be no recall bias, but it is also important to note that EMA methods will also lessen the bias from the use of estimation strategies for an overall score. This is because EMA utilises multiple repeated assessments, and thus instead of estimating how a symptom is overall

throughout a day, multiple assessments of the symptoms' score in one day provides a quantifiable value.

Besides data collection method, the scheduling for measurement also needs to be determined. EMA measurements can be either randomised, scheduled throughout a day, or event-based (Smyth & Stone, 2003). This means that participants could either fill in EMA surveys at random times throughout the study period, or at selected scheduled times, or only after a certain event has happened. In the context of investigating symptom variability in a RA cohort, event-based measurements are unnecessary since the variability throughout a day is the main objective. Having random measurement times may also provide insufficient data at a certain time of day, thus fixed measurement times throughout a day is the suggested method for following chapters. The frequency of EMA measurements typically varies from every half an hour over a period of a few days, to once a day over a year as seen in the scoping review carried out in Chapter 3. The frequency is determined by the requirement of the study and limited by the amount of patient burden that is ethical. There will still be some aggregation due to the inability to measure every minute of the day, however the possible bias from estimation is drastically lessened. As it was noted in Chapter 1, symptoms of RA fluctuate throughout the day. This means that only one data collection per day may not be enough to capture the dynamic changes throughout the day. Asking for an overall score for pain for the past week, or even past day would result in an inaccurate score because of the difficulty for the respondent to take into account the possible fluctuations. This means that it is important to be able to track how symptoms change over time which is a key aspect of EMA.

Another benefit of using EMA is that it maximises ecological validity, which is the ability to generalise to the individuals' real lives. This is because EMA assess participants in a real-world environment instead of in a clinical setting, which means that the data can be generalised to the day-to-day life of participants. This is useful for RA patients because of the possibility of a spike in symptom severity when not in a clinical setting for the clinicians or researchers to observe. The use of EMA means that it is possible to remotely measure symptoms of participants in settings outside of the clinic, which will allow the daily fluctuations to be recorded, and possible interactions due to the fluctuations to be discovered. This means that EMA allows for ecologically valid data to be collected which

enables the data to be generalisable to real life experience for participants (S. Shiffman et al., 2008).

4.2.2 Application of EMA

The previous section showed the advantages of using an EMA approach in the field of RA to allow for generalisable data to be collected that can capture the dynamic and fluctuant changes of RA symptoms and experiences. As mentioned before, EMA is a collection of methods that share the same underlying principles, and thus it is important to note the optimal methodology to use in this thesis to track the symptoms of RA and depression.

Chapter 3 displayed 21 studies in the field of musculoskeletal disorders that utilises intensive longitudinal data collection to look at symptom variability. The methods used range from palmtop computers or pocket-sized PCs (Graham-Engeland et al., 2016), paper diaries (Keefe et al., 2001), phone interviews (Smith & Zautra, 2008a), electronic diary on a smartphone (Bromberg et al., 2016) to custom iPods (Fischer et al., 2016). It can be seen that there are multiple different ways to collect EMA data, but the more recent publications utilize more technology-based techniques, such as iPods and smartphones. Older methods, such as phone interviews, typically only collect data once a day, because of the patient and researcher burden of multiple phone interviews a day, while modern methods using an iPod allows for multiple measurements a day. This trend towards using electronic methods that allow for more measurements a day is ideal for use in RA cohorts where researchers want to examine how symptoms change throughout the day. One measurement a day will not be able to capture diurnal variations throughout a day, while six measurements a day provide a much clearer picture on the dynamic fluctuations within each participant. Thus, in order to collect enough data and following along with the trend of EMA publications in a similar field, study designs for later chapters should incorporate an electronic EMA method.

EMA methods were implemented in order to collect data at multiple points throughout a day for both the IA-COVID and APPro studies. IA-COVID consists of a duration of 10 days, with the first five surveys of each day sharing the same format, while the last survey includes additional questions regarding COVID-19 and sleep. APPro collects 6 times a day for 14 days, and then once a day for 16 days with this lone survey sent out at 8pm. The first 5 surveys a day for the first 14 days share the same questions, while the last survey included

additional questions on physical activity and sleep. The lone survey for the last 16 days possessed the same questions as the last survey for the first 14 days. The surveys were sent out at 9am, 11am, 1pm, 3pm, 5pm and 8pm each day for both studies with the lone survey for chapter 8 sent out at 8pm as well. The spreading out of surveys throughout a day means that assessments will be able to capture symptom severity throughout the day, and also manage to capture any potential fluctuations during the morning or evening. These methods allow for a thorough look at the diurnal variations of symptoms, and possible dynamic changes throughout a day. When considering the number of time points to be selected for symptom measuring, it is important to include sufficient assessments to allow for estimation of within day variability where the higher numbers of assessments are more optimal. Unfortunately, a high number of assessments also mean that there will be increasing burden for participants. 6 was the number that was chosen after input from a patient representative as an acceptable balance between these two factors. Fixed time point is also chosen over random time point because utilising fixed time points help to support analysis like autocorrelation and time series analysis (Saul Shiffman et al., 2008) The studies were also set up during the pandemic, and thus with fixed time points being the easiest to implement, was chosen as the model.

It is important to note that although EMA methods allow for repeated sampling which leads to generalisability across time and environments, the additional burden that repeated sampling presents compared to a cross-sectional method means that there is a possibility of non-adherence to the study protocol. This means that there is a likelihood of bias that arise due to factors that may affect participant adherence, for example a participant with severe symptoms may find it difficult to complete 6 surveys a day, and thus do not present complete data. To combat this, information sheets need to be very clear on study protocol, so participants are aware of the possible burdens. Furthermore, adherence can be improved by optimising access to the questions and making sure the measurements are manageable and easily answered. It is important to note that these issues are true of any study and may simply be exacerbated in studies with intensive longitudinal assessments.

While bias due to missing data are almost inevitable for any longitudinal study, analyses also do not require a full dataset with complete data for all individuals, where approaches such as full information maximum likelihood estimation are used. This means

that all participants starting a study will be included in the analysis even where there are missing data. Furthermore, approaches to identify factors associated with dropout and account for attrition bias are available and relatively straightforward to implement (Enders, 2022) even where data are potentially missing not at random (Muthen et al., 2011).

4.3 Ambulatory Assessment of Physical Activity

Physical activity is one of the most important disease management technique suggested by clinicians for RA patients because it significantly improves muscle function without elevating disease activity (Plasqui, 2008). However, the level of physical activity among RA patients is lower than the healthy population as shown by a systematic review that looked at 16 studies (Tierney et al., 2012). This is largely due to patients lacking the motivation and knowledge to correctly exercise, and clinicians placing insufficient emphasis on the health benefits from physical activity (Verhoeven et al., 2016). This showed the lack of focus on physical activity that should be present, which prompted the inclusion of physical activity in this study.

Having establish the importance of measuring physical activity, it is vital to evaluate the methods of measuring physical activity because it is difficult to be able to objectively assess patients' physical activity patterns (Vuori et al., 2013). It can be seen that past research on physical activity has been based on questionnaire assessments (Lee et al., 2012), while newer studies have begun to take advantage of the technological advances and used other methods such as accelerometers in a smartphone (Althoff et al., 2017). As mentioned above, there is a need to record these data in an intensive longitudinal manner as well to observe the fluctuations of the level of physical activity, and these methods are called ambulatory assessment. Ambulatory assessment consists of FitBit, a type of accelerometer to monitor movement, mobile electrocardiogram to track physiological function and many others (Reichert et al., 2020). These methods do not rely on retrospective self-report and could also maximise ecological validity and showing within-subject variations, and thus is the ideal method to pair with the monitoring of physical and psychological symptoms using EMA.

FitBit Charge 4 were issued to participants before the commencement of the APPro study in Chapter 8. Participants were allowed to test out the FitBit before the study, and was then instructed to log in using researcher-created accounts when the study starts. This was to allow for the researcher to log in and extract data without further participant burden. The information gathered from the FitBit were physical activity defined by steps walked and minutes of intense activity, and sleep defined by number of minutes asleep, and number of minutes in deep sleep. These information extracted consist of both an overall number per day, but also intra-day where number of steps walked each minute, and whether the participant is asleep for each minute are calculated. The FitBit was chosen because of its ability to track not just physical activity but sleep as well which is an important variable to track because it is shown to be significantly associated with fatigue, pain and depression in RA patients (Irwin et al., 2012). Furthermore, the FitBit is also shown to be a reliable method to track physical activity over time. A study on 23 participants that used the FitBit during slow, moderate, brisk walking speeds, and jogging showed that there is strong criterion validity when comparing both step counts and energy expenditure with an indirect calorimeter (Diaz et al., 2015). It was also shown that when compared with two industry-standard accelerometers and an indirect calorimeter device, the FitBit is still a valid and reliable measurement for steps and energy expenditure, especially on a flat surface (Noah et al., 2013). The FitBit is one of the most common commercially available device on the market, and combined with its validity and reliability to track sleep as well, makes it the ideal choice for this study.

4.4 Scales, Screening Tools & Outcome Measures:

There are many different symptoms present in RA patients, and multiple scales and screening tools can be utilised for each of these symptoms. This section will describe the symptoms chosen for each study and how these symptoms are measured. This will be carried out by separating this section into different symptom constructs.

4.4.1 Inflammation and Synovitis

Rheumatoid arthritis is a chronic autoimmune inflammatory disease that manifests as swelling and pain in joints, particular articular joints (Falconer et al., 2018). These inflammation leads to an activation of the synovial lining and inflammation cytokines which causes the swelling and damaged joints (Sweeney & Firestein, 2004). Thus, the measurement of inflammation is a big part of how clinicians measure disease activity. There are multiple ways of assessing RA, such as joint assessment, laboratory testing, imaging, and patient self-report measures (Sokka, 2010). This section will cover how inflammation is measured in the thesis, where it is featured prominently in Chapter 5.

4.4.1.1 Disease Activity Score 28

Disease Activity Score (DAS) was developed in 1990 in order to quantify the severity of RA which included a variety of disease expression and symptoms that vary between patients (van der Heijde et al., 1990).The DAS combines information from swollen and tender joints, inflammation levels, and patient reported outcome measures of general health into a scale that could evaluate the disease activity of a patient (van Riel, 2014). This means that the DAS combines both clinical variables and patients' experience into a single scale. A modified version of the DAS was developed, called the DAS28 which still has the same patient reported measures such as the patient global assessment (PGA), inflammation proteins such as the Erythrocyte Sedimentation Rate (ESR), but instead of 44 joints, only include 28 joints for the hands, arms, and knees, discounting the joints in the feet and ankles (Prevoo et al., 1995). Even though there are discrepancies between DAS and DAS28 due to the decrease in joints counted, the DAS28 is still able to discriminate between different levels of disease activity and was preferred due to its relative ease and feasibility in clinical settings (Carpenter et al., 2018). ESR is generally used as part of the DAS28 scale as part of the biomarker of inflammation, but C-reactive protein (CRP) can also be included as an alternative to ESR (Siemons et al., 2014). The usage of both CRP and ESR in DAS28 were validated for assessing disease activity, and also shown to have agreement in determining disease remission (Wells et al., 2009). The steps for scoring DAS28 can be seen in Table 4.1 below:

Table 4.1: Scoring Criteria for DAS28

Steps to Score DAS28
1) Count number of swollen joints (out of 28) (t28)
2) Count number of tender joints (out of 28) (sw28)
3) Take blood to measure either ESR (mm/hr), CRP (mg/l) or both
4) Patients score global assessment of health (PGA) on a 10cm line from very bad to very good (score of 0 to 100).

After these steps, the formula below is used to calculate the DAS28 score (Prevoo et al., 1995):

$$DAS28 = 0.56 \times \sqrt[2]{t28} + 0.28 \times \sqrt[2]{sw28} + 0.70 \times \ln(ESR) + 0.014 \times PGA$$

A score above 5.1 implies active disease, low disease activity is lower than 3.2, and disease remission at a score less than 2.6. Since there is no gold standard scale for measuring disease activity, physician judgement of severity of disease activity is used instead. Compared to this, the DAS has displayed ability in discriminating between low and high disease activity (van Riel, 2014). Even though DAS28 is validated for use in determining severity of disease activity, there remains some doubts as to whether it is appropriate to assess remission, due to the fact that 19% and 11% of patients respectively still have tender and swollen joints even with a DAS28 score of lower than 2.32 (Makinen et al., 2005).

Inflammation, which is included as part of the DAS28 is collected in both the TITRATE-US and IMPARTS dataset that is present in Chapter 5. With both the IA-COVID and APPro studies consisting of longitudinal data collection methods, the measurement of inflammation is difficult to include because of the additional participant burden and difficulty for participants to self-report inflammation levels.

4.4.2 Physical Symptoms

Even though this section is based on physical symptoms, it is important to note that these are more accurately somatic symptoms because as described in Chapter 1, physical symptoms such as pain and fatigue also has an emotional aspect of it that cannot be

ignored. Disease activity, pain, and function were described by the American College of Rheumatology to be core symptoms that every clinical trial in RA should include (Felson et al., 1993). The understanding of RA has progressed tremendously since the 1990s, and thus it is important to include more symptoms that play an important role in how disease activity and experiences of RA patients were affected. New symptoms were recommended to be included as core symptoms such as fatigue, stiffness, emotional distress, and daily well-being (Bartlett et al., 2015). The use of Patient reported outcomes (PROs) in these symptoms have also been proved to be both reliable and valid when administered online (Bartlett et al., 2015) This meant that when choosing which physical symptoms to be included in this thesis, it is important to extend more than the guidelines from American College of Rheumatology. This section will cover the main physical symptoms that are included in this thesis, and also how the different studies assess these symptoms.

4.4.2.1 Pain

Pain is one of the major symptoms of RA and considered as a core symptom as seen from above. Chapter 2 also showed that it was also one of the most commonly researched symptoms in longitudinal studies. Pain also adversely affects disability, quality of life, and psychosocial outcomes (Walsh & McWilliams, 2014). This means the pain needs to be included as one of the physical symptoms.

4.4.2.1.1 Widespread Pain Index

Widespread pain index (WPI) was developed in tandem with Symptom Severity Scale (SS) by the American College of Rheumatology (ACR) in order to classify fibromyalgia (Wolfe et al., 2010). WPI looks at muscle pain instead of joint pain and includes a list of 19 body parts to be identified. WPI is scored by noting the number of areas that were painful over the past week, and each painful area were given a score of 1. Table 4.2 below shows the 19 body parts that are included in the WPI.

Table 4.2: 19 body parts for WPI

Shoulder girdle, left	Shoulder girdle, right	Upper arm, left	Upper arm, right
Lower arm, left	Lower arm, right	Hip, left	Hip, right
Upper leg, left	Upper leg, right	Lower leg, left	Lower leg, right
Jaw, left	Jaw, right	Chest	Abdomen
Upper back	Lower back	Neck	

Even though WPI was initially developed for use in fibromyalgia, it has since been utilised to capture pain across the body in other chronic pain conditions as well (Dudeney et al., 2019). It shows expected differences in sex and demonstrates good construct validity by comparing WPI to pain regions (Dudeney et al., 2019). The use of WPI showed good validity for investigating clinical pain, however reliability was low if used by itself without the combination of SS (0.34 when used alone, 0.82 for combination) (Galvez-Sanchez et al., 2020). However, WPI has not been used in the field of RA without including fibromyalgia before, even though there were studies that looked at widespread pain, where participants were asked to report pain distribution on a pain manikin instead of using WPI (Bilberg et al., 2018). WPI was used in the TITRATE-US study in Chapter 5.

4.4.2.1.2 Visual Analogue Scale

The Visual analogue scale (VAS) is a measurement tool used to measure subjective or behavioural characteristics and is utilized in many different disorders and research (Flynn et al., 2004). It usually consists of a line 10cm long with descriptive anchors at each end, for example “None” to “Extreme”. Participants will then choose a point on the line to use as measurement for their outcome. One of the advantages of using VAS is that the scale is interpreted as an interval, thus the same sizes between two different sets of scores can be classified as the same differences, allowing for descriptive statistics to be carried out (Klimek et al., 2017).

VAS is used in a wide variety of conditions and is proven to be valid and reliable to measure pain (Bird et al., 2016). VAS has also been used in musculoskeletal disorders, where it is a reliable scale to be used in low back pain, as it has been shown to have a significant correlation of 0.92 with the Brief Pain Inventory Scale (BPI) (Shafshak & Elnemr, 2020). VAS has also been used on RA patients, and after looking at the test-retest correlation, and in comparing its correlation to other scales, it has been proven that VAS is a reliable and valid way to measure pain, depression and anxiety symptoms in a RA cohort (Tamiya et al., 2002). VAS is used in the IMPARTS dataset in Chapter 5 to measure levels of pain and has a score from 0 to 100, with 0 meaning no pain or fatigue, and 100 representing the maximum amount of pain and fatigue that the patient is experiencing.

4.4.2.1.3 Numerical Rating Scale

Numerical rating scale (NRS) is another measurement tool used to measure pain in this thesis. It is scored from 0 to 10, where 0 represents none and 10 represents extreme. NRS differs from VAS only slightly, as VAS allows for a continuous scale where participants can choose scores with a decimal point, while NRS only offers a whole number. However, NRS and VAS are very similar and NRS can be interpreted as the numerical version of VAS with each integer having a specific segment of the scale. It has also been shown that the use of NRS in rheumatoid arthritis patients to measure pain is highly reliable, and highly correlated (0.86-0.95) to the VAS (Hawker et al., 2011). The NRS for pain is actually preferred over all other scales, including the VAS because of its ease of completion and comprehensibility (de Williams et al., 2000) and is also shown to be more responsive to change when compared to the VAS, Verbal Rating Scale, and Faces-Pain Scale Revised (Ferreira-Valente et al., 2011). NRS is preferred over VAS in this thesis because of the mode of survey completion that participants utilise. Participants use a smartphone to complete surveys, and a VAS questionnaire would mean that participants have to be very precise in moving the scale to a specific score. With most RA patients suffering from stiff and swollen joints, it may be difficult for movements that require such finesse and precision. This means that the use of NRS is preferred because it is much easier to drag the slider over to a large segment that covers the integer score. This scale is used in both the IA-COVID and APPro study for the EMA measurements.

4.4.2.2 Fatigue

Even though fatigue was not considered as a core symptom, there is an international consensus to measure fatigue in addition to the core symptoms in all clinical trials (Kirwan et al., 2007). It is also the second most researched symptom as shown in Chapter 2. Fatigue has a 70% prevalence rate in RA patients and was described by RA patients to be as important as pain as an outcome measure (Hewlett et al., 2011). These mean that fatigue is a very important physical symptom to include.

4.4.2.2.1 Functional Assessment of Chronic Illness Therapy - Fatigue

Functional Assessment of Chronic Illness Therapy (FACIT) is a collection of health-related quality of life questions targeted for chronic illness and was originally developed in 1997 (Cella et al., 2019). The FACIT-Fatigue (FACIT-F) scale which is the one that is used in the TITRATE dataset here, is a subset of this scale and was originally developed for gauging the level of fatigue in anaemia (Yellen et al., 1997). The 13 questions, and the score for each of the choices that are included in FACIT-F can be seen in Appendix A. The score ranges from 0 to 52. Questions 7 and 8 have a reversed scoring criteria of an ascending order because of the way the questions are worded. A score that is below 30 indicates severe fatigue. The higher the score, the less fatigue and better quality of life the patient is experiencing.

The scale is stable over time (ICC = 0.87) and also have good internal consistency (Cronbach's alpha = 0.93) and qualitative interviews also showed that patients deem the FACIT-F scale to be sufficient to assess fatigue (Acaster et al., 2015). FACIT-F is now used in other conditions as well, where it is shown in a cohort of psoriatic arthritis patients that both qualitative and quantitative methods proved that FACIT-F is both a valid and reliable method to assess fatigue (Cella et al., 2019) (Cronbach's alpha > 0.90, ICC > 0.80, r > 0.8 with SF-36 Vitality). Most importantly, in a cohort with RA patients (Cella et al., 2005),FACIT-F also displayed good internal consistency (Cronbach's alpha = 0.86) and a strong correlation coefficient (r = 0.84) with SF-36 Vitality, showing good reliability and validity as an assessment measure for fatigue.

4.4.2.2.2 Visual Analogue Scale

The use of VAS was described above and was also shown to be valid and reliable for fatigue (Ozyemisci-Taskiran et al., 2019). It is present again in measuring fatigue in the IMPARTS study in Chapter 5 and is scored the same as pain.

4.4.2.2.3 Numerical Rating Scale

NRS is also used to measure fatigue, and it has been shown to be reliable and sensitive to change when measuring fatigue in the use of the Bristol Rheumatoid Arthritis Fatigue Scale (Dures et al., 2013). This is scored the same as pain and is present in the EMA aspect of both IA-COVID and APPro studies.

4.4.2.3 Joint Stiffness

The last physical symptom that is included in this thesis is joint stiffness. Joint stiffness was chosen instead of joint swelling because joint stiffness is more closely associated with functional disability than joint swelling (Yazici et al., 2004), and function is one of the main outcomes that RA patients are measured in. This means that the inclusion of joint stiffness will not only show the effects of inflammation and disease activity, but also show more information regarding the function of patients. Joint stiffness was also recommended to be included as a core symptom (Bartlett et al., 2015).

Stiffness is only included in the IA-COVID and APPro studies as one of the EMA measurements. This meant that it is also measured using NRS. The use of NRS in joint stiffness has been displayed in RA before, for example when observing stiffness levels after a new treatment (Li et al., 2020).

4.4.3 Mental Health and Psychological Well-Being

Depression and low mood are also found to have a high correlation with other RA disease activity such as decreased function and worse quality of life (Lwin et al., 2020), however not all RA patients have been assessed for psychological well-being. This establishes the importance of capturing symptom severity for mental wellbeing, and also the possibility of having clinically useful information derived from the inclusion of psychological symptoms. The NICE guidelines also published a reporting detailing depression in chronic physical health conditions (NICE, 2009) and state the importance of both recognising and managing depression in those with a chronic disorder. Following this guideline, it meant that psychological symptoms and mood should be recognized as one of the important factors in any physical chronic disorder such as RA. In a study that looked at core symptoms to look for after a pharmacological treatment in RA patients (Sanderson et al., 2010), further 60 outcomes are included such as physical unwellness, emotional health, physical activity, and coping. These shows the importance of including more than the three core symptoms that was mentioned previously, and the importance to include psychological symptoms.

4.4.3.1 Depression

Depression is the most common comorbidity in RA and has negative impacts on the quality of life and well-being on RA patients as shown in Chapter 1. There are around 280 different scales of depression that were developed over the past century and many are still in use (Santor et al., 2006). Common rating scales are the Hamilton Rating Scale (HRSD), Beck Depression Inventory (BDI), Centre of Epidemiological Scales (CES-D), and the Patient Health Questionnaire (PHQ-9) (Fried, 2017). PHQ-9 will be used in this thesis because it is widely used in routine care and research, such as being present in the TITRATE-US and IMPARTS studies and is also psychometrically sound.

PHQ-9 includes nine items linked to each of the main DSM-IV criteria for depression, which are scored in terms of frequency of experience over a two week period from “0” (not at all) to “3” (almost every day)” (Kroenke et al., 2001). PHQ-9 is scored out of 27, and a score of 0-4 is indicative of minimal symptoms of depression, often referred to as ‘none’, 5-

9 indicates mild symptoms, 10-14 moderate symptoms, 15-19 moderately severe symptoms, and 20-27 severe symptoms. The scoring criteria can be seen in Appendix A.

A diagnostic accuracy study of 580 patients from primary care clinics comparing the PHQ9 to an independent structured mental health professional interview indicated that a score of 10 or above in PHQ-9 has 88% sensitivity and 88% specificity for major depression (Kroenke et al., 2001). Sensitivity is the true positive rate, the proportion of those who received a positive result on the test with the condition, and specificity is known as the true negative rate, the proportion of those who received a negative result on the test without the condition. Besides use in a medical setting, PHQ9 is also proven to have good construct validity and can screen for both major depression and subthreshold depressive disorder in the general population (Martin et al., 2006). Most importantly, the validity of use of PHQ-9 in a RA sample has been tested , and it has an 88% sensitivity and 84% specificity while using the cut off score of 10, when compared to a gold standard of patients diagnosed with depression using Structured Clinical Interview (Hitchon et al., 2020).

The PHQ-9 scale is used in the TITRATE-US study in Chapter 5 and measures the individual scores for each of the 9 questions. A shortened scale, the PHQ-2 was used in the IMPARTS study. PHQ2 only includes two items; 1) Little interest or pleasure in doing things, 2) Feeling down, depressed, or hopeless and is scored the same way as PHQ-9. PHQ-2 was also validated in a primary care setting against a reference standard interview, and there is an 86% sensitivity and 78% specificity for detecting major depression when using a cut off score of 2. In IMPARTS, PHQ-2 was given to patients initially and if the score is above 3, then the other PHQ-9 items were scored as well.

4.4.3.2 Anxiety

Anxiety is another major comorbidity that RA patients suffer from, with symptoms of anxiety playing a role in exacerbating disease activity and tender joints in RA patients (Matcham et al., 2016). Anxiety and depression are also highly connected in RA patients, with around 15.9% of patients suffering from mixed anxiety-depressive disorder (Isik et al., 2007). There are many common measures for anxiety, such as the Hospital Anxiety and Depression Scale, Beck Anxiety Index, State-Trait Anxiety Inventory, and the Generalised Anxiety Disorder-7 (GAD-7) (Julian, 2011). GAD-7 will be the scale used in this thesis because

similarly to PHQ-9, it is included in routine clinical care and research such as in the TITRATE-US and IMPARTS studies.

The GAD-7 was developed to identify cases of GAD and assess symptom severity by using the DSM-IV criteria (Spitzer et al., 2006). It was tested on 15 primary care centres in a sample of 2740 patients, where sensitivity and specificity were 89% and 82% respectively using a cut-off score of 10. It has good agreement between other patient-reported and clinician administered scales as well. The scoring criteria for GAD-7 can be seen in Appendix A. The scores of 5, 10, and 15 are used as cut-off points for mild symptoms, moderate symptoms, and severe symptoms of anxiety respectively. Typically, a score of 10 is the score used to screen for GAD. This scale has been validated for use in the general population by a study of 5030 participants in Germany (Lowe et al., 2008). It was shown to be in comparison with the Rosenberg self-esteem scale, but also reliable with high internal consistency across 7 questions. In RA, the GAD-7 is shown to have acceptable sensitivity and specificity values of 64% and 86%, respectively. GAD-7 also have a test-retest reliability intra-class correlation coefficient of 81%, where the test-retest reliability is the reliability of applying the same test twice over a period of time to the same group.

GAD-7 was used in the TITRAT-US dataset, focusing primarily on individual scores for the 7 questions. For IMPARTS, GAD-2 was used instead which included the first two questions of GAD-7 but were scored the same way. These two questions are; 1) Feeling nervous, anxious, or on edge, 2) Not being able to stop or control worrying. A systematic review that looked at 12 total samples (Plummer et al., 2016) showed that using a cut-off score of 3, the sensitivity and specificity is 76% and 81% respectively in screening for GAD.

4.4.3.3 Affect

As detailed in Chapter 1, the model of depression in this thesis will be based upon the network model, where individual symptoms of emotional distress will be considered instead of depression as a whole. This model meant that instead of using latent variables and asking participants for the presence of depression or the use of the PHQ scale, the study would ask patients for observable symptoms. The use of depression scales to observe psychological symptoms in RA patients is difficult, because it is shown that in the seven most common depression scales, there are considerable differences in content and consists of 52

symptoms (Fried, 2017). With how diverse the depressive symptoms are, the results that are observed from one cannot be applied on a different scale. This reinforces the idea that to accurately measure emotional distress, individual symptoms need to be measured.

The study of emotions and mood was based on the theory of basic emotions started by Darwin in the 1800s and developed and built on by various other psychologists (Gu et al., 2019). This theory states that humans have distinct and independent emotions that are biologically basic, namely happiness, sadness, fear, disgust, anger, and surprise (Wilson-Mendenhall et al., 2013). These emotions are what drive all behavioural patterns and psychological disorders (Ekman, 1992). However, this theory is unable to explain the presence of co-morbidities in mental and affective disorders which often share the same basic emotion.

Affect is a psychological construct that looks at anything emotional, including moods, feelings, and emotions (Rosenberg, 1998). One of the main fundamental concepts in emotion is the distinction between the level of valence (Shuman et al., 2013) thus the structure of affect is split into positive and negative affect which can be interpreted to include all affective states with a positive (joy, enthusiasm) or negative (anger, fear) valence respectively (Ryff & Keyes, 1995). This structure was reaffirmed by a re-analysis of a large number of studies on affect (Watson & Tellegen, 1985), and stated that positive and negative affect are the two dominant and independent dimensions of affect. Further development produced the circumplex model of affect (Russell, 1980), which proposes that affect is not just influenced by valence, but also by arousal. In this context, arousal can be interpreted as a state of activation in the neural system. This means that each emotion is a combination of different degrees of valence and arousal, which means that instead of having just independent basic emotions which groups together emotions such as sad and upset, the circumplex model separates sad and upset by differing in the degree of arousal. This model allows for overlapping experiences between the different emotions felt and also treats emotions as measures that depend and correlate with each other. This circumplex theory of affect can be seen in Figure 4.1 below. The diagram shows the arousal scale as activation and deactivation, and valence scale as pleasant and unpleasant.

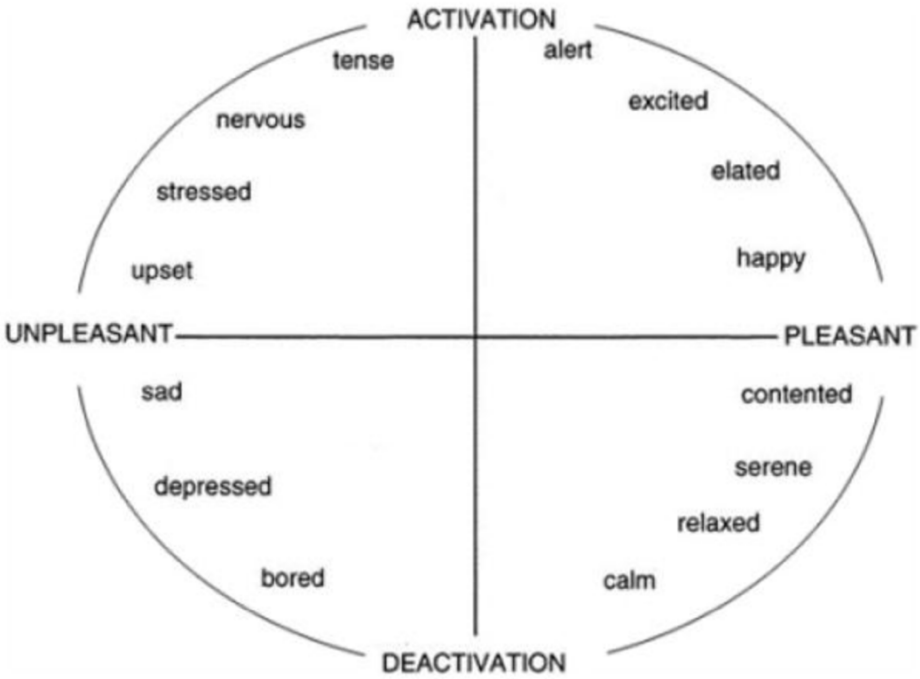


Figure 4.1: Graphical representation of circumplex model of affect (Posner, Russell & Peterson, 2005)

Both positive and negative affect have shown to have a significant association with the presence of depression and anxiety (Fredrickson, 2001). With Chapter 1 discussing the strong comorbidity between depression and RA, this association means that using the concept of affect to choose psychological symptoms will be beneficial to investigate this comorbidity further. It is important to not only look at the negative valence of affect even though there is an increased emphasis on negative mood compared to positive mood in psychology research (Hoyt et al., 2015) because it was shown that positive affect is an important factor to physical symptoms as well (Pressman & Cohen, 2005). Furthermore, in a longitudinal study (Ambrona & Lopez-Perez, 2014) that looked at positive and negative affect alongside physical health, it is shown that both positive affect and negative affect predict physical health both 1 month and 1 year later. These studies show the importance of utilizing the concept of valence in affect when choosing psychological symptoms for the empirical chapters in this thesis.

Symptoms of affect chosen for this thesis needed to have varying degrees of a combination of both dimensions of valence and arousal to allow the full range of emotions to be captured. In order to choose the specific outcome measures, a previous study that

utilizes similar EMA techniques on affect and physical activity (Wichers et al., 2012) was used as a guideline. This study (2012) utilized 10 affect symptoms, namely insecure, lonely, anxious, low, guilty, suspicious, cheerful, content, energetic, and enthusiastic. Another study looked at all the symptoms of major depression compiled from 7 different depression scales (Fried, 2017) and discovered that there are 52 unique outcome measures and was used as a framework as well to look for overlap of symptoms between both affect and depression.

6 affect symptoms were chosen for IA-COVID studies for Chapters 6 and 7, namely lonely, anxious, irritable, content, enthusiastic, and cheerful. Lonely and content were measures that were of low arousal state, while the rest were of high arousal state. Negative valence symptoms were all present in the study by Fried (2017) while irritable was the only one that was missing from study by Wichers et al (2012). However, no positive valence symptoms were provided in Fried (2017) and thus all were picked from the other study. The same symptoms were included for the APPro study, but sad and relaxed were included as well. Both are low arousal measures from the study by Wichers et al (2012) and were included to make the number of low arousal symptoms equal.

The 6 and 8 affect symptoms for IA-COVID and APPro studies respectively were measured using NRS. They were captured using the same EMA method and scored in the same 0-10 scale as physical symptoms.

4.4.4 Physical Functioning

Physical function is one of the original core symptoms of RA defined by the American College of Rheumatology(Felson et al., 1993) and is one of the major concerns for RA patients. This was specifically measured in the TITRATE-US study, however in the longitudinal studies, it was measured as part of well-being and will thus be shown in the next section.

4.4.4.1 Health Assessment Questionnaire – Disability Index

The Health Assessment Questionnaire (HAQ) was first developed in 1978 (Fries et al., 1980) for use in rheumatic diseases to measure a wide variety of patient-reported outcome. Only the domain of functional limitation (HAQ-DI) was used in this thesis, specifically in the TITRATE-US study in Chapter 5. The HAQ-DI consists of 8 main sections of dressing, arising, eating, walking, hygiene, reach, grip, and activities. There are either two or three questions in each sections, adding to a total of 20 questions. Scoring for each section remains the same, from a score of 0 (without any difficulty) to 3 (unable to do). The score given to each section is the highest score for any of the questions in that section. The total score is calculated by summing the scores for each section and then dividing by the number of sections. HAQ-DI also incorporates questions regarding the use of aids or help for some of the functioning questions. It may increase the category score by one or two, however the use of the aids section is not necessary (Maska et al., 2011). The HAQ-DI can be both self-administered or clinician administered, and the test is valid only if at least six sections are scored. As mentioned before, it is scored by taking the highest score for each section and adding them together, then dividing by the total number of sections included. It is rounded off after division to the nearest 0.125, and the total score ranges from 0 to 3. The higher the score, the greater the functional impairment. The scoring criteria can be seen in Table 4.4 in Appendix A.

The test-retest correlations of HAQ ranges between 0.87 to 0.99 (Bruce & Fries, 2003) and in RA patients, there is an intraclass correlation coefficient value of 0.97 and Cronbach's alpha of 0.95 for internal consistency (Linde et al., 2008). HAQ demonstrates strong criterion validity with an overall correlation of 0.88 with observed functional performance (Fries et al., 1980). HAQ also has strong predictive validity, with it being the strongest predictor of mortality and long-term outcomes like work disability compared to other patient measures like joint counts and inflammatory biomarkers (Wolfe et al., 2003).

4.4.5 Disease Impact and Health-related Quality of Life

A meta-analysis that looked at 31 studies found that RA patients have a significantly lower health-related quality of life compared to other physical illnesses and the general public (Matcham et al., 2014). The impact that RA has on the patient spreads to other aspects of life as well such as physical activity and social contact. The following sections will show the different impact that RA has, and which quality of life measures were collected. Furthermore, the scale used for measurement will be introduced as well.

4.4.5.1 Physical Activity

The IA-COVID study was carried out during lockdown, which meant that levels of social interactions and physical activity were affected. There are evidence of social interaction and physical activity influencing mental health (Alexandratos et al., 2012), and physical activity is also one of the main self-management tools for improving disease activity (Metsios et al., 2015). This association with both physical and mental health meant that it is important to track how physical activity changed as well. The APPro study also has an interest in physical activity, as FitBits were given to the participants to provide an objective measurement for physical activity.

The study by Wichers et al (2012) examined physical activity in an EMA environment as well, and used a 7 point Likert scale that ranges from resting, sitting, walking, household chores, biking, tennis, to running. This scale was a good model to adapt from, but certain points such as biking and tennis were too limited. In order to have a question that could be answered by more participants, a similar scale that utilizes more general exercise ranges were utilized. It was shown that there are five main categories of physical activity intensity, from sedentary, light, moderate, vigorous to high (Norton et al., 2010). This was incorporated into the scale, and thus the final options that participants could choose from were seen in Table 4.3 below:

Table 4.3: EMA measurement of physical activity

What was your highest level of physical activity (for at least 10 minutes)?
(1) Resting (e.g. napping)
(2) Sitting (e.g. watching tv, working)
(3) Standing (e.g. cooking)
(4) Walking slowly (e.g. doing housework, gardening, yoga)
(5) Walking briskly (e.g. fast walk as a form of exercise, cycling)
(6) Moderate intensity exercise (e.g. carrying light loads, jogging, social tennis)
(7) Vigorous or high intensity exercise (e.g. swimming, HIIT (high intensity interval training), workouts, sprints).

The intensity scale provided were distinguished by oxygen intake levels and heart rate, but requesting participants to measure these to answer a question is not practical. Thus, the questions were designed so participants were given example activities for each category and they could choose what is closest to their activity. These examples were extracted from the same paper that provided the intensity categories. This question covered all the possible intensity categories of physical activity and provided ease for participants to choose the most appropriate answer. This EMA measurement of physical activity was asked in both the IA-COVID and APPro studies.

4.4.5.2 Sleep

RA patients were shown to have bad quality sleep, with only 18.5% reporting sleep of good quality (Goes et al., 2017). It also shown that sleep plays a role in enhancing pain perceptions in RA (Lee et al., 2013), and sleep loss exacerbates fatigue and depression in RA patients (Irwin et al., 2012). One of the objectives of the APPro study was also to test the feasibility of FitBit and compare its objective measurements with subjective measurements, and thus measuring sleep through self-reported outcomes is necessary.

FitBit measures sleep by the number of minutes asleep and the number of minutes that were in REM sleep and deep sleep. REM sleep and deep sleep are both indicators of sleep quality (Ohayon et al., 2017), which can be used as an objective measurement for

sleep quality. This meant that when designing questions for sleep, both sleep quality and hours of sleep could be used. Both IA-COVID and APPro studies use the same format of questions for sleep, which include asking for the hours of sleep for the previous night, rating sleep quality using an NRS, and asking if participants took a nap during the day. These questions were asked once a day for both studies. Full details can be seen in Appendix C and D for IA-COVID and APPro studies.

4.4.5.3 Well-Being

4.4.5.3.1 Musculoskeletal Health Questionnaire

The Musculoskeletal Health Questionnaire (MSK-HQ) was developed in 2016 (Hill et al., 2016)through a co-production process with patients based on patient-reported outcome measures (PROMs). These PROMs identify key outcome measures that are relevant to both clinicians and patients across a range of different musculoskeletal disorders such as osteoarthritis, RA, and low back pain. With different musculoskeletal disorder patients experiencing symptoms in different regions of the body (Kamaleri et al., 2008), a single outcome tool that could be used across a range of conditions and settings needed to be created for these patients to be accurately and efficiently diagnosed. The MSK-HQ was created so it could be used generally across different musculoskeletal disorders, sensitive to change to enable changes over time to be measured, and also easily accessible in routine clinics (Hill et al., 2016).

The different domains that MSK-HQ capture are pain severity, physical function, work interference, social interference, sleep, fatigue, emotional health, physical activity, independence, understanding, confidence to self-manage and overall impact. These domains were covered using 14 questions, with one last question at the end asking how many days in the last week did the participant have 30 minutes or more of physical activity. These domains were identified by experts and patients as the main domains that all musculoskeletal disorders covered, and are more suitable to be measured. The

The MSK-HQ showed high completion rates in 4 different musculoskeletal disorder groups and excellent test-retest reliability ranging from 0.79 to 0.93. It also displayed convergent validity when comparing to other scales such as the EQ-5D-5L which is one of

the most commonly used scale internationally for health status (Devlin & Krabbe, 2013), and Oxford Hip, Knee, and Shoulder scores (Hill et al., 2016). Furthermore, when used on a group of primary care patients with musculoskeletal pain, it was shown to be valid, and more sensitive to changes than the EQ-5D-5L scale (D. I. C. Scott et al., 2020). The MSK-HQ is used to measure well-being in the baseline surveys that are present in the APPro study. It was not suitable for the EMA measurements because of the number of questions that it asks which will increase participant burden. The full MSK-HQ can be seen in Appendix D.

4.4.5.3.2 Numerical Rating Scale

Because of the inability to measure MSK-HQ often, NRS was used to measure some elements of well-being as well, such as the impact of physical symptoms, function, enjoyment from everyday activities, and social interactions. The questions that are asked are:

1) How much have your joint or muscle symptoms bothered you today?
2) Did you experience any problems physically performing the tasks you were doing today?
3) How much enjoyment did you experience from your activities today?
4) How satisfied were you with the amount of social interactions you had today?
5) How supported by others did you feel today?

These questions are scored from 0 to 10 and are measured once a day at the end of the day for both IA-COVID and APPro studies.

4.4.5.4 Social Interaction

The IA-COVID study was carried out both during lockdown and right after a lockdown, thus the amount and form of social interaction that occurred are important factors that could influence symptoms. The full reasoning and rationale could be seen in Chapters 6 and 7, and this section will be used to design the questions to measure social interaction. The first question involved asking participants what they were doing in the past hour before the

survey. Participants were allowed to pick multiple options from resting, leisure activities, household activities, or working. They were then asked about the company they had during those activities, and if it was virtually or in-person. The full questions could be seen in Appendix C.

4.5 Analysis Methods

Chapter 5 utilises secondary cross-sectional data from existing studies, while Chapter 6, 7, and 8 all contain rich longitudinal data that were collected at least once a day, with the majority of the dataset consisting of 6 measurements a day. This rich and intensive longitudinal dataset require appropriate advanced analytical methods to fully explore the dynamic associations that exist between variables. This section provides a comprehensive look at the different analytical methods used for the empirical chapters. The two main analytical methods that were utilised were mixed effects regression model and network analysis. The mixed effects regression model was used to achieve different goals, such as finding if there were significant differences between groups of data, and also in use in dynamic regression where the longitudinal aspect of the data was examined. As mentioned in Chapter 1, the network approach was the model used to understand depression and the comorbidity with RA by handling not just high frequency longitudinal data, but also a large number of variables.

The words “interact” and “interaction” is used commonly in this thesis with reference to the associations between different variables. It is important to note that the use of these words do not always mean the statistical “interaction” where one variable modulates the effect of an exogenous variable on an endogenous variable (also known as *effect modification*).This term is often used in network science to indicate where nodes in the network have connected edges and thus information is considered to flow through the network via multiple “interacting” nodes in a manner that is typically referred to as *mediation* in the psychological sciences (Epskamp, 2020).

This chapter will thus be split into two main sections, the first to cover regression models and the second to cover network analysis. An overview will be presented for each of the analytical techniques to introduce the general approach of these methods and show

how the techniques work. Following that, how these methods could be utilised in the chapters are shown.

4.5.1 Regression

4.5.1.1 Introduction

Regression is a statistical concept that is used to estimate the relationship between a dependent variable, and one or more independent variables. The purpose of regression is to investigate the effect that the independent variables (explanatory variables) have on the dependent variables, which is the primary interest (Fahrmeir et al., 2007). Regression is often used to either predict what will happen in the future based on existing information of the relationship or to infer a causal relationship between the variables. However, in reality, it is often difficult to infer a relationship because of the potential confounder effects of other variables, and also the possibility of other unobserved variables that play a part in the relationship. The regression model can be seen below:

$$Y_i = f(X_1, \beta) + e_i$$

Y_i is the dependent variable while X_i is the independent variable. β are unknown parameters that influence the independent variable, for example in the case of a univariate linear regression, the slope and y-intercept of the line. Last but not least, e_i is the error term that account for factors which were not included in the data. In a real-life situation, there are never perfect independent variables that predicts dependent variables, and thus error terms are required to explain the certainty of the function. $f(X_1, \beta)$ is the function that researchers have to specify to determine the dependent variable, and thus this function is what will drive the regression model. Thus, it is important for the researcher to choose the appropriate function that could estimate the data, which would depend on the structure of the data. The specific types of regression that were used in the different chapters will be covered in the next section.

4.5.1.2 Mixed effects regression for longitudinal data

In order to decide which regression model to use, the type of data that was going to be analysed had to be discussed first. In Chapters 6, 7, and 8, the data collected were all EMA data, ranging from frequency from once a day to six times a day. All the measurements collected were also longitudinal, meaning that it was asked over a period of time, with the majority asked six times a day and the lowest denominator for the frequency of the repeated measurement is once a day. This meant that observations are nested among the participants, where the individual observations are referred to as being at level-1, and the participants are considered to be level-2. Other levels of nesting are also possible, for example, where there are multiple observations per day there would be observations at level-1, day at level-2 and participant at level 3. This nesting meant that a multilevel model would be used, specifically a mixed-effects model, which is also known as a multilevel model for repeated measures. A multilevel model thus allows for variability at each of the given levels. The within participant effects mostly occur in level 1, where the repeated measures are, and level 2, which is the level of the participant consists of mostly between participant effects (Howard, 2015). The mixed effects regression model can be seen below:

$$Y_i = f(X_1, \beta) + Zu + e_i$$

Similar to the model show in 4.5.1.1, Y_i is the dependent variable and e_i is the error term. With the addition of the random effects, $f(X_1, \beta)$ is interpreted as the fixed effect term and Zu is the random effect term. The random effect includes both random intercept and random slope.

Because these observations were measured from the same participant multiple times, it meant that these measurements are not independent and are correlated with each other among the participants. This meant that multiple regression cannot be used because of the assumption of independence of observations, and thus random effects had to be included in the model. In order to understand what a random effect is, it is important to discuss a fixed effect model first. A fixed effect is when an independent variable has a fixed relationship with the dependent variable across all observations. This meant that each of the independent variable has fixed categories as answers, and all responses fit under one of

these categories, for example sex where the only possible outcomes are male or female. Random effect model on the other hand assumes that the fixed effect, or the fixed relationship between independent and dependent variables may vary from one observation to the next. This meant that the categories of the variable are just a sample of all possible outcomes that might occur. In other words, assigning a random effect to a variable meant that it is possible to take into account the variability from picking the sample of categories from all the possible outcomes (Peacock & Peacock, 2011). This meant that if the relationship to be explored contains both fixed and random effects, the final model that need to be utilised is the mixed effect model that allows for both fixed and random effects. Thus, considering the data that was collected that contained high-frequency longitudinal repeated measures, the best model would be the multilevel mixed effects model. In a multi-level model utilising longitudinal data, it was shown that the use of a model with random effect estimates the relationship better than a fixed effect model (Shor et al., 2007). One of the benefits of using a mixed effect model is also that it takes into account the non-independence between the level 1 observations, which is applicable in this situation.

Traditionally, the repeated measures analysis of variance (ANOVAs) is the analytical method chosen for any repeated measures studies. However, the use of the repeated measures ANOVA is not optimal because of its inability to take into account variability for both participant and observation levels. This meant that only one variability could be accounted for which reduces the statistical power of detecting a relationship (Barr, 2008). Most importantly, any significant associations that repeated measures ANOVA detect would not reveal information about its magnitude and direction, which decreases the amount of information that this test could provide (Brown, 2021). Furthermore, repeated measures ANOVAs assume sphericity of residuals, which is likely untenable, and require list-wise deletion of participants with missing observations. A multilevel model will be able to handle the variability on both level 1 and level 2, missing observations within individuals, and the inclusion of random effects also helped with the correlation of observations.

In order to understand random intercept and random slopes accurately, it is first important to identify that the model itself is a linear model. This meant that the relationship between independent and dependent variables can be described with a line. A fixed effect is used to refer to a parameter that is estimated for the entire sample and assumed to be the same for each participant, as with a regression parameter in a standard linear regression

model. Random effects, both intercepts and slopes, thus mean that each participant is estimated to have a different parameter. For a model including only a random intercept, the slope of the line is the same for each participant, and only the point of intercept between the line and the y-axis varies by participant. This meant that the rate of change and relationship between the two variables are the same for each participant, however the regression line moves up and down the y-axis according to its deviation from the mean. A random slope meant that the gradient of the line changes for each of the participants, while the starting point on the y-axis is the same for each line. This meant that the change for each observation is the relationship between the two variables while the starting point on y-axis remains the same. In the event of a random intercept random slope model would mean that each will have a unique line in terms of the combination of both gradient and y-intercept. Figure 4.2 below (Midway, 2019) shows the difference between fixed effects, random intercepts, and random slopes.

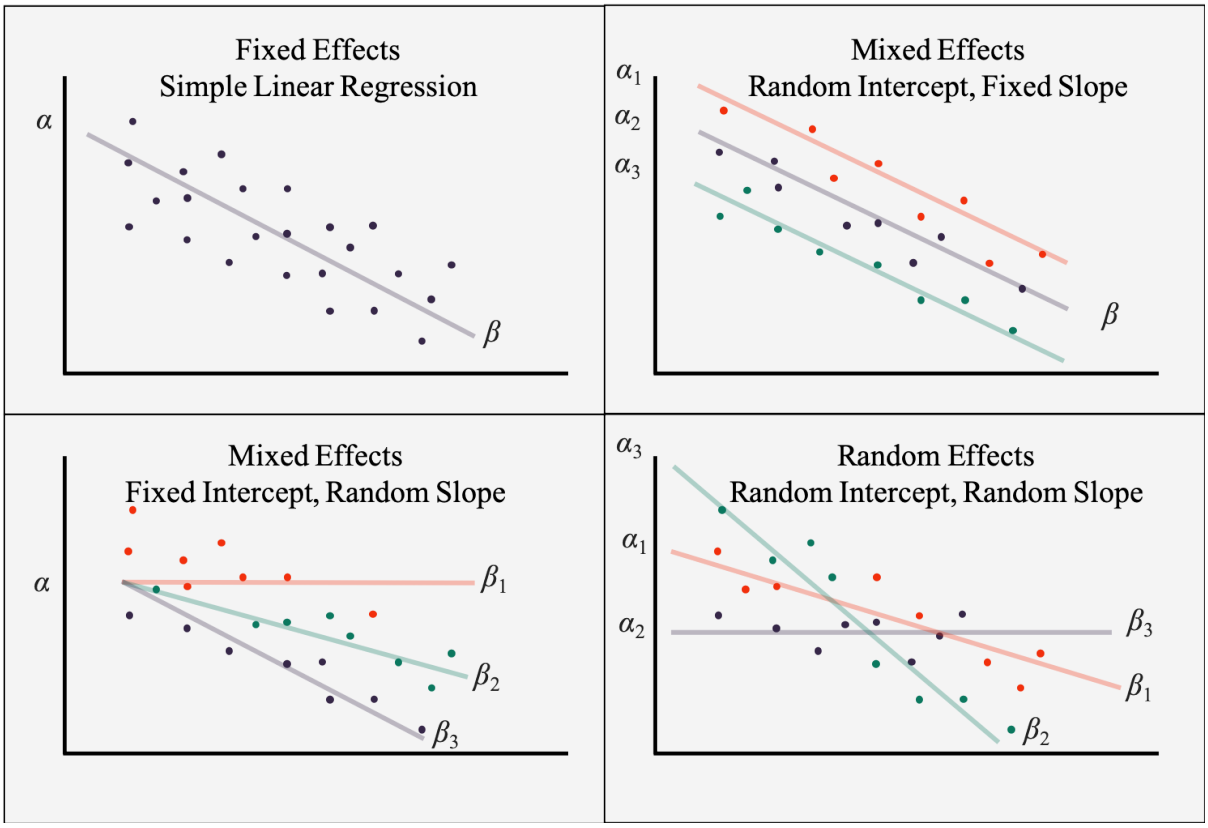


Figure 4.2: Graph of fixed effect, mixed effect, and random effect plots (Midway, 2019)

Where there are repeated measures data, it is typically necessary to include a random intercept to reflect the clustered nature of the observations being nested within individuals. However, a model including both random intercepts and random slopes is often needed to ensure the most accurate interpretation of the data in most cases, in particular including a random slope of a time variable to account for individual differences in the rate of change in a symptom across the day for different individuals

4.5.2.3 Application of Mixed-Effects Regression

IA-COVID study collected the EMA outcome measures a maximum of 60 times per participant, while APPro collected a maximum of 100 times per participant. This rich repeated measurement dataset meant that dynamic within-subject temporal associations could be discovered between the different categories of symptoms, including physical symptoms and psychological symptoms. The advantages of investigating within-subject temporal associations is two-fold, with both within-subject and temporal associations providing different benefits. Within-subject associations reduces the risk of confounders from subject-level factors such as socioeconomic status, education level, and gender. This is because within-subject explores the potential associations that occur in the same participants, which meant that any potential confounders such as education level remains the same for each of the repeated measurements that are investigated. The investigation of within-participant effect can capture the effect of how the independent variable changes over time. Next, for temporal associations, researchers and clinicians could capture the daily realities and fluctuations of participant experiences rather than just a snapshot (Myin-Germeys et al., 2009). The use of mixed effects regression is present in Chapters 6, 7, and 8. Mixed effects regression was used to carry out different analysis in the empirical chapters. It was used to examine the change in variables over time to show the diurnal variations in IA-COVID study, and also used to observe significant differences between different periods in both IA-COVID and APPro. Most importantly, it was also used to observe temporal associations between symptoms over time. The observations were nested in the participants, which meant that it was a multilevel design. The repeated measurement structure of the data also meant that this is a time series data, which could allow for a time-lagged structure to be formed. Each symptom can be examined with regards to the

symptoms measured on the previous time points', which would then allow for temporal associations to be investigated. In order to create the time-lagged structure, lagged variables needed to be created for those outcome measures that were analysed. A lag-1 variable meant that there is a delay of one period, where the first observation of the lag-1 variable will happen at the same time as the second observation of the original variables. These lagged variables were used as the explanatory variables in the mixed effect regression models against the dependent variable, and a significant association between the two variables meant that there was a temporal association. Given the structure of the data, with observations nested within days within participants, two random intercepts were specified in this case allowing the level of the outcome to vary not only across participants, but also within participants over each day of observation.

There was also a random slope of the time of day to allow the rate of change over the day to vary across participants. Random slopes allowing the rate of change to vary within participants across days were not estimated due to issues with convergence, which appeared to be due to these random effects being extremely small and close to zero and thus uninformative. To aid interpretation, the coefficients describing associations between lag-1 components and current period variables form different models were graphically displayed as a cross-lagged panel model, as seen in Figure 4.2 below. The panel model was to provide ease of identifying significant temporal associations immediately, while showing the magnitude and direction of correlation between the variables.

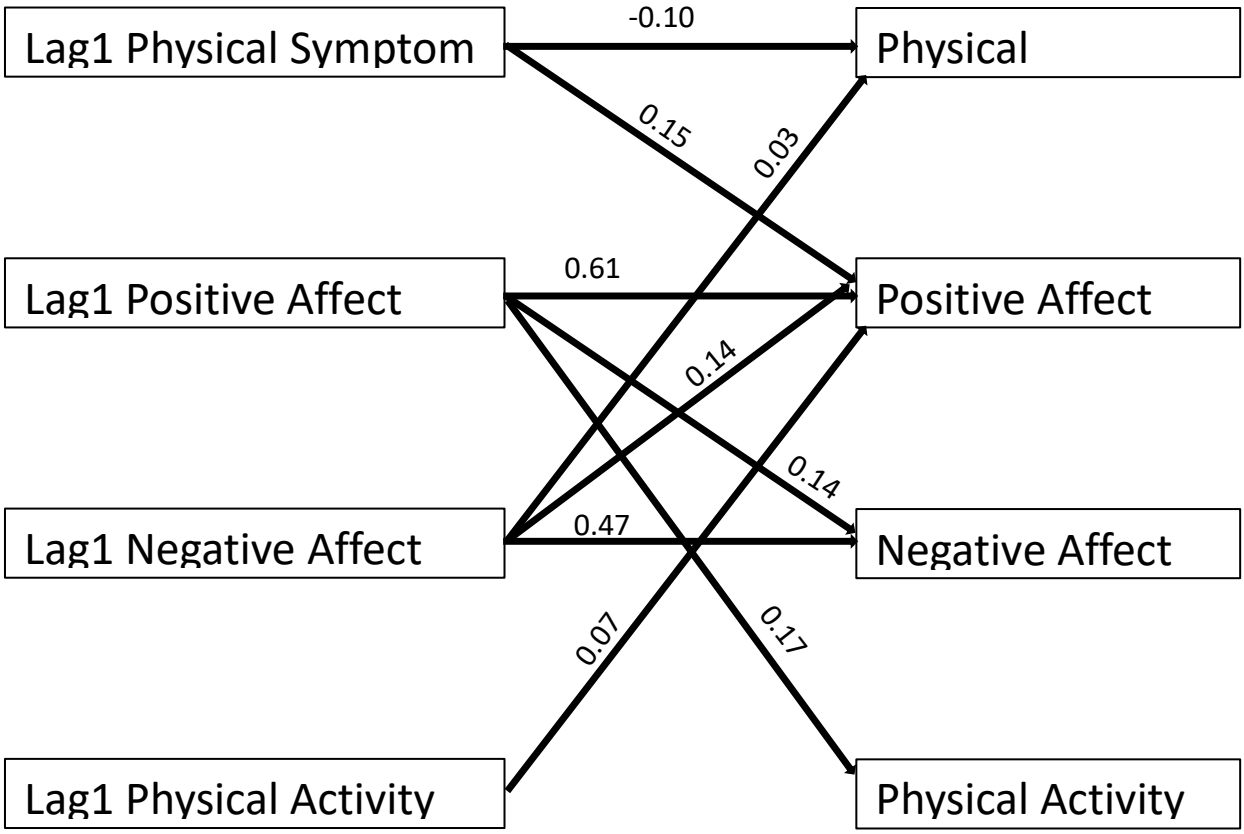


Figure 4.2: Example of a cross-lagged panel model copied from Chapter 6

4.5.2 Network Analysis

4.5.2.1 Introduction

In Chapter 1, the network approach was discussed in relation to depression and the comorbidity between depression and RA. It was established that instead of a latent variable approach where symptoms are a common cause to the disorder, the network approach states that each symptom is a unique contributor to the disorder and interacts with each other. Symptoms are thus viewed as part of the causal system that makes up the disorder. This meant that in order to have a complete picture of patients' disease activity for depression, it is important to include multiple outcome measures to take into account all the potential interactions. As seen in Figure 4.2 above, a dynamic regression consisting of only four variables and their lagged components created a panel model that is full of

information. Extending this panel model to 10 symptoms would mean that the result would be too cluttered with information and impossible to decipher what is important. This meant that another analytical method is needed to allow for simultaneous analysis of a large amount of outcome measures. Furthermore, the use of network analysis provides additional information that traditional methodologies do not (Boschloo et al., 2016), thus proving the importance of using network analysis in this thesis.

Network analysis allows for each of the outcome measures and interactions between the measures to all be shown in a graphical manner. In order to perform network analysis, there are three main sections that need to be achieved. These are network structure estimation, network description, and network stability analysis. The following paragraphs will detail how these steps are achieved.

4.5.2.2. Creation of Network Plot

The first step to network analysis is to choose what symptoms are included to be the nodes, and what relationship is represented by the edges. The nodes in this thesis will be the outcome measures that are collected in each of the studies. Edge selection is the next task in order to develop a network model for this data. The edges between nodes are dependent on the data itself, and could be partial correlations, lag-1 correlation, odds ratios or even any causal mechanism provided by the data (Borsboom & Cramer, 2013). In this case, the most suitable option is to explore empirical associations between the outcome measures that were collected in the studies. The use of a correlation matrix as the empirical association is one of the most common methods and it allows for easy identification of strongly connected clusters of symptoms, however there are insufficient power to deduce any causality between these symptoms (Borsboom & Cramer, 2013). The use of a correlation matrix meant that the correlation discovered between two variables could be due to the influence of another. In order to combat this, one of the options is to use partial correlations where all other symptoms are controlled for and only the correlation between the pair is considered. A partial correlation network model will be able to show accurately what common pathways are between symptoms in a between participant design. These pathways need to be validated in another independent sample, but some information about

causal relations can be derived from these (Borsboom & Cramer, 2013). With similar network plots drawn for Chapters 6,7, and 8, any common pathways between symptoms that appear in all three studies suggest that there is possible causal relationship.

This information about causal relationship has an unclear direction because the link that is created is undirected. In order to deduce the direction of the causation relationship, the network graph created needs to be directed. A directed network graph is particularly useful for showing cross-lagged relationships among outcome measures, which mean that the data used must be longitudinal (Bringmann et al., 2016). Even though the longitudinal dataset that was collected in these studies are ideal for a directed network graph to be created, the network models created in this thesis will all be undirected. This is because the main purpose of network science in this thesis is to show its utility, and with so much other analysis being carried out, there was insufficient time to create directed network graphs as well. The use of directed network is planned for future papers, particularly in comparing with the dynamic regressions that were carried out to examine the feasibility of it. This means that the longitudinal time series data collected for these studies will be used as a single time point data, or in other words, a cross-sectional data by disregarding the time component in network analysis.

The description of the edges in terms of pairwise statistical associations is the pairwise Markov random field (PMRF) model (Epskamp, 2020), and this model is the most commonly used model for network analysis that utilises statistical interaction. PMRF is also typically used for undirected network models, which makes it the ideal choice here (Hevey, 2018). As mentioned above, the data will be interpreted into a cross-sectional design to be used in network analysis. A cross-sectional network analysis is able to describe differences between participants, but is unable to fully describe the differences for any within-subject differences (Hamaker et al., 2015). This means that when creating network plots for Chapters 6, 7, and 8, the aim has to focus on between-subject difference rather than within-subject difference. PMRF is separated into two different types, the Gaussian graphical model, and the Ising model. Ising model specialises in binary data, which does not fit the outcome measures collected in the empirical chapters. The Gaussian graphical model allows continuous data, and uses partial correlation coefficients as the edges (Roverato & Castelo, 2017). Thus, Chapters 6, 7, and 8 will use the Gaussian graphical model. Last but not least, even though network analysis allows for a large number of nodes to be analysed at the

same time, a large number of nodes still requires more estimates which may be unstable (Babyak, 2004). The use of partial correlations also meant that variations would need to be taken into account, and that there will be multiple spurious edges created from weak correlations. In order to address this, the partial correlation also has to be regularised. Regularisation is a technique that adds an additional term to control for overfitting, which will restrict the value of the coefficient estimates, thus leading to less variance.

The most commonly used regularisation method is the graphical least absolute shrinkage and selection operator (GLASSO) (Friedman et al., 2008). GLASSO performs well in partial correlation coefficients and is able to reduce weak correlations to zero, which prevents any spurious edges from forming (Fan et al., 2009). Studies have also been carried out to simulate GLASSO networks, and it was found that false positives are unlikely, suggesting that if there is an edge, it is highly likely that the edge is not spurious (Kramer et al., 2009). One of the potential problems of using GLASSO is the reduction of significant edges to zero because of the estimation. This can be fixed by setting a tuning parameter, which will determine the threshold to remove edges from the network. In order to find the optimal tuning parameter, GLASSO creates multiple network plots ranging from a fully connected graph to a graph with no edges, and the researcher has to choose the optimal network. This can be done by minimising some information criterion, in particular the Extended Bayesian Information Criterion (EBIC) (Chen & Chen, 2008). The EBIC method has been shown to be able to choose the right model correctly (Foygel Barber & Drton, 2015), and the combination of GLASSO and EBIC has proven to have good sensitivity and specificity in picking the right network model. This still needs to be taken with caution because there is still the possibility of the reduction of significant edges to zero, and the EBIC method only helps to choose the model that has less likelihood of this happening but cannot prevent it from happening. The models chosen by the EBIC method follow best practices at the time of the analysis, but these types of models are sensitive to specification, thus giving different answers when different approaches or settings are used. This is a possible source of bias for the analysis and is addressed in empirical chapters by running sensitivity and stability analysis to evaluate if different specifications result in broadly similar results.

A network model presents a topological view which is visually appealing and consists of a large number of nodes and links which enable researchers to make quick observations on potential clusters and connections. In order to get more information, network

description is the next step. Network science allows for the calculation of centralities which lead to the discovery of a central node. The central node is an influential symptom that when activated, will spread and activate other symptoms faster than a peripheral node. Network centrality is thus a quantitative method to calculate influence in a symptom network which is clinically useful information (Fava et al., 2018). This is because if the symptom network was dormant, the activation of a central symptom will mean that other symptoms will be activated and develop at a much faster rate because of the strong connections that it has. In RA, the identification of a central symptom could mean that flares can be identified in advance. The central symptoms can be a guide to which symptom should be given priority in interventions (McNally, 2016). As mentioned in Chapter 1, comorbidity can also be explained by the use of network analysis, and the use of centralities can allow for the identification of the bridge symptom that is likely to develop comorbidity (Fried & Cramer, 2017). This meant that finding the central symptom can also help in preventing the development of a comorbidity.

Having created the network plot and computed the centrality plot, the last step is to ensure the accuracy of the estimates and results. Because of the limits in sample size, the parameters used may not be accurate which leads to a questionable interpretation of the network, thus inaccurate result for the centralities as well. Because of the methodology used to create the network plot, estimation of the edges between nodes are included. Furthermore, the uncertainty of the network meant that the centrality values derived could not necessarily mean that nodes with different centrality values are significantly different from each other. Stability analysis will therefore be important to address these points, even though only a few network analysis papers regarding psychology have taken accuracy into account (Epskamp et al., 2018). In a tutorial paper on estimating cross-sectional network papers' accuracy (Epskamp et al., 2018), it was shown that in order to conduct sensitivity analysis, it is important to estimate accuracy on edge-weights using bootstrap confidence intervals, assess stability of centrality by dropping cases, and test for significant differences between edge-weight and centrality. It was stated that estimating accuracy on edge-weights and stability of centrality should be done for every network paper.

In order to estimate accuracy on edges weights, bootstrapping is used to create a 95% confidence interval. Bootstrapping is appropriate because it is one of the methods that can be applied to regularised correlation, which was created using EBICGLASSO previously

(Hastie et al., 2015). A non-parametric bootstrap, where the model is not assumed was also chosen instead of parametric because of its suitability with regularisation and does not require the need to have a parametric model to sample from. The bootstrapped results can be used to show the accuracy of the estimates of edge-weight and to compare edges with each other. For stability of centrality to be calculated, it will be done by calculating centrality values on subsets of the data, which is referred to as case-dropping subset bootstrap. The correlation stability coefficient (CS-coefficient) is invented by Epskamp, Borsboom and Fried (2018) which represents the maximum proportion of cases that can be dropped such that there is a 95% probability that the correlation between the original centrality indices and new centrality indices is 0.7 or higher. CS-coefficient should not be below 0.25, and any value above 0.5 is good.

4.5.2.3 Application of Network Science

In a systematic review on the use of network analysis on psychopathology (Contreras et al., 2019), it was revealed that out of 65 papers, 42 (65%) used an association or regularised partial correlation network as the network model, showing that this is the most commonly used method in the field of psychology. 55 (85%) calculated centrality as well to provide quantifiable information, which is also going to be utilised in this thesis. However, only 21 (32%) performed a sensitivity analysis which is required to assess the robustness and accuracy of the estimated parameters. This low percentage is likely because of the difficulty to perform a sensitivity analysis, but it will be carried out in this thesis in order to ensure robustness. This thesis will utilise data as a cross-sectional format to create network graphs. The symptoms measured will be the node, and the edge will be determined by partial correlation. The EBICGLASSO regularisation technique will be used to choose the network plot. Centralities will also be carried out for most of the graphs, followed by a sensitivity analysis to ensure robustness. All network models utilised will use the aforementioned method to calculate edges and statistical models, with the same techniques used as well to investigate centrality and to conduct sensitivity analysis.

4.5.2 Issues of Causality

Even though there are suggestions that the temporal associations discovered in this thesis may be indicative of a causal relationship, it is important to note that deducing a causation between variables is very difficult and that the discovery of temporal associations is insufficient to suggest causation in itself. In order to be able to draw causation from associations, Table 4.4 below shows the Bradford Hill criteria needed to justify any causation drawn (Cox, 2018).

Table 4.4: Bradford Hill Criteria

Bradford Hill Criteria	Inference
Strength of association	Strong associations more likely to be causal
Consistency of Findings	Results need to be consistent across populations, study designs, etc
Temporality	Cause needs to precede effects
Biological plausibility	There needs to be possible biological explanations
Coherence	It has to be coherent with present knowledge
Analogy	Similar causes have similar effects
Experiment	Reducing the “cause” should reduce the “effect”
Specificity of Effects	The specific cause needs a specific effect
Biological Gradient	Larger the cause, larger the effect.

The Bradford Hill criteria can be used as a guideline to base causality after, but it is important to note that not all criteria is applicable to every study, and each criteria has its own weakness as well. It was concluded that the most important criteria to follow is Experiment, Consistency, and Temporality (Ioannidis, 2016). There are also two main methods to deduce causal relationships between variables, which is the Granger causality

and the Bayesian Network Inference Approach (Zou et al., 2009). The Granger causality is best used on time series data, which determines a causal relationship from one time series to another by looking at how the prediction of one time series data can be improved by incorporating another (Geweke, 1982). The Bayesian Network Approach is basically the network science approach where nodes and direct edges are created from a set of data and can be used on both static and time series datasets (Friedman, 2004). Both these methods however are only an estimate of the parameters of causality, and thus may provide superfluous causal relationships. Furthermore, it is also important to note that the data used in these chapters are observational data, and as there is no direct manipulation of exposure, it is not possible to conclude that associations are proof of causality. Thus, the utility of certain Bradford Hill criteria as listed above such as consistency and temporality is important to help build the weight of evidence in this thesis.

5. Utility of Network Science in Cross-Sectional Data

5.1 Overview of Utility of Network Science in Cross-Sectional Data

Chapter 5 utilises the secondary data collected in both TITRATE-US and IMPARTS studies to test the usability of network science in the field of RA and depression. The purpose of this Chapter is to establish a basic network structure of this comorbidity, and to identify any symptoms that connect the psychological and physical symptoms. This Chapter is based on a paper that is due for publication, and thus there are overlaps in the introduction and methodology sections that may have been present in other Chapters.

5.2 Introduction

Arthritis is a leading cause of disability worldwide and incurs massive costs to patients and healthcare providers alike due to the number and severity of symptoms, and patients' loss of functioning (Messier et al., 2004). Inflammatory arthritis (IA) is one of the main types of arthritis, and Rheumatoid Arthritis (RA) is the most prevalent type of IA. Depression is the most common co-morbidity of RA (Dougados et al., 2014). Rheumatoid arthritis patients have an abnormally high rate of depression, about 16.8% on diagnostic interview (Matcham et al., 2013). This is likely to be due to high physical disability, difficulties coping with the impact of the having arthritis, and the limited support available to help patients (El-Miedany & El-Rasheed, 2002)

There is a clear need for more comprehensive understanding of the interactions between mental and physical health in those with RA in order to be able to effectively target treatments and mental health interventions. The scoping review in Chapter 3 showed that longitudinal studies of people with musculoskeletal disorders, that examine symptoms dynamically, typically only investigate associations among at most 3 variables (e.g. pain, function, mood). RA is a disorder associated with lots of different symptoms and markers of disease activity, ranging from physical (pain, joint stiffness, fatigue) to inflammation (power doppler, joint tenderness) and psychological (mood, anxiety). Given the variety of symptoms

present in RA, considering associations between only two or three symptoms is insufficient to be able to gain an accurate picture of the association across symptoms and their interactions.

Borsboom's (2017) network theory of mental illness is gaining traction as a symptom-based model for depression which incorporates biological, social, and psychological aspects of depression by looking at the interactions between symptoms. This approach is not limited to studying mental illnesses and can be readily extended to include other variables as well. The network approach considers each symptom as a separate node (i.e. variable) within a complex dynamic system where nodes may be linked directly or indirectly via other nodes. An advantage of network-based approaches is that they allow for individual symptoms to be included in the analysis simultaneously. It is common in most RA research to consider composite or total scores as indicators of overall disease activity (e.g. DAS28) or symptom severity (e.g. RA Impact of Disease Questionnaire; RAID) rather than specific symptoms or distinct components within symptoms that may themselves be multifaceted. Disease flare provides a useful example of how network approaches might allow researchers to look at interactions between inflammatory markers and symptoms. In the case of a disease flare, inflammation may result in joint swelling and increased pain, but also increased fatigue via other mechanisms increased fatigue. Increases in pain and fatigue, may then cause a spread of activation throughout the network, for example also impacting on other physical symptoms such as functional limitations and on psychological symptoms such as mood.

This means that it is possible to identify a bridging symptom that may play a mediating role in between two conditions. A bridge symptom is a symptom that connects different clusters of symptoms together, where the clusters could be different disorders (Castro et al., 2019). Bridge symptoms could either be a symptom that belong to both clusters, for example fatigue that is present in both depression and anxiety, thus creating a perfect overlap (Cramer et al., 2010), or a symptom that belongs to only one disorder but plays a major role in the other (Levinson et al., 2017). The study by Castro et al (2019) proved that the identification and treatment of both central and bridge symptoms will deactivate the system of symptoms, which means in this case, the identification of the bridging symptom should enable the cessation of the spread of activation and improve the quality of life in patients.

The purpose of estimating the network structure of physical symptoms, psychological symptoms, and inflammatory markers of RA is to test the utility of using network analysis in two RA datasets. The literature regarding associations between physical or mental health symptoms in those with RA is vast and unequivocally demonstrates associations. However, this literature focuses on broad constructs of mental health and is essentially limited to assessing bivariate associations between the severity of physical symptoms (e.g. pain and fatigue) and the severity of mental health disorder (e.g. depression). As discussed in Chapter 1 "Background", mental health disorders are not homogenous and involve constellations of different symptoms that while being correlated are distinct (e.g. anhedonia, dysphoria, sleep disturbance). A useful comparison in RA is disease activity, which is assessed using a composite of factors (e.g. DAS28 involves tender joint count, swollen joint count, biomarkers of inflammation, self-reported assessment). Building on the evidence gap identified in Chapter 3 "Scoping Review" which indicated that no studies had to date involved more than three symptoms in a longitudinal dataset and none had considered individual components of mental health, this chapter adds to the literature by seeking to better understand the associations between individual markers of disease status (e.g. joint counts), individual physical symptoms, and individual components of mental health in two RA samples. With the utility of this new analysis approach, where a network structure is estimated, it is possible to better understand new potential associations that traditional analysis is unable to.

Currently no study has considered a network approach to mental and physical health symptoms in RA. The main aim of this study is to determine whether the application of symptom network methods is feasible as a method to further understand the association between different characteristics in this population. The study has two key objectives, which are addressed using two samples of patients attending hospital outpatient appointments:

1) To estimate the network structure of physical and mental symptoms and inflammatory markers of rheumatoid arthritis.
2) To identify whether there are potential bridging symptoms between physical and psychological symptoms.

5.3 Methods

5.3.1 Participants

This study uses data from two sources. Data from the Testing and Identifying Targets in Rheumatoid Arthritis Therapy ultrasound study (TITRATE-US) is used as the primary research dataset for analysis. Data from the Integrating Mental and Physical Healthcare (IMPARTS) patient reported outcomes system is used as a validation cohort to determine whether similar results are derived in relation to the TITRATE-US sample.

TITRATE-US

The objective of TITRATE-Ultrasound (TITRATE-US) Study was to investigate whether active inflammatory RA (defined by positive power doppler ultrasonography (PDUS)) could be differentiated from non-inflammatory rheumatoid arthritis by an algorithm of clinical, laboratory and patient-reported outcome measures. This cross-sectional study recruited 158 patients attending outpatient clinics at Guy's Hospital between 3rd May 2015 and 29th December 2016, who were at least 18 years old, clinically diagnosed with RA, and had active disease as indicated by a score of at least a 2.8 score on the Disease Activity Score (DAS28). This sample is ideal for considering associations between markers of inflammation and synovitis alongside physical and mental health symptoms.

IMPARTS

The Integrating Mental and Physical healthcare: Research Training and Services (IMPARTS) data is from patients attending rheumatology clinics at King's College Hospital and completing patient reported outcomes (PROs), including mental health screening, as part of standard care. Over 1000 patients completed PROs with a subsample of 211 patients with clinical diagnosis of RA and aged over 18 years where psychological screening and inflammatory markers were recorded concurrently (<14 days) extracted for this analysis. These data were collected between April 2012 and October 2018. The screening tools used were the two-item Patient Health Questionnaire (PHQ2) and the two-item Generalised Anxiety Disorder (GAD2), which assess the core symptoms of depression and anxiety: low

pleasure/interest, low mood, high anxiety, uncontrollability of worry. Additional data recorded were joint counts and visual analogue scales for pain, fatigue and patient global disease activity.

5.3.2 Measures

The TITRATE-US study recorded current medications, pain visual analogue scale (VAS), global health VAS, assessor global VAS, 68 tender, 66 swollen joint counts, fibromyalgia tender point count, ESR and CRP. This study also looks at power doppler, which is an inflammation marker calculated by blood flow in vessels. Subjects also completed the following PROMs: Health Assessment Questionnaire (HAQ), Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale (Yellen et al., 1997), Patient Depression Questionnaire (PHQ9), Generalized Anxiety Disorder 7-item (GAD-7) scale and the 15 item Somatic Symptom Severity Scale (PHQ15). The components of the fibromyalgia diagnostic criteria, the patient-reported widespread pain index and the physician-reported symptom severity scale were also collected.

Since data from the IMPARTS sample are routinely collected data, the range of assessments is more limited. Clinical data extracted from the electronic health record including the components of the DAS28 (28 swollen joint count, 28 tender joint count, PGA, and CRP). PROs collected were pain VAS, fatigue VAS, HAQ, Work and Social Adjustment Scale, HAQ, Patient Depression Questionnaire (PHQ9), and Generalized Anxiety Disorder 7-item (GAD-7). Since the tools were implemented for mental health screening, the completion of the full PHQ9 and GAD7 was undertaken in a staged approach with only those screening positive for the PHQ2 or GAD2, involving the first two items of the respective full scales. As a result of data from the PHQ9 items 3 to 9 and GAD7 items 3 to 7 being missing by design for most patients; only the first two items from each scale are used in the analysis to avoid potential selection effects.

The full scale of PHQ and GAD is only used in the IMPARTS dataset if participants test positive for the shortened version of PHQ2 and GAD2 respectively. Even though both PHQ2 and GAD2 are shown to be reliable screeners and also have acceptable sensitivity and specificity at the threshold of a score of 3 (64% and 85% for PHQ2, 71% and 69% for GAD2) (Staples et al., 2019), there is still the possibility of measurement imprecision if the full scale were not used. There may be misclassification where participants do not reach the cut off

score for the shortened scale to be given the full scale, but actually have depression or anxiety. This is a valid concern, but IMPARTS is a self-reported outcomes system where patients complete these questions while attending clinics. It is vital to decrease participant burden in this case, and giving the full scale for both PHQ9 and GAD7 may take up too much time. Furthermore, a study carried out on a RA sample showed that the sensitivity and specificity of PHQ2 is actually higher than PHQ9 (88% to 87% for sensitivity; 84% to 77% for specificity) (Hitchon et al., 2020), suggesting that the use of PHQ2 to screen initially should not pose much problems.

5.3.3 Statistical Analysis

Two network models, specifically Gaussian Graphical Models (GGMs) (Lauritzen, 1997) (Epskamp et al., 2018), were estimated for the TITRATE-US data. The first model included the core symptoms of depression (anhedonia, dysphoria) and anxiety (feeling anxious, uncontrollable worry), plus pain (tender joint count, Pain VAS, WPI), fatigue (FACIT-F), functional limitation (HAQ), inflammation and synovitis (swollen joint count, power doppler score, ESR, CRP). For fatigue only items 1, 4, and 7 regarding feeling “fatigued”, “tired” and “having energy”, were included in the total score calculation to avoid overlap with other constructs. The second model included the other mental health items from the PHQ9 and GAD7.

Each network model involved two steps in its estimation. In the first step, a regularised correlation matrix is created, where the correlation between two variables is estimated that partials out the effects of potential confounders and a shrinkage factor applied to retain only important associations. Regularization involved the ‘least absolute shrinkage and selection operator’ (LASSO) method (Epskamp, Kruis, et al., 2017), which does not rely on significance tests that are problematic and can result in spurious associations being identified in situations where multiple tests are conducted (Hastie et al., 2001). Age, gender, ethnicity, disease duration, seropositivity are controlled for in the TITRATE-US sample, whereas only age, gender, and seropositivity were sufficiently complete for the IMPARTS sample.

A network plot is created to graphically represent the regularised correlation matrix using the R-package *qgraph* (Epskamp et al., 2012). This is used to depict the network structure of the variables included in the analyses. Considering that these data are cross-sectional, the network plot is "undirected", which means that the edges may represent bidirectional associations and cannot be interpreted causally. These network plots include nodes (circles) for the symptoms, and edges (lines) for the association between the different nodes. The layout of the nodes is determined by an algorithm that places nodes that are more related closer to each other.

The next step of the analysis involves the calculation of centrality indices that aid the interpretation of the network. Centralities attempt to quantify influence of each node within the network. Four centralities are calculated: Degree centrality, Closeness centrality, Betweenness centrality, and Expected influence. Degree centrality indicates how many significant associations a particular node has with other nodes, where nodes with higher degree centrality are more highly related to other nodes in the network. In order to comprehend closeness and betweenness centrality, the concept of shortest path needs to be understood first. The shortest path theory states that nodes will aim to reach every other node using the shortest path possible. Closeness centrality indicates how short the average shortest path to all other nodes are, that is, the average number of nodes that edges pass through to reach another node. Betweenness centrality indicates how often a node is in the shortest path between other nodes. A node with high closeness centrality will thus be able to spread information and affect other nodes effectively, while a high betweenness centrality means that the nodes has a high influence on the flow of information across the network. Nodes with high closeness and betweenness centrality provide potential targets for treatment where the aim is to reduce overall levels of activity across all symptoms in the network. Bridge strength centrality will also be calculated for one of the TITRATE-US network plots to discover which node has the highest influence in connecting the clinical variables and psychological symptoms.

5.4 Results

5.4.1 Sample characteristics

Table 5.1 displays the demographic and clinical characteristics of the two samples included in the analysis. There were some extra information that the TITRATE dataset records that is missing in the IMPARTS data, and are not shown in the table, for example disease duration, frequency of drug, and past drug records. The patients have an average disease duration of 12.9 years (SD 10.3 years) and out of the 137 patients with data available, 47 were prescribed biologics DMARDs either in combination with a conventional synthetic DMARD or alone, 83 conventional synthetic DMARDs only, and 7 patients not recorded as currently taking any DMARD. For the analysis, only those with no missing data for all symptoms will be included, and thus only 137 out of 158 patients will be used for TITRATE.

Table 5.1: Demographics

	IMPARTS	TITRATE
Total Number	211	158
Average Age (S.D.)	54.1 (1)	58.8 (12.9)
Gender	164 Females (77.7%) 47 Males (22.3%)	124 Females (78.5%) 34 Males (21.5%)
Seropositive for Rheumatoid Factor or ACPA	148 (70%)	116 (73.4%)

5.4.2 Network Plots and Centrality

TITRATE-US networks

The short code for each of the nodes are shown in Appendix B. Figure 5.1 below shows two network plots, both from the TITRATE-US dataset, but one containing only a simplified version of the psychological symptoms (PHQ2 and GAD2) which will be labelled A, and the other containing all psychological symptoms (PHQ9 and GAD7) which will be labelled B. The

nodes are distinguished by the type of symptom they are, where inflammatory symptoms are coloured red, physical symptoms are coloured green and psychological symptoms are coloured white.

The symptoms network plots of the 137 patients are weighted networks, which means that the strength of the line (edge) connecting two nodes (variables) varies across nodes; as indicated by the width and intensity of the lines. The colour of the lines indicates the direction of the association, with green lines indicating a positive association between nodes and red a negative association.

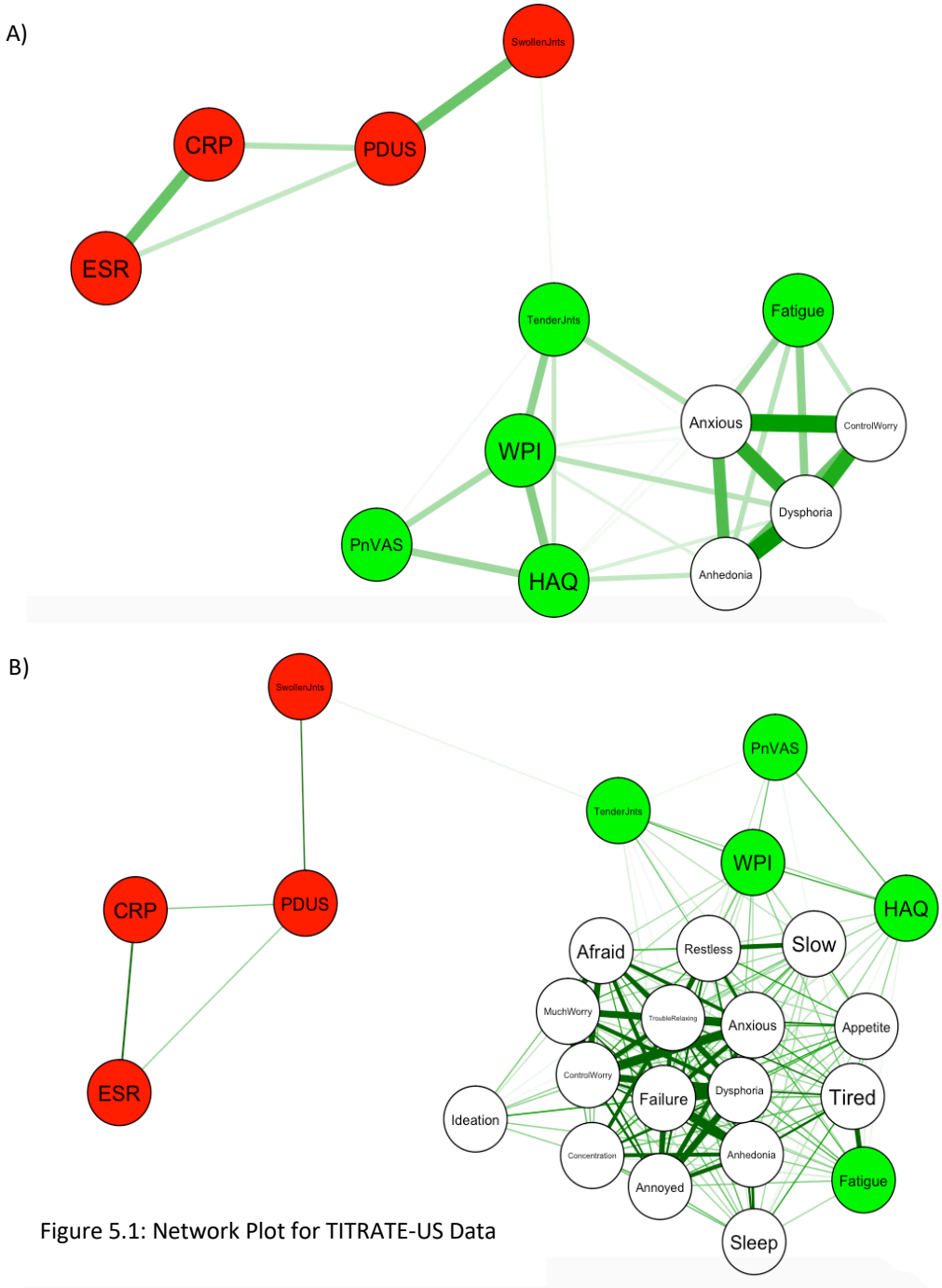


Figure 5.1: Network Plot for TITRATE-US Data

Both network plots provide a clear indication that nodes cluster into two sets of related features: patient reported symptoms of physical and mental health, and markers of inflammation and synovitis. Patient reported symptoms are also split quite clearly into the physical symptoms and psychological symptoms. However, both plots show fatigue as the odd one out, in which fatigue is very closely connected and clustered with psychological symptoms, particularly in B. An important feature to bear in mind is that nodes that are not directly linked still have an indirect association with each other. For example, in A, fatigue and tender joints do not have a direct link but are connected indirectly through anxiousness. This provides an indication that the effect is mediated; that is a change in tender joint counts may lead to a change in anxiousness, which will lead on to a change in fatigue.

Simplified TITRATE-US Centrality

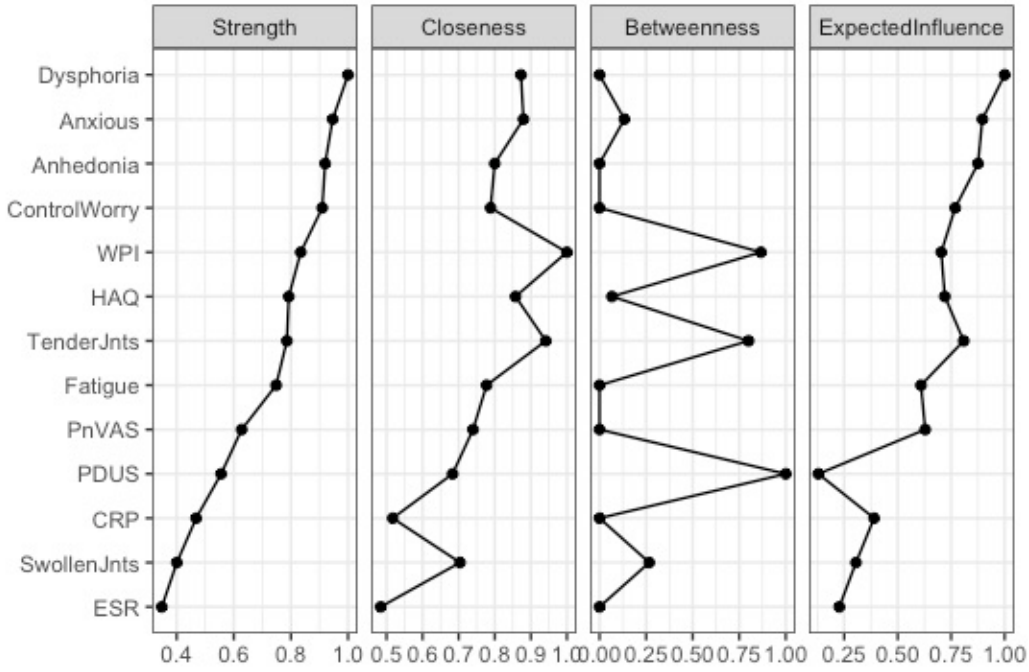


Figure 5.2: Centrality Rankings for Simplified TITRATE-US Plot

Figure 5.2 above shows the centrality plots, summarising the centrality values for each nodes relative to each other. The higher the degree centrality, the more nodes a symptom has a significant association with. Dysphoria (PHQ2) has the highest degree centrality, followed by feeling anxious (GAD1). WPI has the highest degree centrality for physical

symptoms, while PDUS has the highest degree centrality of the inflammation symptoms. The top 4 degree centrality symptoms are all psychological symptoms though, suggesting that in this plot, psychological symptoms are the most connected out of all symptoms.

A high closeness centrality symptom means that changes in that symptom will lead to fast changes in other symptoms as well. WPI has the highest closeness score for closeness, followed by Tender joints, Anxious and Dysphoria, tender joints and PainVAS. This suggests that a change in physical symptoms will lead to a very fast change as well in other symptoms, while psychological symptoms do not prompt such a quick change. Inflammation symptoms are the lowest in the list, suggesting that a change in inflammation will only lead to a change in other symptoms after a significant amount of time.

A symptom with high betweenness score will affect connections between other symptoms, and the removal of one will mean that symptoms will need to find other paths to travel, which might result in a collapse in the network. In this plot, it is led by PDUS, WPI and Tender Joints. This shows that even though inflammation is not well-connected in the graph, it still plays a vital role in how the symptom plots operate.

Expected influence accurately measures the nature and strength of each node, taking into account whether the association is positive or negative. Dysphoria and Anxiousness has the highest expected influence, followed by dysphoria and tender joints.

Expanded TITRATE-US Centrality

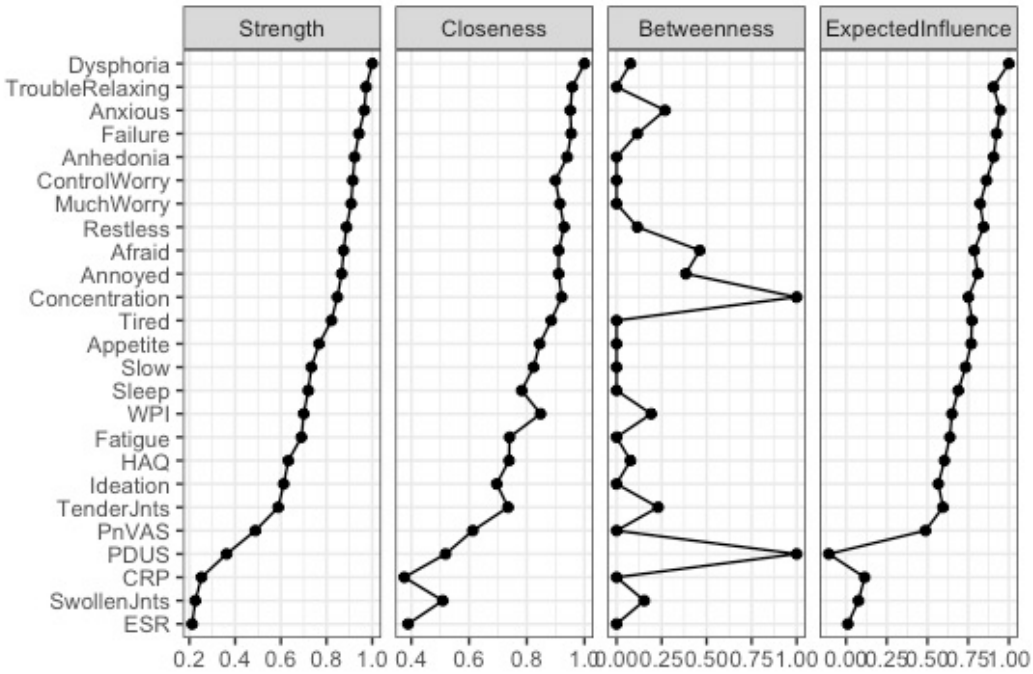


Figure 5.3: Centrality Rankings for Expanded TITRATE-US Plot

The network plot for Expanded TITRATE-US (B in Figure 5.1) is separated into 3 main sections again, with inflammation on the left side, and physical and psychological symptoms on the upper right and lower right respectively. Fatigue, a physical symptom is situated among psychological symptoms. This is likely because of the addition of more psychological symptoms, particularly the PHQ9 item relating to sleep and tiredness, pulled fatigue towards a symptom that connects the physical and psychological side. This may reflect fatigue being a potential bridge symptom between physical and mental symptoms. The table of all centrality values can be viewed in Appendix B, and Figure 5.3 shows the centrality values relative to other symptoms.

It is shown that Dysphoria, Trouble Relaxing, and Anxiousness have the highest degree centrality, with WPI and PDUS having the highest for physical and inflammation symptoms. The same symptoms are also the highest ranked ones for closeness centrality.. TPD has the highest betweenness centrality, followed by PHQ7 (Trouble concentrating). The possibility of fatigue being a bridge symptom is reflected in the centrality scores, where relative to the simplified plot, fatigue is scored much higher on every centrality score. It shows that with an emphasis on psychological symptoms in the plot, fatigue became the key

physical symptom to look out for in a patient. Fatigue being much more influential in this plot suggests that the addition of multiple psychological symptoms has a positive impact on how fatigue affects the total network.

Bridge Centrality for Simplified TITRATE-US

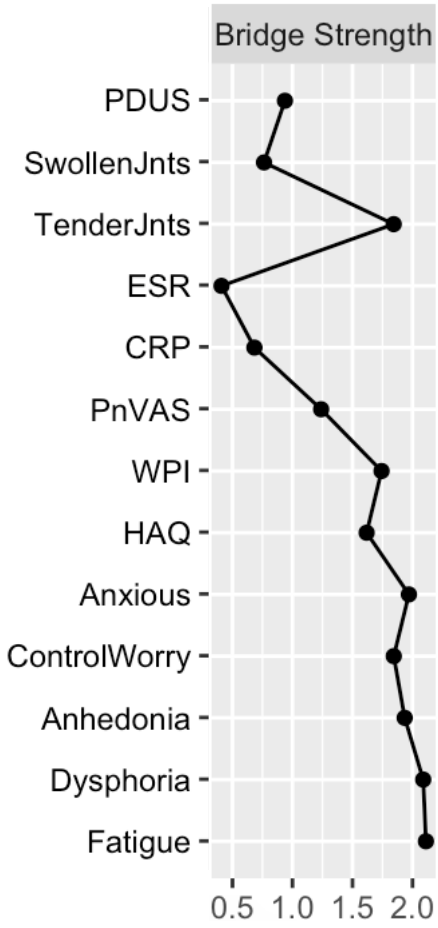


Figure 5.4: Bridge Centrality Rankings for Simplified TITRATE-US Plot

As shown above, the expanded TITRATE-US network was heavily affected by the additional psychological symptoms which resulted in most central symptoms to be psychological symptoms. This meant that in order to have a more accurate bridge symptom, the simplified TITRATE-US plot will be used instead. The network is split into three communities: inflammatory markers, physical symptoms, and psychological symptoms. It could be seen from Figure 5.4 that the nodes with the strongest bridge strength are fatigue and dysphoria respectively for physical and psychological symptoms. Inflammatory markers all have low bridge strength, which meant that there are not much impact from the

inflammatory markers to the other communities of symptoms. This reinforced the idea that psychological symptoms are very central to the symptom plots, and fatigue is the physical symptom that has the highest association with the psychological aspects in RA.

IMPARTS Network and Centrality Plot

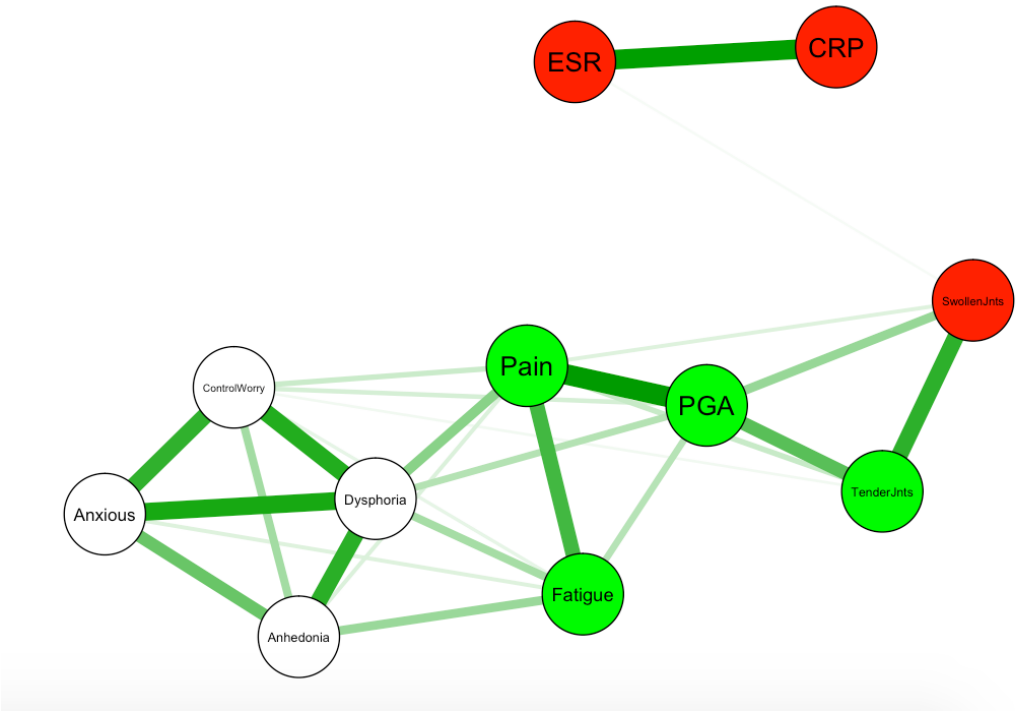


Figure 5.5: Network Plot for IMPARTS data

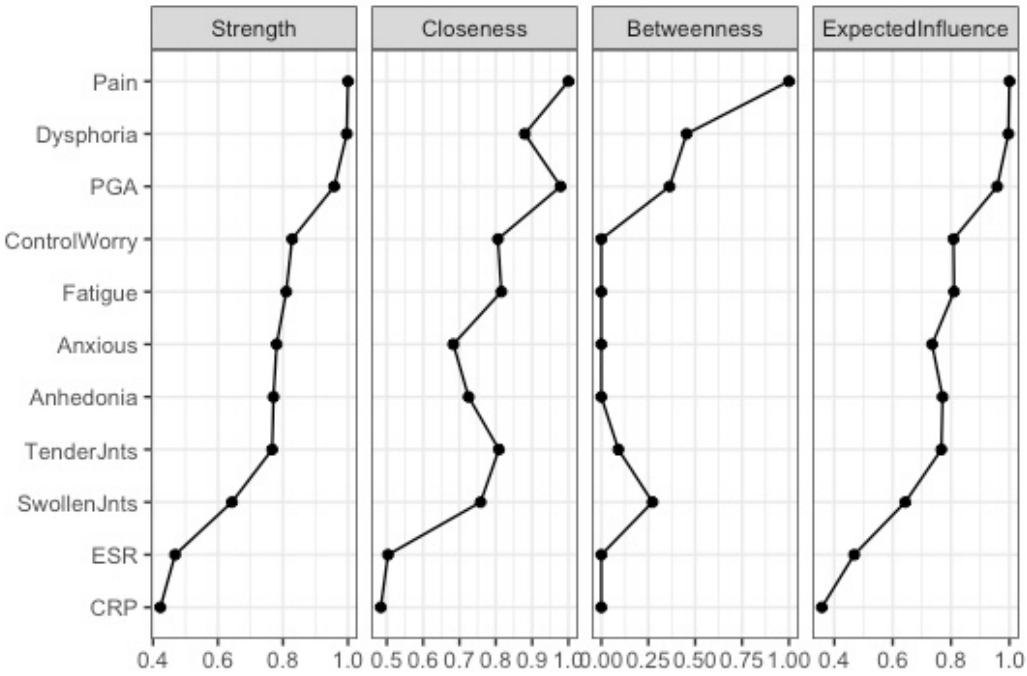


Figure 5.6: Centrality Rankings for IMPARTS data

Data from the IMPARTS sample were used to test the reproducibility of the network shown in the TITRATE dataset. Results shown from the IMPARTS dataset demonstrate a similar pattern of connection, albeit with a smaller set of nodes from variables that are routinely collected, as seen in Figure 5.5 above. This dataset affirms the TITRATE plot because there are several significant similarities between them. The symptom nodes are clustered respectively for psychological, physical and inflammation. The inflammation symptoms are also likewise very low on centrality scores. Psychological symptoms are also very strong generally except for pain that has the highest score

Figure 5.6 shows the centrality values in relation to each other and indicates that pain and dysphoria has the highest degree centrality, while pain, patient global and dysphoria has the highest closeness centrality. Pain and dysphoria again have the highest betweenness centrality, likewise with expected influence. Fatigue is being rated at a lower influence in this dataset compared to TITRATE. However, pain and dysphoria are the most influential symptoms in this dataset, and this is reflected in TITRATE as well. Dysphoria in particular is the psychological symptom that has the highest influence in both datasets, suggesting that mood of a participant is very important as to how their symptom plots react. Inflammation also does not appear to have a strong influence on the psychological symptoms for both datasets.

5.4.3 Stability analysis

Two graphs were created for each network plot to test the accuracy of both edge-weights and centrality. The first graph looked at the accuracy of edge-weights by comparing both bootstrap means and sample means, and the 95% confidence interval was shown as well. The x-axis is the edge strength of each edge, while the y-axis is each of the edges, but the labels will not be shown because of the large number of edges involved. The particular edge is also not of particular interest, because this section aims to test the overall robustness of the edge-weights. Any edge that has an edge strength of larger than or smaller than 0 will be seen on the network plot. The next graph showed centrality stability, which showed the correlation of each centrality at different percentage of subset of the sample with the original sample's centrality. This is to help calculate for the correlation stability coefficient (CS-coefficient). The CS-coefficient as mentioned in Chapter 4, is the maximum proportion of cases dropped such that there is still a 95% probability of the correlation between the centrality indices and the original centrality indices is 0.7 or higher.

IMPARTS:

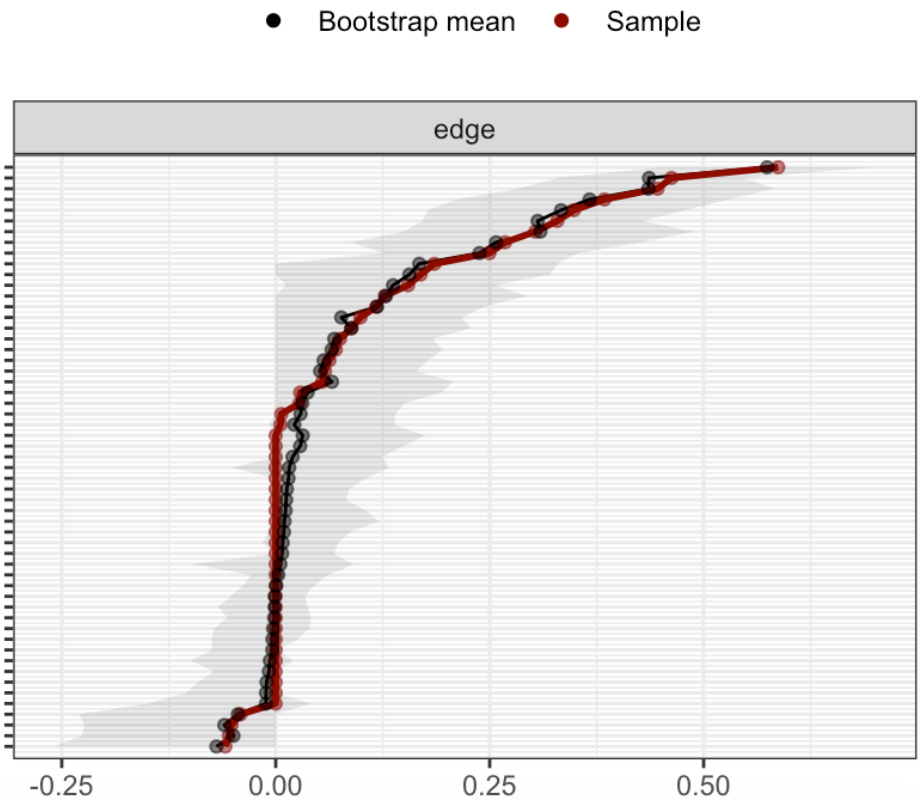


Figure 5.7: Graph for edge-weight accuracy in IMPARTS

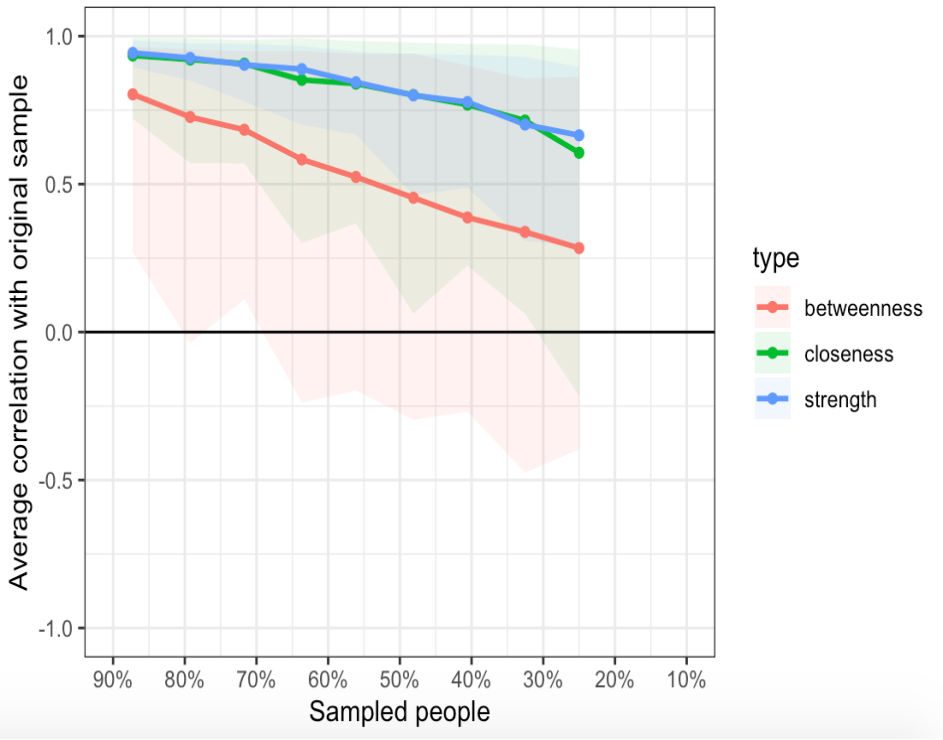


Figure 5.8: Graph for centrality stability in IMPARTS

Figures 5.7 and 5.8 were created to investigate the edge-weight accuracy and centrality stability of the IMPARTS network. Figure 5.7 showed edge strength on x-axis, and all the different edges on y-axis. Any edge that is larger than or smaller than 0 will be seen on the network plot. Figure 5.7 showed that the sample and bootstrap mean are quite close, with the sample underestimating some edge-weights which could have increased the number of links in the plot. However, the confidence interval is quite large around the mean, which means that across all the estimations, there is some variability. Overall, there is evidence to say the edge-weights can be confidently interpreted but should be taken with care.

Figure 5.8 showed the graph for centrality stability, which showed the correlation of each centrality at different percentage of subset of the sample with the original sample's centrality. This is to help calculate for the correlation stability coefficient (CS-coefficient). The CS-coefficient for betweenness, closeness, and strength are 0.052, 0.283, and 0.439 respectively. This meant that betweenness centrality scores for IMPARTS are not very stable, while closeness and strength are stable enough to interpret centrality differences, but not ideal.

Simplified TITRATE-US

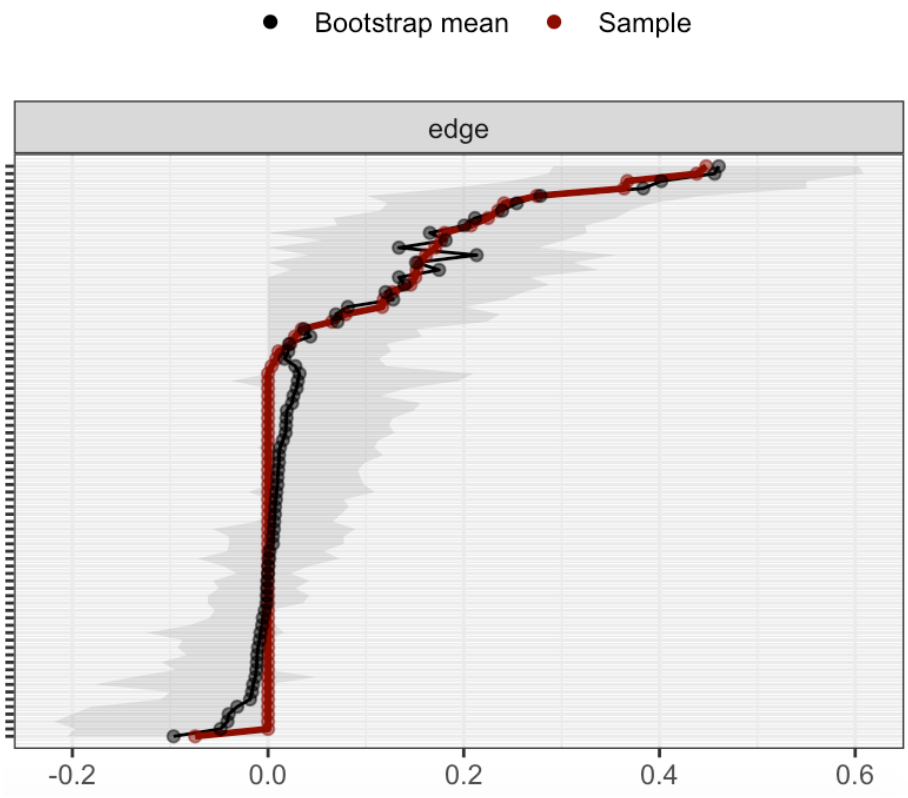


Figure 5.9: Graph for edge-weight accuracy in Simplified TITRATE-US

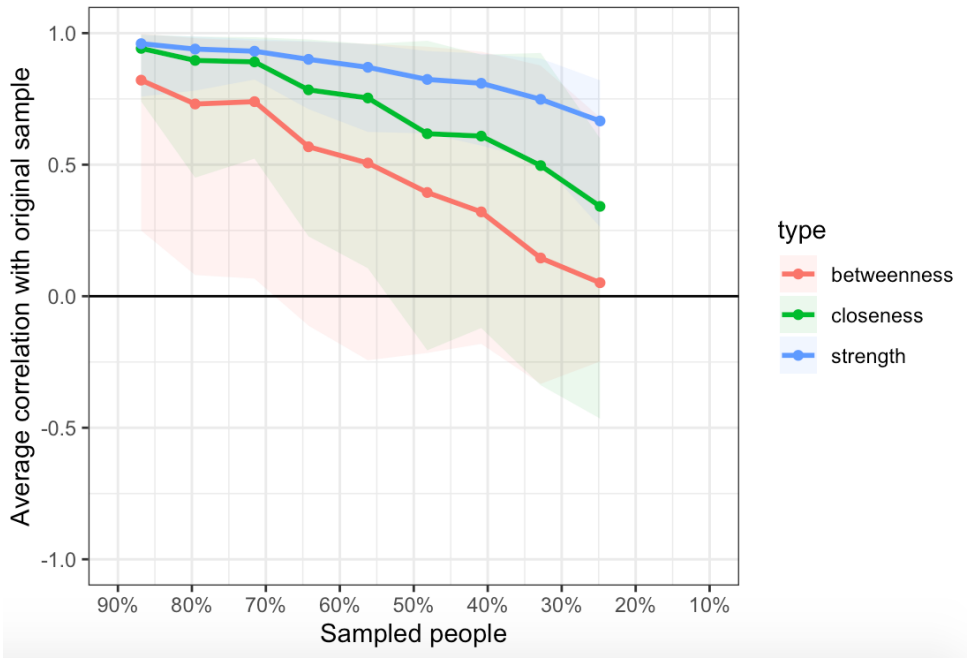


Figure 5.10: Graph for centrality stability in Simplified TITRATE-US

Figures 5.9 and 5.10 were created for the Simplified TITRATE-US network. Figure 5.9 showed that the bootstrap mean and sample mean were quite close, but should have included more edges in the network as some sample means were 0 when bootstrap mean were not. The confidence interval was large as well. This meant that the edges created were reliable but should be interpreted carefully when comparing between edges.

Figure 5.10 showed the correlation of centrality indices with the original centrality indices. It is calculated that the CS-coefficient is 0, 0.131, and 0.438 for betweenness, closeness, and strength respectively. This meant that both betweenness and closeness were not stable enough, but strength centrality was stable enough to interpret differences in node strength.

Expanded TITRATE-US

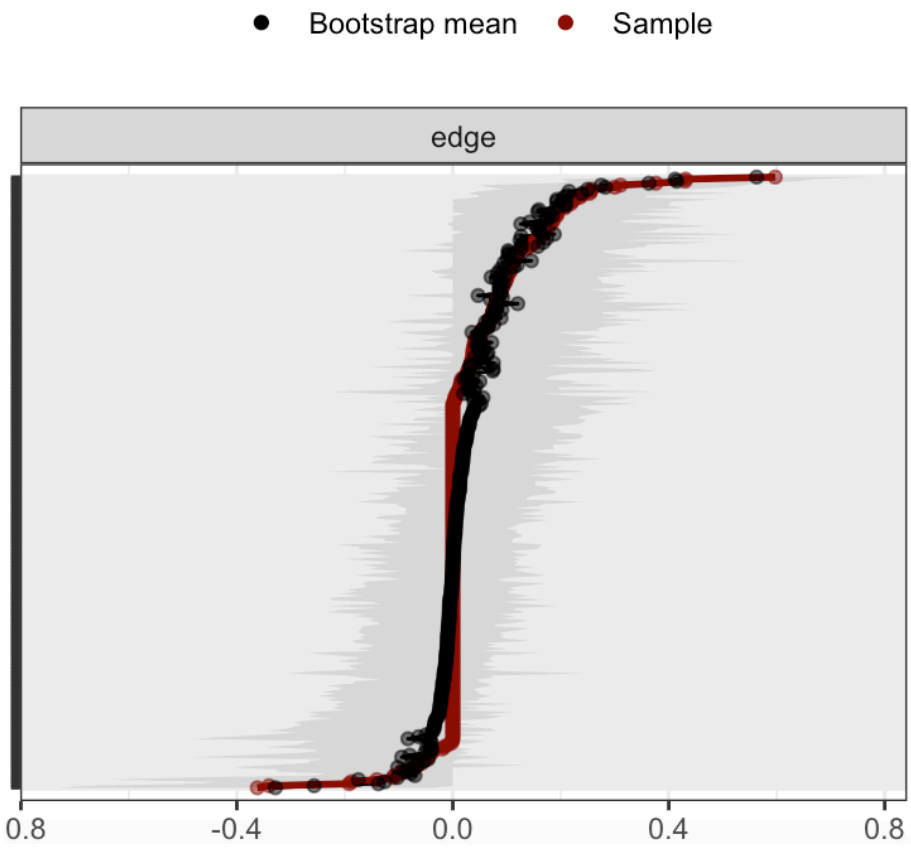


Figure 5.11: Graph for edge-weight accuracy in Expanded TITRATE-US

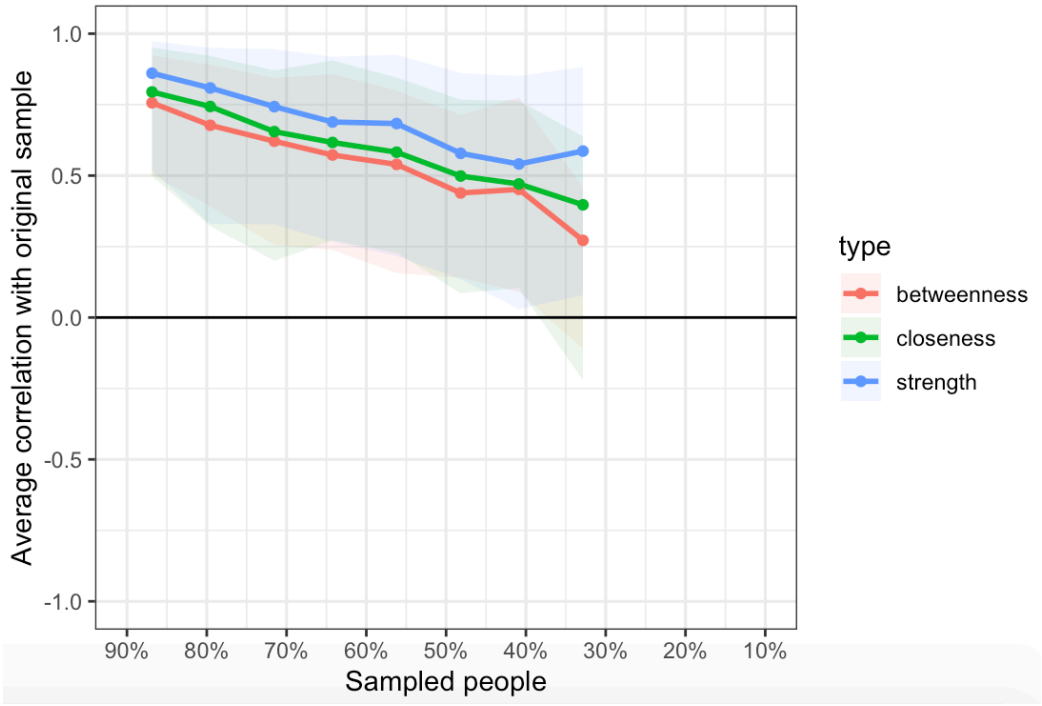


Figure 5.12: Graph for centrality stability in Expanded TITRATE-US

Figure 5.11 shows that the bootstrap mean and sample mean values are close, with the exception of some sample means interpreting the edge-weight as 0 when bootstrap means thinks an edge exist. The confidence interval is also quite large. This meant that the edges created are accurate but comparing between edges need to be considered carefully.

Figure 5.12 showed the stability of centrality indices. The CS-coefficient for betweenness, closeness and strength are 0, 0.051, and 0.051 respectively. This meant that the stability of centrality values are not very stable for all three centralities, and that comparing between nodes could be difficult. This is mainly due to the small sample size as the simplified TITRATE plot, but the addition of more nodes meant that the stability dropped even further.

5.5 Discussion:

Three network plots derived from 2 different datasets have been shown in this study, with consistent elements between them and existing literature to show the reproducibility of the findings and network plot in the TITRATE dataset. It has also allowed additional results to be

derived, which will be seen in the paragraphs below. There are some differences in between the two datasets as well, in particular how fatigue is interpreted. This can be explained by how fatigue is being scored, for example fatigue in IMPARTS is being scored on a 0-10 scale, while fatigue in TITRATE is being scored by the FACIT scale that considers more psychological aspects. There are also fewer nodes included in IMPARTS, which means that the full effect of fatigue may not be shown in comparison to TITRATE.

To answer the first objective, we need to look at the structure in both adaptations of the TITRATE data network plots. Inflammation symptoms including ESR, CRP, Total PD, and Swollen joints are very distinctively separate, while the physical symptoms (Tender joints, WPI, FACIT, HAQ, PainVAS) and psychological symptoms (PHQ and GAD) are on the other side, with less of a difference between them. The proximity of each type of symptoms to each other demonstrates that a change in one of the symptoms in that particular type will bring about a change in that cluster faster than others. FACIT score (fatigue) is the node that has the strongest connection to the psychological symptoms and it can be seen to be among the psychological symptom nodes in the B graph in Figure 5.1. Tender joints seem to be the main link between physical and inflammation symptoms. It can also be easily seen that inflammation symptoms do not have direct links to psychological symptoms, suggesting that the associations between these two groups is indirectly through physical symptoms. Inflammation symptoms do not have strong links with other symptoms, which suggest that doctors prescribing anti-inflammatory drugs will not be enough to cure patients of the other symptoms. A decrease in inflammation severity will lead directly to reduced tender joints, but if patients want to see a fast and direct effect on other symptoms like depression, a decrease in inflammation will not yield much benefit. This means that doctors need to treat not just inflammation for RA patients, but to be aware of the importance of other symptoms and how they affect the patients as a whole.

This network structure is also reflected on a different dataset, which exhibits reliability of the utility of network science on symptom plots in rheumatoid arthritis. There are also 3 distinctive sections in the less data heavy IMPARTS data, but the general gist of information that was presented above is also evident in this plot. This achieves the first objective of estimating a network structure of symptoms in RA. It can be seen that the distinctive types of symptoms do cluster among themselves, with the exception of fatigue.

Inflammation symptoms are very different from other symptoms, most often only being connected by one symptom node (swollen joints).

After achieving the network plot, further analysis can be carried out. A high degree centrality means that that particular node has many direct links, and thus a change in that node will have a major effect on many other nodes. Even though there are only four psychological symptoms out of the 15 total symptoms included in the network, dysphoria and anxiousness have the highest degree centrality. This hints towards how vital it is for doctors to not only care for the patients' physical health, but also consider their psychological health. An increase in the severity score of PHQ2 (dysphoria) in depression will thus lead to an increase in severity in multiple other symptoms, for example pain and cognitive function (Brown et al., 2002), fatigue (Ulus et al., 2011), and disability (Peck et al., 1989). Inflammation symptoms do not have high degree centrality scores, which can be partly explained by those symptoms being rather disconnected on the lower part of the network plot. However, one third of the symptoms included are inflammation, which shows that even though high inflammation scores suggest a high disease activity, symptom severity does not seem to share that association.

Closeness centrality shows how closely linked symptoms are, and a node with high closeness centrality scores can spread information quickly along a network, and in this case, affect other symptoms effectively. Dysphoria and Anxiousness do not have the highest closeness centrality scores, suggesting that even though they are directly linked with many other symptoms (which results in a very high closeness score), the distance they have between inflammation symptoms is too large to give a high overall closeness score. Physical symptoms like Pain and Tender joints have the highest closeness score, which coincides with the network plot showing physical symptoms being in the middle, and thus have the shortest distance to all other symptoms. This means that any change to these physical symptoms will allow in quick changes in severity across the network. If clinicians want to quickly address several symptoms that are spiking, treating one of the physical symptoms that are abnormally high should prove to be more useful than just providing anti-inflammatory drugs.

Betweenness centrality shows how influential a node is to the entire network. Nodes will always travel between each other using the shortest path. A high betweenness score will mean that that particular node is in the middle of the shortest path of a lot of other

nodes, and thus the removal of this particular node will cause a lot of the shortest path to be diverted, thus having a huge effect on the overall network. Interestingly, an inflammation marker, total PD has the highest betweenness centrality score. It can be explained that total PD is the only connection that the entire network has with ESR and CRP, and thus a high betweenness score is created because every node travels through total PD to create a shortest path to ESR and CRP. RA is caused by a high level of inflammation, and a complete removal of inflammation in a patient will naturally mean that the patient should suffer from no more symptoms and thus the network will fall. However, it is not possible for inflammation to be completely removed. This means that even though inflammation symptoms do not possess the same influence as other major symptoms like PHQ2, GAD1, and fatigue, it is still helpful to keep inflammation as low as possible. A low degree, but high betweenness score suggests that inflammation do not have much direct links to most symptoms, but its indirect association still plays a significant role in how the network plays out.

Expected influence, a concept coined by Robinaugh et al (2016), takes into account whether the edge weight (the correlation between two nodes) is positive or negative. Expected influence is only applied in weighted networks, which means that the there is an accurate association value between nodes instead of just 0 or 1, indicating whether there is a link or not. This is applied in this case because the regularised correlation shows that there are quite a lot of negative edge weight especially between total PD and other symptoms. Expected influence will thus be able to more accurately measure the weight and importance that any node has to the network. Robinaugh et al (2016) argues that a symptom with a lot of negative edges should not be classified as just a highly problematic node, but instead could mean that it will reduce the severity of other nodes. Total PD has the highest negative edge weight with Fatigue (-0.23 and thus not shown on network), which is interesting because it suggests that an increase in inflammation coincides with a decrease in fatigue. This could be due to patients with high inflammation being more unlikely to have less exercise, and thus less corresponding fatigue. The psychological symptoms, Dypshoria and Anxiousness have the highest expected influence which coincides with the centrality scores. This shows that psychological symptoms play a very important role in patients' suffering in RA and has a large impact on many other symptoms in the network.

Bridging symptoms are key symptoms that connect between different areas of a symptom plot, which is something that will be of interest in this scenario in which we can estimate the symptom that led to such serious psychological symptoms in RA. However, no formal quantitative method exist yet (Jones et al., 2021), and a common way with high sensitivity (92.7%) and specificity (84.9%) is to look at bridge strength centrality. It is shown that fatigue is the physical symptom that has the highest bridge centrality score, while dysphoria has the highest score for psychological symptoms. Inflammatory markers all have low bridge centrality scores, which meant that there is not much influence on the other symptoms.

Overall, psychological symptoms play a much bigger role in symptom networks in RA patients than expected. Mood in particular score the highest among several criteria, suggesting that a spike in low mood will play a big part in how other symptoms react. However, it is also shown that physical symptoms are very significant, and that with the high closeness centrality score, an immediate lowering of physical symptoms' severity will lead to a quick effect on other spiking symptoms. This means that physical symptoms should be prioritized, instead of inflammation if physicians are looking for a treatment with fast effect on patients' overall health. Evaluating the difference between physical symptoms' centrality scores between the two TITRATE plot show that fatigue is scored much higher in the plot with the full PHQ and GAD symptom nodes. PHQ9 and GAD7 adds to a total of 16 psychological symptoms, which is 64% of the total 25 symptoms included in the expanded TITRATE plot. With how closely connected psychological symptoms are, it is logical for these symptoms to have the highest centrality scores. This seem to suggest that fatigue is much more connected to psychological symptoms than other physical symptoms, suggesting the possibility of fatigue being the bridging symptom between Rheumatoid Arthritis and Depression. This is also affirmed by the bridge strength score that ranked fatigue as the symptom that has the highest influence on other communities. This makes sense because fatigue is regarded to have both physical and mental aspects (Mehta & Parasuraman, 2014). This means that a network plot that contains more psychological symptoms will make fatigue more central to the entire network which is reflected in the difference of the network plot for parts 1 and 2 of the TITRATE dataset. PHQ2 (mood) is the other symptom that has high overall scores with the possibility of being the bridging symptom. This shows

the duality of symptoms in RA and how important it is for clinicians to consider the psychological symptoms in patients when regarding the health and well-being.

Having achieved both of the objectives, this study has shown that network science is indeed a valid and feasible method to utilize in looking at symptom severity in RA. It has allowed many symptoms to be included in the analysis and showed the distinctive clusters that different types of symptoms form. Common conceptions of symptoms are also reflected here, for example the influence of pain, the importance of inflammation and the strong associations between physicianVAS and swollen joints. The inclusion of a different dataset to affirm the network plot also helped with the reliability of this methodology. Network science revealed new findings, in particular fatigue being the main bridging symptom and the importance of psychological symptoms as a whole to RA patients. This can be interpreted as a connected finding because the importance of psychological symptoms increased the importance of fatigue, a physical symptom with strong links to the psychological aspects as well. Pain has always been the symptom that is heavily focused on by clinicians when prescribing treatment, but the revelation of fatigue as a bridging symptom should shift the focus. The dynamics of fatigue is something that needs to be considered and should be further researched on as to how does fatigue get activated in a RA network plot.

Even though there are no current studies that looked at more than 3 symptoms in a longitudinal dataset, there are existing studies that looked at symptom associations in a cross-sectional format, using structural equation modelling approaches. These studies provide further rationale in exploring symptom interactions across many symptoms temporally. For example, a study consisting of 228 RA patients looked at fatigue using structural equation modelling (Rongen-van Dartel et al., 2016) discovered that there are multiple dimensions to fatigue, that these are directly influenced by sleep and physical functioning, and indirectly influenced by mood and pain. Furthermore, a different study that consists of 108 RA patients (Nicassio et al., 2012), also looking at fatigue using structural equation modelling, discovered that sleep quality, disease activity and mood are the main influencing factors for fatigue. While these studies provide important insights there is an important limitation of this approach. Specifically, the ‘network’ of symptoms in these studies study is still relatively limited, particularly in the number of endogenous variables that can be included, and the associations must be specified directly as regression paths

that are assumed to be causal, though in reality cannot be (Hofmann et al., 2020). While the number of endogenous variables included is not typically an issue for structural equation models based on cross-sectional data, models with large numbers of endogenous variables applied to longitudinal data become increasingly difficult to estimate and interpret (as will be considered in the next chapter). Furthermore, control for confounding across highly related variables can be problematic leading to the overestimation of some coefficients, that require shrinkage, and underestimation of other (Epskamp & Fried, 2018). A network approach solves both of these problems (Hofmann et al., 2020). Though, as both structural equation modelling and some network approaches can be seen as extensions to the standard general linear model, it is possible to consider a network approach as essentially an extension to structural equation models. In fact, generalisations combining features of structural equation models (e.g. latent variables) within network approaches are available (Epskamp, Rhemtulla, et al., 2017). Combined this evidence point strongly to the need for the use of network approaches in RA to further the understanding of the complex dynamical association between individual symptoms over-time.

One of the major weaknesses of this methodology is the inability to see the direction of the edge. This is due to the nature of the dataset, and thus a longitudinal dataset is required to ascertain the direction. The revelation of direction in a network plot will enable more understanding in between symptoms, and allow researchers to try and gauge causality. The problem of a bridging symptom is also more likely to be solved with the inclusion of longitudinal data. Fatigue is calculated using questions 1, 3 and 7 of the FACIT scale, and a possible method to improve on this study is to separate fatigue into these 3 components in the network plot. This study has shown that fatigue is a major symptom to be considered, and thus a deeper dive into how components of fatigue affect other symptoms will be very helpful for clinicians. It will also be important to see how inflammation is connected to the components of fatigue, because inflammation is very often the activator in a RA network plot. It is also important to note that both studies involved in this data analysis were cross-sectional studies which means that the results derived from this analysis should be considered with care, and not be taken as direct evidence of causal links. Significant associations that derive from cross-sectional datasets are not sufficient to show either the direction of the association let alone a causal link between the variables. Though, were an association is not observed there is strong evidence

against a causal link. This chapter can be considered as more of an assessment of the utility and the feasibility that looked at the possibility of using network approach to analyse a large amount of data and variables. As such, it provides an indication of the topography of symptoms through a biopsychosocial continuum, and manages to reflect current literature and also show promise in divulging new associations through further analysis

The results from this study show that network analysis of cross-sectional data coincides with a lot of existing study on the findings. Pain, fatigue are symptoms that plays a major role in how a RA patient experience life daily, and that inflammation is an important key to having low overall disease activity. However, it also shows that common treatments currently (anti-inflammation drugs) are not always enough to treat patients, especially those with a high psychological severity score. GAD1 and PHQ2 have very high degree centrality scores and expected influence in the network plot, and thus are important symptoms to watch out for as well. Network structure of a RA symptoms has been estimated using different datasets, and the possibility of a bridging symptom is also investigated, thus reaching the aim of proving the feasibility of network science in RA. This study can be improved though, in terms of using longitudinal data that will have provide the possibility of looking at direction of influence, and causality.

6. Longitudinal Assessment and Effects of Symptom Variability

6.1 Overview of Longitudinal Assessment and Effects of Symptom Variability

This chapter uses the longitudinal data collected in the IA-COVID study that is during a time with no governmental restrictions. Even though there are no governmental restrictions, it is important to note that RA patients were advised to engage in shielding practice during the pandemic (Mikuls et al., 2021). This means that RA patients were likely to still be relatively isolated from the public and social distancing since quarantining was strongly encouraged even during periods of no governmental restrictions. The main IA-COVID study, a prospective observational study of 338 people with inflammatory arthritis over one year from June 2020 to June 2021 identified that in June 2020, 79.9% of respondents reported social distancing by staying at home all or most of the time. This shielding naturally leads to social isolation for many people, which has implications for their mental health (Cook et al., 2021).

This builds on the previous chapter by utilising network science to look at individual symptom plots, and also the inclusion of analysing longitudinal data to explore the symptoms. The purpose of this chapter was to check if there are any diurnal variations in symptoms, and also uses a mixed effect model for the first time in this thesis to test for temporal associations. Furthermore, the effect of symptom variability is also investigated by the use of network science. This Chapter is adapted from one of two IA-COVID papers that will be published, and thus there will be repetitions in introduction and methodology.

6.2 Introduction

Inflammatory arthritis (IA), including rheumatoid arthritis (RA), psoriatic arthritis and ankylosing spondylitis are chronic inflammatory disorders, which may lead to disability, and increased comorbidity and mortality risk (Lee et al., 2018; Scher et al., 2020; Smolen & Aletaha, 2015). IA has many symptoms, including most commonly joint stiffness & swelling, pain, and fatigue, plus other factors associated with comorbidities such as low mood (NHS,

2019). Managing the severity of these symptoms is the focus of most treatments and research, but several studies (Finan et al., 2010; Smith & Zautra, 2002) highlighted the fluctuating nature of these symptoms, which typically vary across weeks and days. Research on IA symptoms over-time is generally confined to assessment that are months or even years apart, limiting our understanding of fluctuations in symptoms over shorter periods.

A study considering biomarkers in arthritis (Kong et al., 2006) indicated that there needs to be a standardized time for biomarker samplings such as serum hyaluronan (HA) and high-sensitivity C-reactive protein (hsCRP) because of the significant variations throughout a day. Biomarkers reflect the level of disease activity (Boyd et al., 2020), and thus this diurnal variation in biomarkers will most likely suggest that symptoms fluctuate throughout a day as well. It has been established that pain, fatigue and stiffness vary from day-to-day (Schanberg et al., 2003; Zautra et al., 2007). However, no studies have objectively considered intra-day fluctuations. Diurnal variation in stiffness has been considered, with early morning stiffness being a classic feature of rheumatoid arthritis (Scott, 1960), but patterns for pain and fatigue currently have not (Harkness et al., 1982). Intra-day variations have been investigated in other conditions, for example cancer where fatigue, sleep, depression, and activity are looked at before and after infusions to see if there are any differences (Jim et al., 2011). It was shown that there are significant changes in all symptoms measured after infusions, and that associations between symptoms changed as well after infusions. It has also been established that there are diurnal variations in depressive symptoms, with an exacerbation in early morning classified as part of the DSM criteria (Wirz-Justice, 2008). The variability of mood in particular has been investigated in several studies that looks at mood in depressed patients and gender differences in mood (Adan & Sanchez-Turet, 2001; Haug & Fahndrich, 1990). It is also established in a systematic review by Dickens et al (2002) that there is a strong association between depression and arthritis, which suggests the fluctuant nature of mood which is a key symptom in depression, is likely to be influential in patients with arthritis as well.

The scoping review in Chapter 3 demonstrated that most studies only capture less than three symptoms over a limited number of data points, and without examining dynamic changes over time specifically while focusing mainly on the associations between symptoms. These studies mostly only gather 1 to 3 data points a day, or in studies where there are more than 5 data points a day, is only carried out for a week. None of the studies

also looked at how symptom variability may be an independent predictor of symptom outcomes. This means that studies have been unable to reveal diurnal variations and fluctuations of symptoms over-time. Intensive longitudinal data capture, through ecological momentary assessment (EMA), allows for symptom severity to be tracked throughout the day; allowing for the possibility of symptom variabilities to be explored (Kratz et al., 2017). A recent systematic review of the use of EMA in chronic pain (May et al., 2018) shows the feasibility of using EMA for pain, which is one of the main symptoms of IA. A total of 105 papers from 62 projects of EMA in pain research is included in this review, showing the availability and feasibility of using EMA in pain. It was also discovered that most of these studies studied the within-person associations between pain and other variables, showing the potential uses of intensive longitudinal data for each participant. The average completion rate among those projects were 86%, suggesting the viability of using EMA. However, none of these studies were related to IA, showing the gap in literature.

EMA studies capturing multiple symptoms are challenging to analyse because of the number of possible interrelations between variables that can be considered. The network approach to psychopathology by Borsboom (2008b) considers disorders as an interacting system of mutually reinforcing symptoms that considers the associations between all symptoms. This theory has been gaining traction and is a growing area of research interest (Robinaugh et al., 2020). Symptom networks can readily be extended to incorporate physical as well as psychological symptoms, ideal for looking at comorbidities (Cramer et al., 2010). Network models may provide additional insights into within-day symptom fluctuations by demonstrating the strength of the association between different symptoms over-time.

6.3 Aims and Objectives:

The aim of this study is to investigate within-person variability in symptoms of physical and mental health in a sample of people with inflammatory arthritis over a period of ten days. It is important to investigate whether collecting intensive longitudinal data is useful, and necessary to provide extra information that cross-sectional data could not. This will be achieved through these objectives below:

1) Determine variability in symptoms of physical and mental health during the day.
2) Identify temporal associations by looking at how physical symptoms, mental symptoms, and physical activity are influenced by previous time points'.
3) Are there any differences in symptom network plots between patients with fluctuating data compared to one with not much changes throughout the 10 days?

6.4 Methods

6.4.1 Patients and Study Design

Participants who had participated in the main IA-COVID observational study and consented to contact for further studies were contacted via email, where they were sent a participation information sheet and consent form. This email invited the participants to participate in two further studies, a telephone interview study and the EMA component that Chapters 6 and 7 are based on. Only those that indicated consent for the EMA component were then further emailed to be invited to participate in the EMA sub-study. Recruitment was done in batches on a weekly basis until the minimum target sample size for each of the sub-studies was achieved.

This prospective observational study used an EMA approach, with participants providing assessments six times per day for a period of ten days. Specifically, surveys were sent at 9am, 11am, 1pm, 3pm, 5pm and finally at 8pm asking participants to complete ratings of physical and mental health symptoms, plus information about activities and social interactions in the last hour. The final survey at 8pm contained additional questions regarding functioning during the day and sleep during the previous night and during the day. This study received approval from the King's College London Research Ethics Committee (Ref Number: LRS-19/20-18186). Data were collected during July and August 2020, during a period when pandemic related restrictions were relatively relaxed. Participants were recruited from the IA-COVID study, a mixed-methods prospective study which recruited a participant pool in June 2020 through communications on social media (i.e. Twitter,

Facebook) and also through charities (e.g. Arthritis Action). Participants in the IA-COVID study provided consent for contact for potential recruitment to further studies. In total, 338 patients were recruited to the IA-COVID study, of these 328 (97%) provided consent for contact. We approached a total of 218 participants to achieve our target sample size of at least 30 participants; recruiting 31 in total. Similar sample sizes were recruited for other longitudinal studies involving EMA and musculoskeletal disorders (Tung et al., 2021). Initially, the APPro study was supposed to be carried out before but due to the COVID-19 pandemic, it was delayed. This means that this study was then designed and carried out during the pandemic to collect data. Thus, the sample size here is based on that of the APPro study and presented as an opportunity as a pilot for both the data collection methods (EMA Surveys) and also the sample size.

One participant had no data for the baseline survey, and thus is omitted from the study, resulting in only 30 participants. Participants were only recruited to participate in the EMA sub-study upon consent of the original baseline survey study. This means that there might be an issue with the ID generated, for example the ID did not get automatically pulled through from the invitational email link to Qualtrics due to a technical error, which cause a patient's baseline data to not be linked to the EMA data. Another possible reason is that someone passed on the link to the EMA study to a friend, which resulted in there being no baseline data related. The surveys that are sent to the participants can be seen in Appendix C.

The inclusion criteria for the IA-COVID study were a diagnosis of inflammatory arthritis (e.g. rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis), at least 18 years of age, and living in the UK. We did not have any specific exclusion criteria that were applied for this study, though individuals without access to a mobile phone with internet capability would have not been able to sign up.

6.4.2 Measurements

Questions regarding physical symptoms were asked six times a day, using a numerical rating scale (NRS) from 0 to 10, with 0 being none, 5 being moderate and 10 being extreme. The symptoms included are pain, fatigue, and joint stiffness. Pain and fatigue are the most commonly included physical symptoms in EMA studies in musculoskeletal disorders, with

pain appearing in 17/21 studies and fatigue in 3/21 studies (Tung et al., 2021). Joint stiffness is included because it is very common in IA patients and also associated with inflammation, which is key in IA (Khurana & Berney, 2005).

Psychological symptoms, including both positive affect and negative affect were also asked six times a day, using the same scale as the physical symptoms. These symptoms include lonely, anxious, irritable, content, enthusiastic and cheerful. These measurements were chosen to fairly depict both positive and negative affect and also include both high valence and low valence psychological symptoms. Irritable and Enthusiastic are symptoms taken from Positive and Negative Affect Schedule (PANAS) that is developed by Watson, Clark & Tellegen (1988). Anxious and mood symptoms like content and cheerful are included to get a gauge of participants' depression and anxiety states, while loneliness was chosen because it is significantly associated with both depression and anxiety (Ebesutani et al., 2015).

There are three physical symptoms, three positive affect symptoms and three negative affect symptoms so that all aspects of participants' symptoms can be measured. The number of symptoms included in the study were capped at nine to prevent over-burdening the participants with too many questions. Pilot tests have been run that ensured 9 measurements to be a suitable number. More symptoms could have been included, however because of the number of times that participants have to follow up, it has been decided that there should be a limit on the number of symptoms recorded so that participants will not be over-burdened.

The use of the numerical rating scale from 0-10 is acceptable in this case, as it has been validated for use in pain by three different datasets in a study by Von Baeyer et al (2009). Although the visual analogue scale (VAS) is the most popular and reliable method of measuring pain (Bijur et al., 2001), the NRS has been shown by Bijur, Latimer & Gallagher (2003) to be a reliable substitute. The NRS has also been established as a reliable and valid scale for fatigue (Nicklin et al., 2010). Three new variables are also created from the aforementioned nine measurements, named physical symptom, positive affect and negative affect. Physical symptom includes the average score for pain, joint stiffness, and fatigue, positive affect includes the average score for content, enthusiastic, and cheerful, and negative affect includes the average score for lonely, anxious, and irritable. These average

scores were created so that we can look at each aspect of symptoms as a whole and to allow analysis between each aspect easily.

The rest of the measurements were recorded once a day, at 8pm because of the static scores. These include daily well-being questions which were scored using the same NRS, including questions about joint and muscle symptoms, problems performing tasks, enjoyment from tasks and social interactions and support available throughout the day. These questions were asked only once a day because they are unlikely to vary as much throughout a day, or are regarding the culmination of the whole day, for example the social interaction questions. Participants were also asked if they may have COVID-19, or are experiencing any of the symptoms including fever, difficulty breathing, coughing, headache, and loss of smell/taste. These questions were asked because severe COVID-19 symptoms would impact on the survey answers from before, and thus will have to be checked. The hours and quality of sleep from the previous night, and if there was a nap during the day were also asked. Sleep is an important variable to investigate because sleep pattern is significantly associated with pain in Rheumatoid Arthritis (Drewes et al., 1998). RA patients are also shown to have poor sleep quality overall, with a significant association with depression as well (Goes et al., 2017). This shows that sleep has a connection with both the physical and psychological aspects of IA, and thus will be important when looking at variability in those symptoms over time. One of the main strength of EMA methodology is the elimination of recall bias since participants are asked questions that concern the current situation. However, questions regarding sleep are only asked at the end of the following day at 8pm for this study. It was designed this way because of input from expert patients that indicate the preference for minimising response burden by having only one longer questionnaire each day that has additional questions asked once per day. Furthermore, with the need to enquire about naps throughout the day, it is not possible to ask questions regarding sleep at the beginning of each day. This means that in a bid to balance patient burden, it is necessary to ask questions regarding sleep quality in the last measurement of the following day.

6.4.3 Statistical Analysis

In order to commence with analysis, the survey data has to be manipulated into a form that can be used in STATA first. Time variables are recoded to allow for a time series analysis to be set up. This is done by creating variables for each day, and also each time of day and combining them together to create a unique time point for each input. Some variables, for example physical activity and COVID-19 symptoms are also re-coded to enable analysis.

Missing data were looked at to make sure that there was enough longitudinal data to be analysed. Participants were included in the analysis if there are consecutive measurements collected on least five days. It was also being observed if there is a particular time or day that data collection dropped. This is done by creating bar graphs for each time interval, and day interval with the y-axis showing the percent of surveys completed at each interval.

Descriptive statistics including mean, within and between person standard deviation were carried out. This shows how variables vary between participants and within participants throughout the study. Histograms were also created for physical symptoms, positive affect, negative affect, and physical activity to see the general distribution of scores. Line plots were then created for each symptom relative to the 6 time points to display how the symptom scores vary throughout the different time points from 9am to 8pm. This addressed the first objective of looking at variability throughout a day. Effect size were also calculated for each of the symptoms to see if the variability is significant. This is done by dividing the difference between the highest point and lowest point of the line chart by the between standard deviation. It is important to look at effect size instead of just p-values because while with a large sample, a statistical test will ultimately demonstrate a significant difference even where the actual difference is negligible, and effect sizes are not influenced by a large sample size (Sullivan & Feinn, 2012). Furthermore, effect size also helps to determine the size of the effect and helps to inform about situations where a non-significant finding may be a Type 2 Error and an effect exists, for example, when the test is underpowered. The framework for which effect size is being interpreted follow Cohen's rules of thumb for interpreting a mean difference standardised against the pooled standard deviation (termed Cohen's d), where a small effect size is considered to be 0.2, medium effect size 0.5, and large effect 0.8 (Selya et al., 2012).

To achieve the second objective, lagged variables are created for each of the main symptoms, which is a variable that starts in a preceding period. This allows researchers to investigate associations not just between variables, but also between different time points of each variable. To calculate temporal associations, lagged variables need to be detected for association with the original variables. A cross-lagged correlation table is created first to observe for any possible connections between variables and the lagged counterparts. After establishing possible connections, the time-series data was then used in a dynamic autoregressive model to look for direction between any associations between variables. Mixed effects regression was carried out to test for significance between variables and lag-1 variables, and these mixed models were used to account for observations nested within patients, and the correlation between the residual errors follow an autoregressive process of order 1. The significant associations were then exported to a panel model to be displayed in the results section

In order to address the third objective, line plots for the severity of symptoms over the 10 days for all participants were created. From these plots, 4 participants were chosen, one with very high variability of symptoms, one with a flare in symptoms, and two with low variability but varies in severity. Only 4 was chosen out of the sample because it was only necessary to choose participants with different variability of symptoms, and only qualitative output was derived from the network plots. These network plots will allow further understanding of how the fluctuant nature of symptoms affect participants and the interactions between symptoms. Any notable differences between a fluctuant symptom network plot and a stable symptom network plot may allow researchers to understand the dangers of symptom variability in IA. After choosing the four participants, a correlation matrix for each was created and then a network plot derived from those.

The analysis was mostly carried out in STATA including the line plots for the third objective. Only the network plot was created using *qgraph* in R.

6.5 Results

6.5.1 Demographics and Descriptives

Two additional participants were excluded in the further analysis of participants because not enough longitudinal data were achieved; out of 60 possible data inputs, they only

contributed four times and 13 times respectively. The 28 included participants have had a mean of 50 entries. Table 6.1 shows the demographics for all.

Table 6.1: Demographics

		N = 30
Age (Mean (Range))		47.9 (38-59)
Gender	Male	7 (23.3%)
	Female	23 (76.7%)
IA Subtype	Psoriatic Arthritis	16 (53.3%)
	Rheumatoid Arthritis	7 (23.3%)
	Spondylarthritis	4 (13.3%)
	Connective Tissue Disease	3 (10.0%)
Diagnosis Year		2011 (2006-2018)
Ethnicity	White	27 (90.0%)
	Black	1 (3.3%)
	Mixed	2 (6.7%)
Education	No formal education	2 (6.7%)
	O levels	2 (6.7%)
	A levels	10 (33.3%)
	Undergraduate	8 (26.7%)
	Postgraduate	8 (26.7%)
Smoker	Never smoked	15 (50.0%)
	Ex-smoker	10 (33.3%)
	Current smoker	5 (16.7%)
BMI		29.2 (24.8 – 33.2)

6.5.2 Missing Data

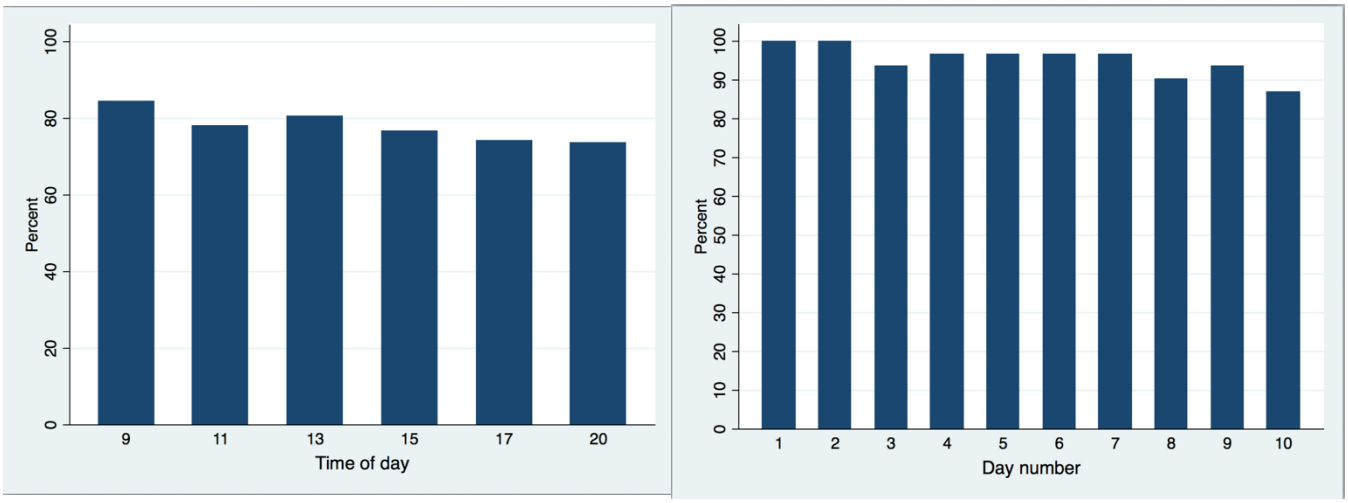


Figure 6.1: Percentage completed for each day, and each time of day.

From the 28 participants included in this study, it is important to see how much missing data there are and if there are any particular time or day that may stand out. There is a general downward trend of completion from 9am, but there is still about a 75% completion rate at 8pm. The first two days of the study have a 100% completion rate, with a slight dip in day three. It rose again for a constant percentage from day four to day seven which suggests that the dip is likely not very important. The percentage completed each day never drops below 87% though, which shows quite a constant participation throughout the study.

Figure 6.2 below shows the respective percentage for each score of the three main aspects of symptoms, and physical activity (physact). It shows that the average scores for physical symptoms (physymp) and positive affect (paffect) are quite close to 5, while negative affect (naffect) seems to be very low, with 50% having a score of 0 or 1.

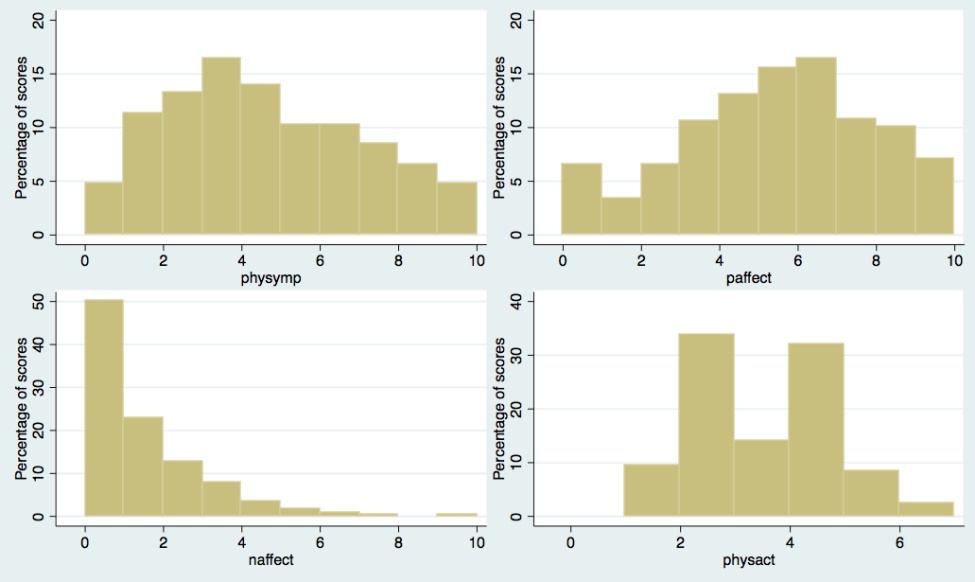


Figure 6.2: Distribution of percentage of scores for physical symptoms, positive affect, negative affect and physical activity

Table 6.2: Descriptive Statistics for Symptoms

Variables	Number of participants (average number of assessments)	Mean	Between S.D.	Within S.D.
Pain	28 (50)	4.2	2.6	1.2
Joint stiffness	28 (50)	4.4	2.4	1.3
Fatigue	28 (50)	4.4	2.6	1.5
Loneliness	28 (50)	0.6	0.8	1.0
Anxiousness	28 (50)	1.4	1.6	1.4
Irritable	28 (50)	1.5	1.4	1.6
Content	28 (50)	5.3	2.1	1.8
Enthusiastic	28 (50)	4.8	2.0	1.7
Cheerful	28 (50)	5.5	2.3	1.7
Joint pain effect	28 (8.4)	4.7	2.3	1.2
Difficulty performing task	28 (8.4)	4.3	2.4	1.4
Enjoyment from task	28 (8.4)	5.8	1.5	1.7
Satisfaction from social interaction	28 (8.4)	6.3	1.9	1.9
How supported they feel	28 (8.4)	6.2	1.8	1.9
Quality of sleep	28 (8.4)	5.2	1.8	1.5

Table 6.2 shows the descriptive statistics for all symptoms measured in this study. Both between and within person Standard Deviation are shown here. Between-person standard deviation describes the variation of symptom severity scores between different participants, while within-person describes how a certain symptom varies within a participant throughout the study. For example, pain has a between-person standard deviation of 2.6,

and a 1.2 for within-person standard deviation. This showed that pain scores vary much more between participants, compared to how pain scores vary throughout the study for each participant. A symptom score with very high within-person standard deviation, for example irritable with a score of 1.608 compared to 1.409 for between-person, signifies that irritability scores are quite similar for all participants, but has a large variation for each participant throughout the study. Within-person standard deviation thus allows a quick look into the variability of symptoms, albeit for the whole duration of the study. This means that in order to address the first objective, diurnal variation needs to be looked at to see how symptoms vary through the course of a day. Table 2 shows that the average score for negative affect is relatively low (range of 0.6 to 1.5) compared to positive affect (range of 4.8 to 5.5). The standard deviation of negative affect is high, suggesting that negative affect is prone to fluctuations throughout the study. Only four variables have a within S.D. that is higher than between S.D., and 2 of the variables, loneliness and irritability, are negative affect symptoms. This seems to suggest that negative affect is relatively stable between participants, but varies throughout the study for each participant more.

6.5.3 Diurnal patterns

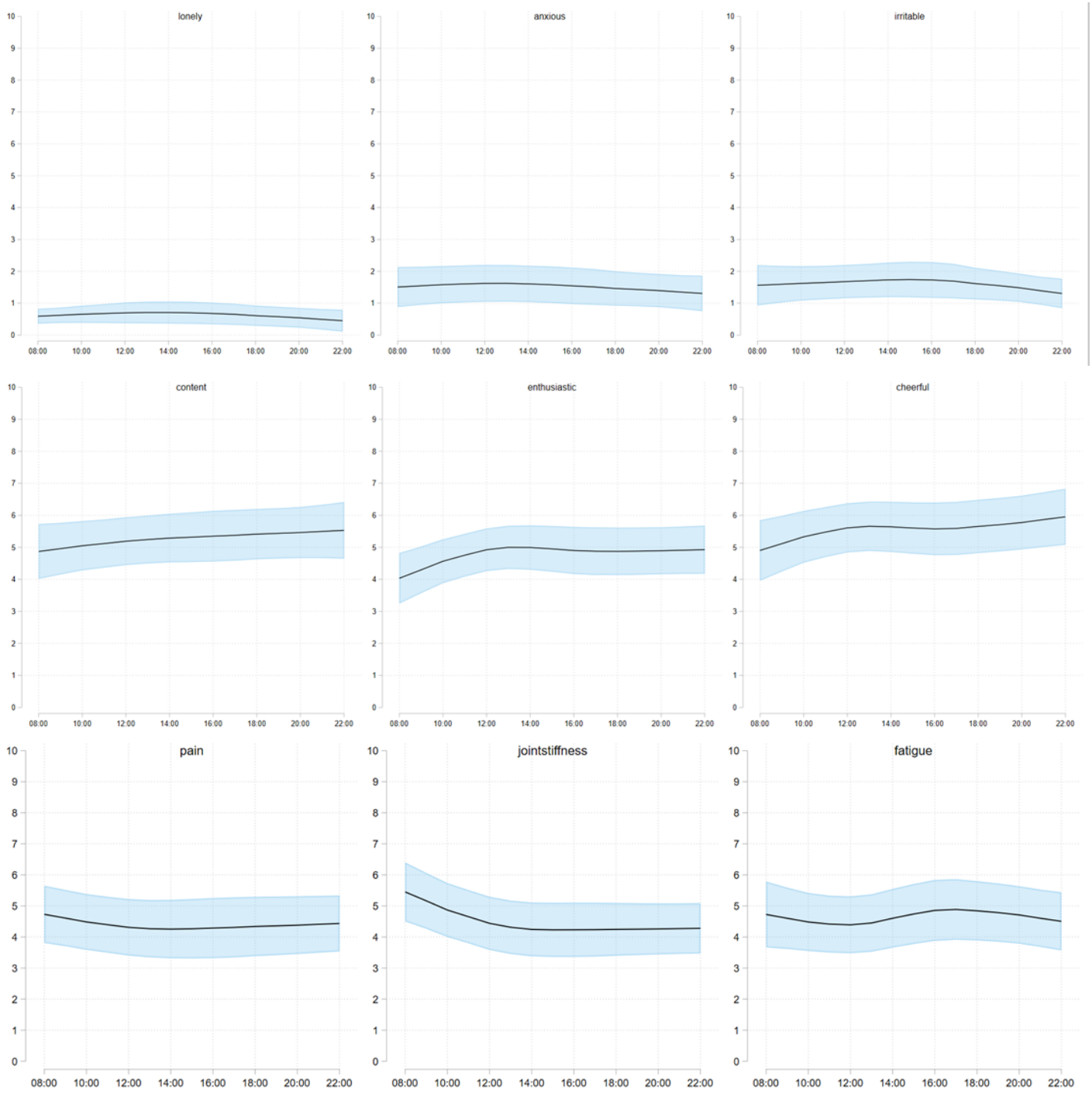


Figure 6.3: Line plots of symptom severity throughout a day

To address the first objective of looking at variability throughout a day, line plots for each symptom scores over time are shown in Figure 6.3. Negative affect symptoms (loneliness, irritability, and anxiousness) are consistent throughout the day (effect size = 0.30). Positive affect symptoms (contentness, enthusiasm and cheerfulness) have a constantly increasing score from 9am to 8pm (effect size = 0.43), suggesting that participants feel more positive as the day goes on, coinciding with the drop in physical symptoms. Physical symptoms (effect size = 0.14) drop in severity as the day goes by, with joint stiffness (effect size = 0.43) having a massive decrease after the first measurement at 9am. This coincides with what is known about joint stiffness being much higher in the morning. Fatigue had a short increase at around 4pm but decreases again after 6pm. From the diurnal patterns, negative affect does not have much variation throughout the day, with a small decrease at the end of the day. Positive affect on the other hand increased as the day goes on, coinciding with decreasing physical symptoms. After defining the variability of measurements through the course of a day, it is important to investigate if there are any influences on the variability, and how different measurements affect each other's variability. This corresponds to the second objective, where temporal associations between measurements and their lagged components are looked at.

6.5.4 Cross-correlation and Dynamic Modelling

In order to look at temporal associations, 6 lagged variables are created for each of the EMA measurements. There should be a high correlation between the lagged variables of each individual measurement because a certain symptom should be similar to the previous measurement of just a two hours ago. This autocorrelation of each variable and its lagged products can be seen in Appendix C. Physical symptoms have the strongest correlation amongst the lagged variables, with the association between lag 1 and lag 6 having a correlation value of 0.87. Negative affect symptoms on the other hand had the lowest lagged correlation, with lag 1 and lag 6 having a value of 0.58.

After establishing the validity of the lagged variables through the autocorrelation, the next step will be to identify possible temporal connection between measurements. This is done by using cross-correlations between physical symptoms, positive affect and negative affect symptoms which can be seen in Table 6.3 below.

Table 6.3: Cross-lagged correlations

	Physical Symptoms	Negative Affect	Positive Affect	Lag-1 Physical Symptom	Lag-1 Negative Affect	Lag-1 Positive Affect
Physical Symptoms	1	0.37	-0.06	0.90	0.35	-0.02
Negative Affect		1	-0.22	0.35	0.71	-0.16
Positive Affect			1	-0.03	-0.15	0.80
Lag-1 Physical Symptom				1	0.37	-0.06
Lag-1 Negative Affect					1	-0.22
Lag-1 Positive Affect						1

Table 6.3 shows that between each variable and their lagged counterpart, there is a strong correlation (lowest is 0.71 for negative affect and lag-1 negative affect). The significance for all the correlations between the original value and the lagged counterpart is significant, with p-value < 0.01 which reaffirms the autocorrelation values mentioned above. Comparing between symptoms, positive affect, and lag 1 negative affect, and negative affect and lag 1 positive affect showcases a significant negative correlation. This means that an increase in either affect will lead to a decrease in the other affect which is logical. It is also shown that there is a significant weak correlation between physical symptom and lag-1 negative affect, which may suggest that current negative affect plays a part in higher physical symptom severity in the next period. There is also a significant correlation between

lag-1 physical symptom and current negative affect, suggesting that the influence between negative affect and physical symptom may go both ways. The only non-significant correlation here is between physical symptoms and lag-1 positive affect, and positive affect and lag-1 physical symptom.

These correlations show temporal connections between symptoms however it does not show any associations or directions between the correlations. The significant correlations between symptoms exist for both directions, and thus not revealing any causal possibilities. Dynamic regression models between these significant correlations have to be created to show significance tests between variables to infer more from these correlations.

Dynamic Regression Models:

Dynamic mixed effects autoregressive models between physical symptoms, positive affect, negative affect, physical activity, and the lag-1 components are shown in Appendix C. Significant associations between these variables were then gathered and displayed in the form of a panel model in Figure 6.4 below. The only associations shown are significant, and all directions of the arrows are from lag-1 to current period. The coefficients of the significant associations are also shown above the arrows.

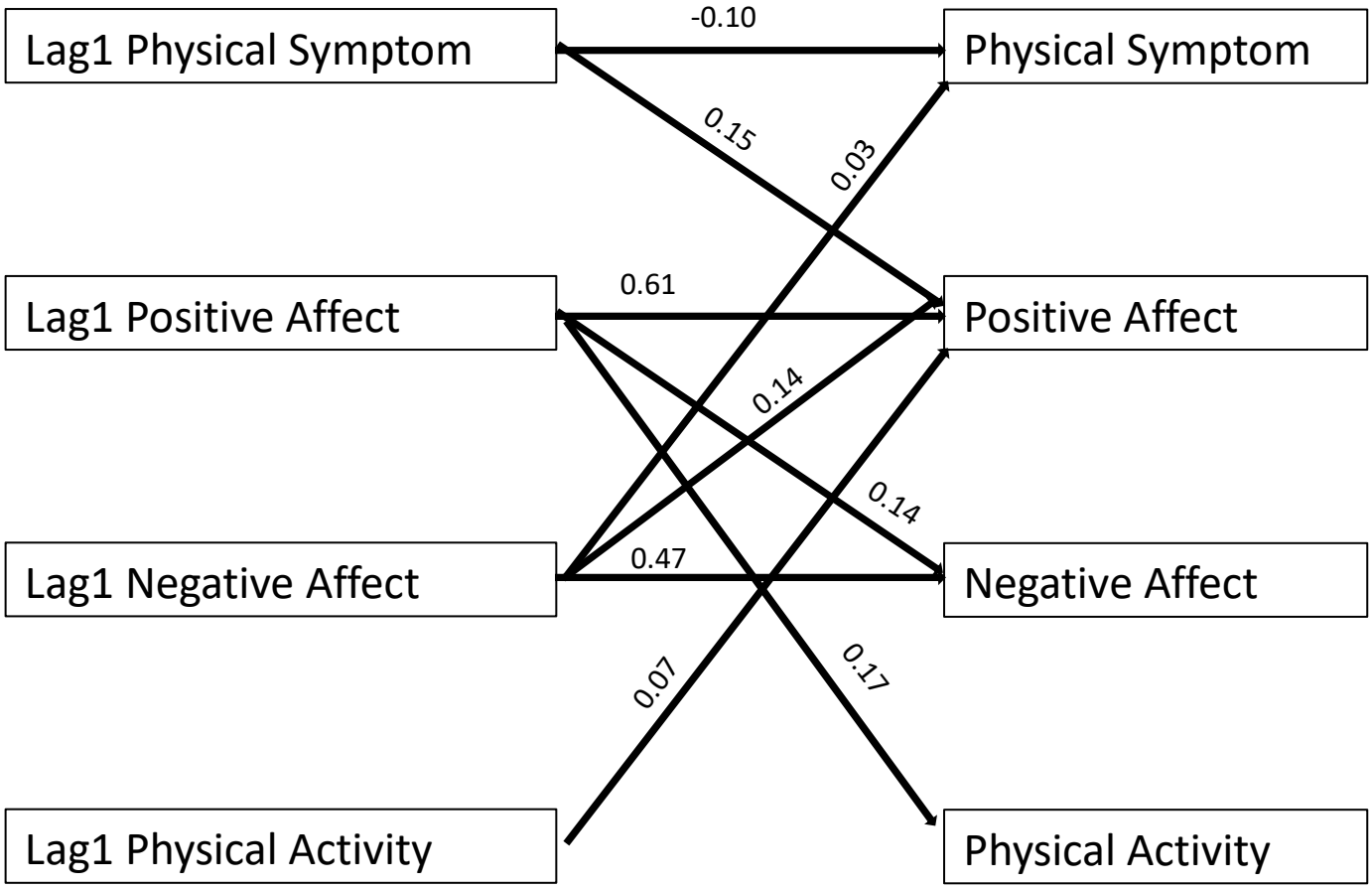


Figure 6.4: Autoregressive Cross-Lagged Panel Model

Dynamic regressions incorporate lagged variables and attempts to see if variables in a lagged period have a significant association with another variable. In Table 6.3, it was found that there is a cross-lagged correlation between negative affect and physical symptom, however the direction of correlation was unclear. Figure 6.4 shows that lag-1 negative affect and physical symptoms is significant with a p value of 0.020 and 95% CI [0.0053,0.062], however it also does not show any significant associations between lag-1 physical symptom and negative affect. This is suggestive of a causal relationship where current negative affect has a causal relationship with physical symptom in the next time period, while physical symptoms do not seem to have much effect on the next period's negative affect symptoms.

Lag-1 physical symptoms are also significant with positive affect with a p value of 0.008 and 95% CI [0.041, 0.27], while there is a lack of significance between lag-1 positive affect and physical symptoms. This suggests that current physical symptoms play a major

role in positive affect of the patient in the next time period. In Table 6.3, it was discovered that there are only non-significant correlations between positive affect and physical symptom, suggesting no linear and temporal correlations between the two variables. This showed how vital it is to carry out mixed effects regression to have a more accurate look at how variables influence each other. Compared to the non-significant association with negative affect (p-value = 0.89), physical symptoms play a bigger role in influencing positive affect compared to negative affect for the next period. Positive affect is significantly associated with lag-1 of all other symptoms, suggesting that a positive affect is more easily affected by other symptoms and physical activity, and that it may be a very fluctuant symptom.

Finally, it is also shown that lag-1 positive affect is the only variable that is significant with physical activity with a p value of 0.006 and 95% CI [-0.30, -0.05]. This suggests that a high positive affect will probably influence participants to be more active in the next time period. There are no significant associations between physical symptom and physical activity.

6.5.5 Network Model

The dynamic mixed effects models revealed significant associations and potential direction between variables through time, but those were based after all participants' data. Participants' symptom variability change over time, and as mentioned by Tung (2021), is a key factor that should be investigated which may affect symptom severity. This leads to the third objective, which investigates if network plot of fluctuant symptom severity has any distinctive differences compared to network plot of stable symptom severity. Relative to all other participants, a participant with particularly high variability in symptom severity, one with a sudden flare in physical symptoms, and two with low variability (one with high severity and one with low severity) are chosen for the network model analysis by looking at the line graph of each participant. The line graphs of these 4 participants could be seen in Appendix C.

Figure 6.5 below shows the participant with fluctuant symptom, while Figure 6.6 shows a participant that had a spike in symptom severity. Figure 6.7 and 6.8 respectively shows a symptom plot of participant with low variability, however Figure 6.7 has low

symptom severity as well while Figure 6.8 has high symptom severity. These network plots will allow the difference between a fluctuant and stable symptom variability to be investigated, and also how symptom severity may affect the symptom plot.

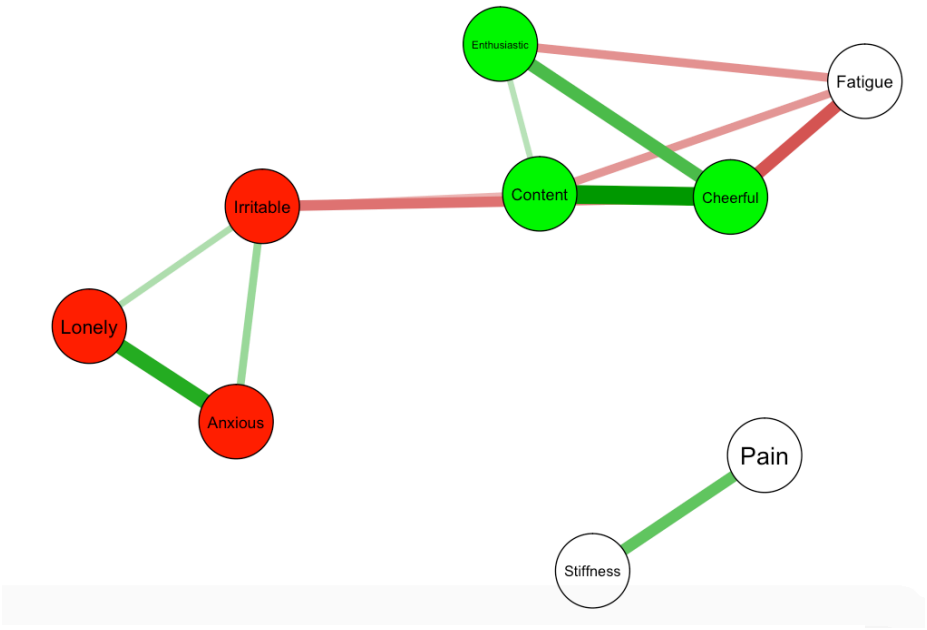


Figure 6.5: Network Plot of Fluctuant Symptoms

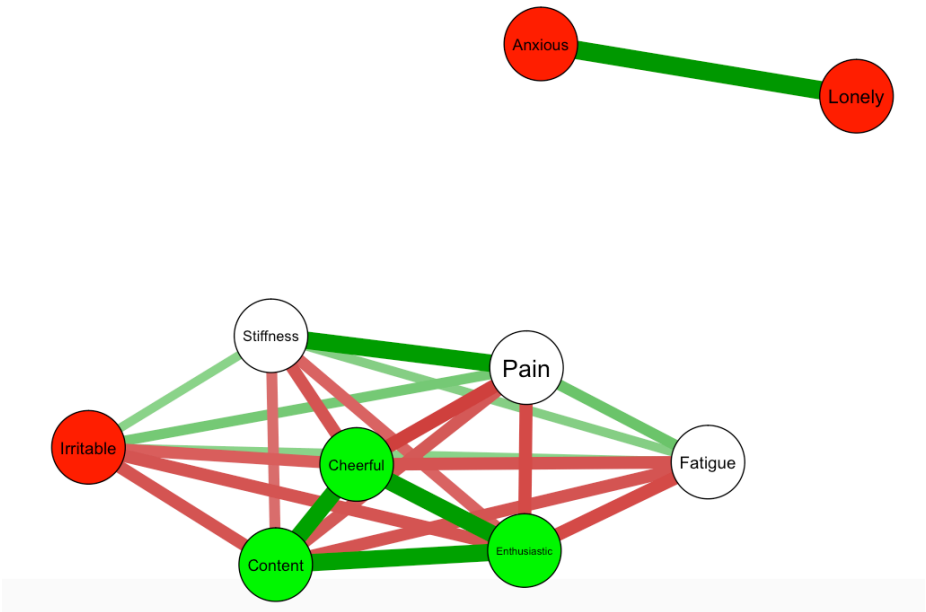


Figure 6.6: Network Plot of Flare in Symptoms

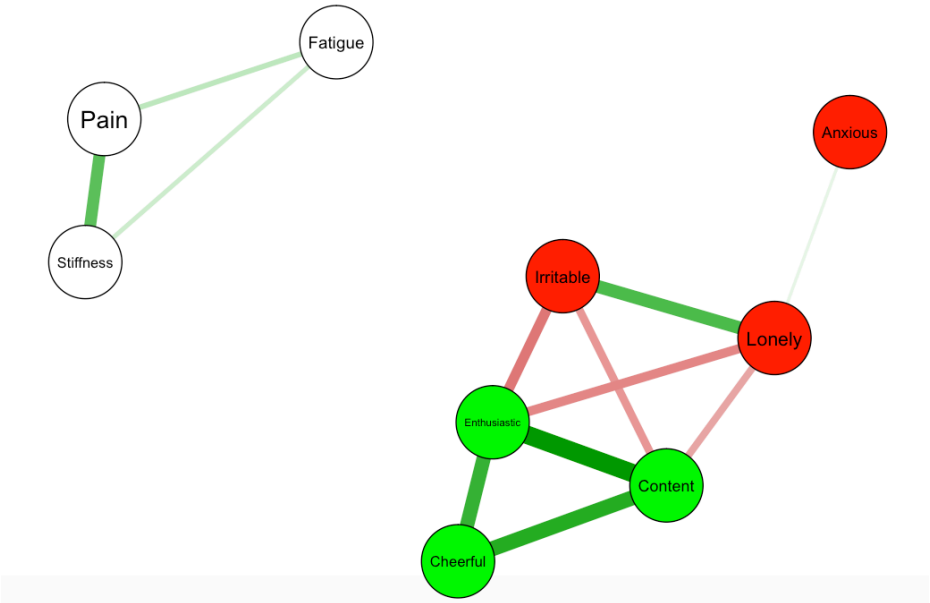


Figure 6.7: Network Plot of Stable Symptoms with Low Severity

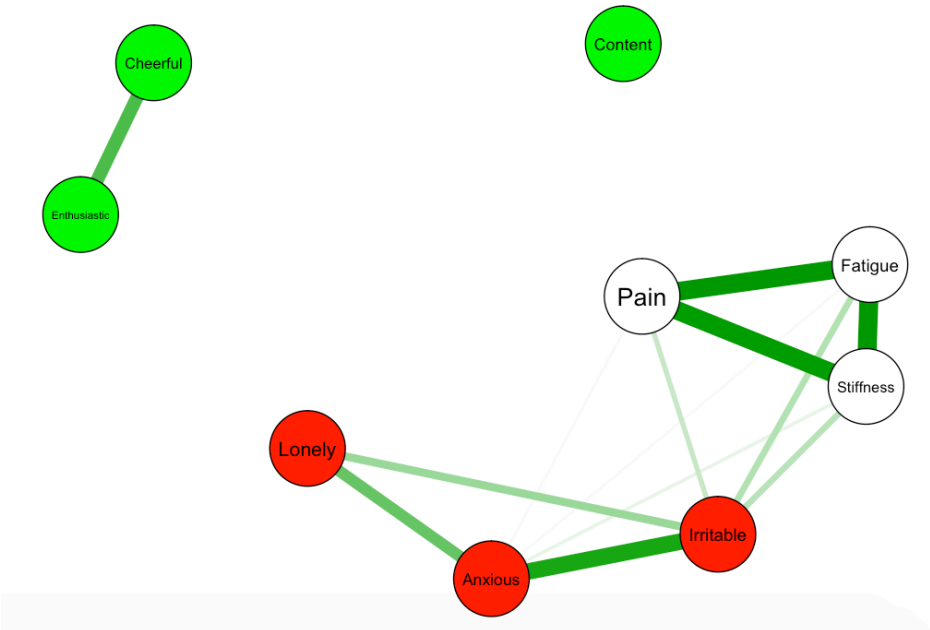


Figure 6.8: Network Plot of Stable Symptoms with High Severity

Comparing Figures 6.7 and 6.8 that to Figure 6.5, we can see that the difference between low and high fluctuating symptoms is that fatigue seems to be disconnected from physical symptoms in a patient with high fluctuating symptoms. Figure 6.5 has Fatigue connected to the positive affect symptoms, while the other physical symptoms are disconnected at the bottom right. In low variability state, fatigue is closely related to pain and joint stiffness in those. This suggests that fatigue is much more closely related to the psychological aspects in a patient with high symptom variability compared to the other physical symptoms.

Figure 6.6 shows a patient with a sudden flare of symptoms. Besides anxiety and loneliness, symptoms are all very closely connected. This shows that a flare in symptom will result in most symptoms being affected simultaneously and resulting in a close-knit network plot, including positive affect symptoms. Only irritability as a negative affect symptom is included, which shows that positive affect seems to be more influenced in the case of a flare.

Panels 6.7 and 6.8 also shows the difference between a consistent low symptom rating and a consistent high symptom rating. In low severity state, the physical symptoms are on their own in the top left-hand corner, while high severity state shows the physical symptoms being closely related to negative affect. This shows that in the situation of low symptom severity, the psychological symptoms are more isolated and less influenced by the physical symptoms. In high symptom severity states, it is thus more likely for physical symptoms to affect the psychological symptoms of participants, meaning that the severity of all symptoms is likely to be higher than usual.

Sensitivity Analysis:

Sensitivity analysis were also carried out on these 4 network models to establish the accuracy of the edges. A graph that compares between the bootstrap mean and sample mean will be shown for each of the network models, and each graph will also contain the 95% confidence interval. The y-axis of the graph represents each of the edges, but the labels will not be shown because this analysis wants to examine the overall robustness of the

edges, instead of particular edges. The x-axis shows the edge weight, and any weight that is above or below 0 should be represented on the network plot.

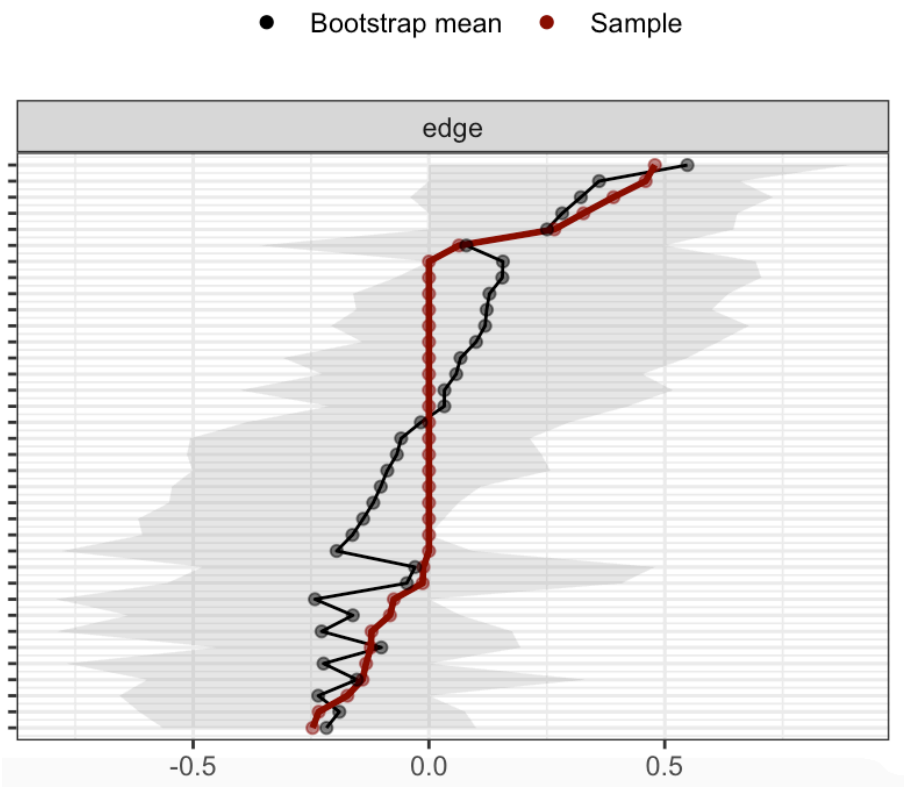


Figure 6.9: Graph for accuracy of edge-weight for Patient A

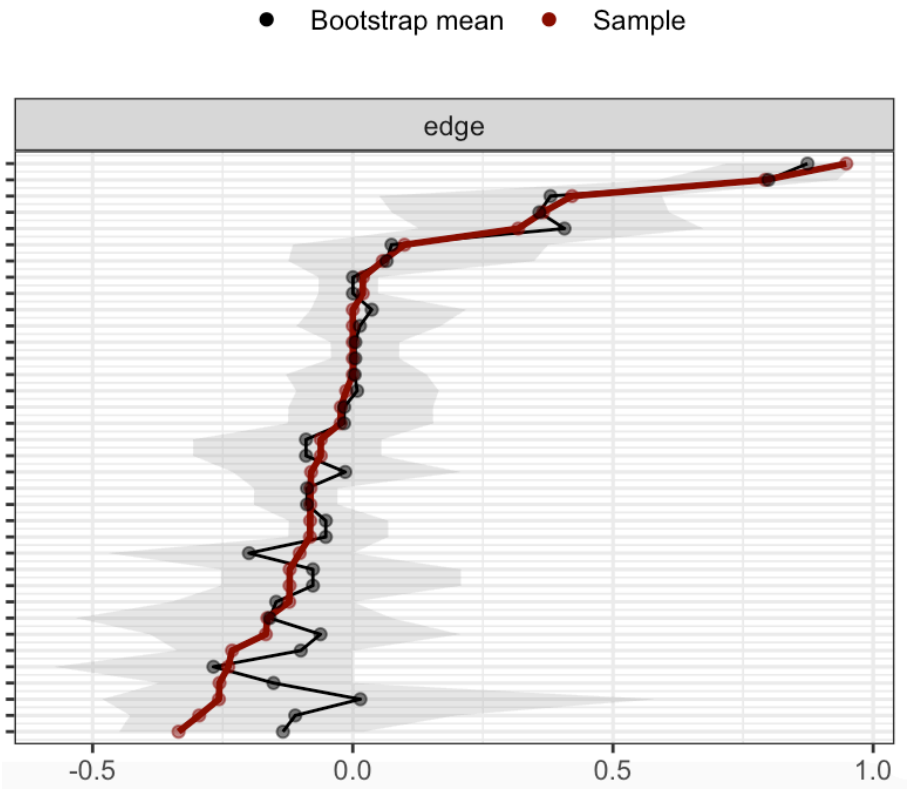


Figure 6.10: Graph for accuracy of edge-weight for Patient B

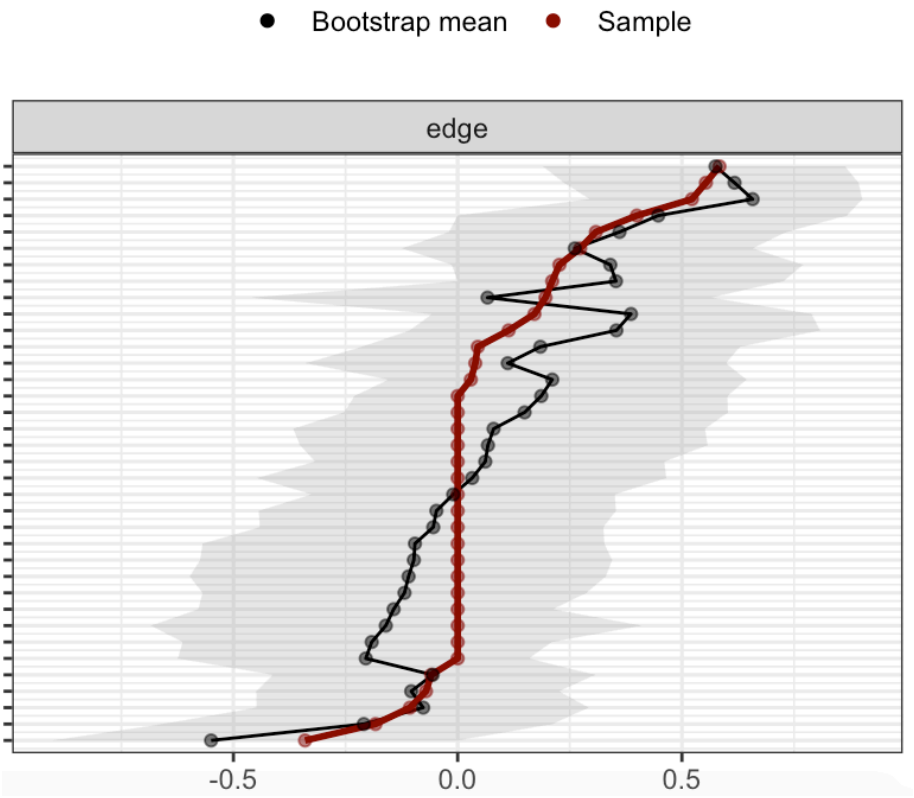


Figure 6.11: Graph for accuracy of edge-weight for Patient C

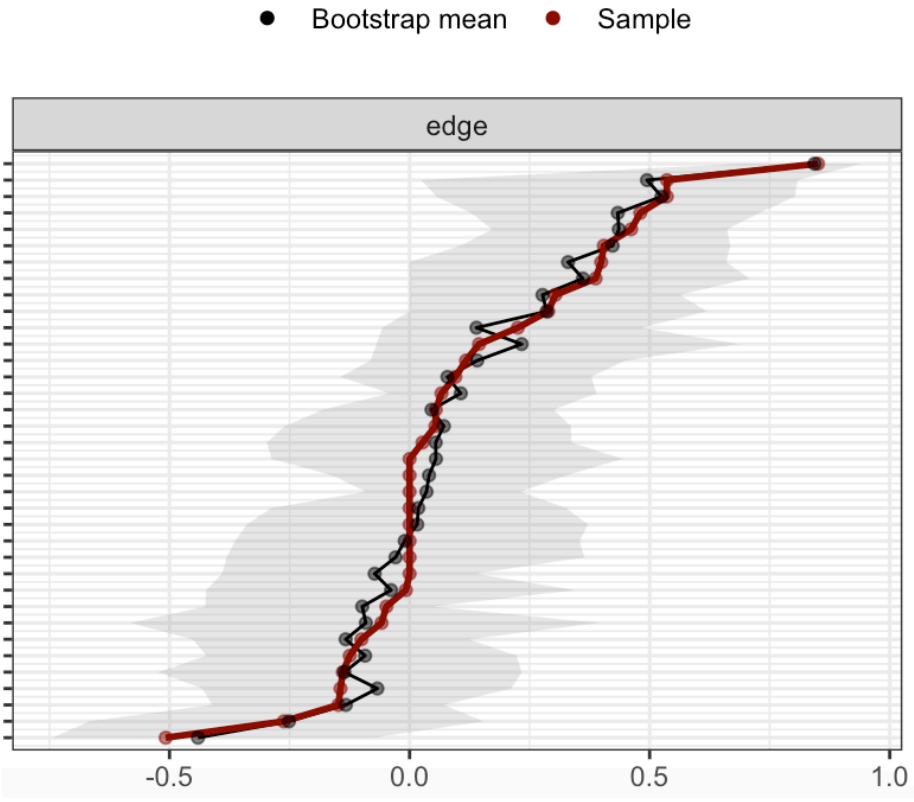


Figure 6.12: Graph for accuracy of edge-weight for Patient D

Figures 6.9 to 6.12 shows the bootstrap mean and sample mean for each of the edges, alongside the 95% confidence interval. It can be seen that in general, all four graphs show large confidence interval, which meant that some care needs to be taken when considering the edges of the graphs. Figures 6.9 and 6.11 especially showed that a large number of edges are missing in the sample data when the bootstrap means showed that it is above or below 0. This is largely because those participants had less data entry than Figures 6.10 and 6.12, and the smaller sample size resulted in a less accurate edge-weight estimation. These accuracy tests showed that doing individual network plots could be difficult especially because of the smaller sample size which means the interpretation of the edges need to be carefully considered.

6.6 Discussion

This longitudinal study carried out during the end of the lockdown implemented by the UK government investigated the variability and temporal associations between physical and psychological symptoms in participants with IA. It is found that most symptoms vary between participants more than within participants, besides loneliness, irritability, feeling supported and enjoyment from task. Both loneliness and feeling supported socially stems from the amount of social contact that participants have at that particular time (Drageset, 2004), which may vary wildly throughout a day. Diurnal variations showed that negative affect does not vary much throughout a day, while positive affect increases and physical symptom decreases. Temporal associations discovered that the direction of association between negative affect and physical symptoms is from negative affect, while the direction between physical symptoms and positive affect is from physical symptoms. Positive affect is also significantly associated with both lag-1 negative affect and lag-1 physical activity, suggesting that it is highly fluctuant because it could vary according to any of these variables in the previous time point. It is also revealed that positive affect is the only variable that affects next time period's physical activity. In order to investigate if fluctuant symptom severity differs from stable symptom severity, network plots between particular participants showed that in a high fluctuant network, fatigue is disconnected from other physical symptoms and are clustered with psychological symptoms instead. High symptom severity

network plots also differ from low severity in a stable variability environment in that physical symptoms are more closely connected to psychological symptoms in high severity.

In addressing the first objective, it is observed that physical symptoms decrease slightly throughout the day (effect size = 0.14), in particular joint stiffness which has a very high score for the 9am time point and decreases drastically (effect size = 0.43). This coincides with the wealth of current research which shows the severity of morning stiffness and its subsequent decrease through a day (Bacci et al., 2017; Cobb et al., 1955; Mok, 2018) and is even included as a classification criteria (Arnett et al., 1988). It is also found that morning stiffness may be a better indication for functional disability and pain than inflammatory markers like ESR (Yazici et al., 2004). This finding highlights the importance for targeted treatment, through identification of those with particularly bad morning joint stiffness scores, as a study by Clarke et al (2011) shows that using low-dose prednisone is likely to decrease morning stiff jointness severity.

The decrease of severity in physical symptoms as a whole most likely reflects on the general uplift in affect for the participants. Negative affect is overall scored quite low but still has a slight decrease, while positive affect has an increasing trend as the day goes on. The effect size for both affect is 0.30 and 0.43 respectively. This displays the potential association of increasing positive affect and decreasing physical symptoms. However, a study carried out on a representative sample of older people aged 52-79 (Steptoe et al., 2011) showed that positive affect increases and that negative affect decreases progressively throughout a day. The diurnal variation discovered in this study could thus be explained by this natural diurnal effect instead. This information would not be possible to glean from a cross-sectional dataset, suggesting the importance of a longitudinal data collection from arthritis patients, particularly because of the severity of morning joint stiffness which will not be captured in a single time point measurement. However, these diurnal variations discovered for the first objective could have been caused by other factors or symptoms, and thus significance test of the associations have to be carried out, which brings us to the second objective.

As noted by Tung et al (2021), current literature only include at most three symptoms for an EMA study which is insufficient to explore the psychological and physical aspects of IA. This study looks at six time points over 10 days with at least nine symptoms measured in each. This means that temporal associations and correlations could be

discovered by using lagged variables and see how symptoms change over time in each participant. The first objective noted a possible connection between physical symptom and psychological symptom, but the diurnal variation is insufficient evidence for association. Table 3 showed a weak correlation between negative affect and physical symptoms, while none was found between positive affect and physical symptoms. This is affirmed by Leventhal et al (1996) who showed that negative affect is a consistent predictor for physical symptoms 6 months later, and a study by Charles and Almeida (2006) showed that physical symptoms such as pain predicted next day negative affect. However, positive affect has also been found to be a significant predictor of good health (defined by the Seriousness of illness rating scale (SIRS)) five weeks later while negative affect was not. This could be explained by the scale used, which not only includes physical symptoms, but also specific cold/flu symptoms. The five weeks in between measurements are also drastically different from the hourly difference here, which could affect the associations. However, these conflicting information on correlation between physical symptoms and affect points out the necessity to run significance tests to identify any possible causations between variables.

Dynamic regression models which take into account time series data and the change over time in symptoms were used to look at the temporal associations between the correlations that were brought up previously. It was discovered that there is actually no significant association between negative affect and lag-1 physical symptom, while it is significant for lag-1 negative affect and physical symptom. This means that if a participant feels irritable and lonely at a certain time, their physical symptoms like pain and fatigue will increase in the next time period. This is a very novel finding as there have been no previous literature on this regarding IA patients, but has been found to be an issue in a study on the general population by Charles & Almeida (2006) which states that previous negative affect does predict pain on the next time point. This finding implies that clinicians should pay more attention to patients' negative affect because it may be the cause of spikes in physical symptom.

Lag-1 positive affect is the only variable significant with physical activity, suggesting that high positive affect in the current time period will lead to an increased rate of physical activity in the next time period. There are evidence of positive affect predicting high exercise frequency controlling for age, gender, occupation and BMI (Garcia et al., 2012), however that is in a cross-sectional study. No study to date has shown any association

between positive affect and next day physical activity. Physical activity is heavily promoted for IA patients (Rausch Osthoff et al., 2018) as a self-management tool, and is found to help with disease activity. It is therefore important to increase physical activity to improve the quality of life for IA patients. This finding points out a possible method to increase physical activity, and thus more research should be carried out on the possible ways to increase positive affect, and on the causation effect between positive affect and physical activity.

The dynamic regressions performed previously showed new findings that have not been discovered in the field of IA before. However, it does not differ between fluctuant or stable symptom severity, which as stated by Tung (2021), is valuable information that is missing from current research. In order to see how symptom variability affects the participants, the third objective has to be carried out. The four network plots presented allows researchers to have a better overview of how every symptom is associated with each other through variety of symptom variability and severity. It was shown that in the presence of a flare, physical symptoms and positive affect symptoms are highly correlated and influences each other, suggesting that a flare in physical symptom will also result in a drastic decrease in positive affect. However, in a consistently high symptom severity patient, it is negative affect that is closely associated with physical symptom. This means that both aspects of psychological symptoms are influenced by physical symptoms, but positive affect is much more influenced in the presence of a flare. There has been no previous research carried out looking at how positive affect changes during a flare in physical symptoms. A possible reason for this will be that those with consistently severe physical symptoms have had enough time to develop habituation to the physical symptoms, similar to how a study by Rodriguez-Raecke et al (2014) shows chronic low back pain patients developing habituation to pain within 8 days.

This habituation to physical symptoms will naturally translate to positive affect as well. Those that experienced a flare did not experience habituation and as a result do not have the time or preparation, thus suffering a decrease in positive affect symptoms. This difference in influence due to the change in situation means that the focus on psychological symptoms should change with regards to the patients. Clinicians who have patients with consistently severe physical symptoms should be very aware of their negative affect symptoms and thus address it as required. A flare can be interpreted as having a sudden variation in symptom at one point in time, and it can be seen that even having just one time

point of variation changed how overall connections between all variables work. When comparing between stable symptoms and fluctuant symptoms for the entire study, the major difference is that fatigue is less connected to other physical symptoms in a high fluctuant state. This means that when patients experience high variability in symptoms, fatigue is more likely to influence, or to be influenced by psychological symptoms rather than physical. There has been no prior research on how fatigue is affected by overall symptom variability, and as stated by Tung (2021), there has been no studies that looked at symptom variability in high frequency measurements in musculoskeletal disorders. These findings showed how symptom variability could result in a change in how fatigue operates in patients, and the potential research theories that could be tested.

Because recruitment was only carried out through social media and charities, it is possible that there is a selection bias present which could exclude certain demographics in the sample. IA patients that are not on social media often, or included in RA charity emails will not be able to participate in this study. This is a valid concern because it may result in poor representation of certain minorities which will skew the results of this study. However, this recruitment methodology was utilised because it was carried out during the COVID-19 pandemic where recruitment through social media and charities mailing lists had to be done, and there was a need to recruit a large amount of participants quickly due to the time constraints of a PhD. As a result the generalisability of the results to under-represented groups may not be possible.

The first and third objective of this study are exploratory, showing possible theories and connections between variables, but not proving any of them. This opens up avenues for future research that will be discussed in the next paragraph. Objective two regarding temporal association showed significant associations, however variables chosen are the sum scores of physical symptoms and affect, and thus there are no specific information available for each of the symptoms. A follow-up study based on the theories that have been proposed by this study, focusing on the individual symptoms will solve most of these problems. As mentioned in the Methodology Chapter in Chapter 4.5.3, these temporal associations discovered in Chapter 6 potentially brings about a discussion for causality, but it is important to evaluate how strong the evidence for causality is. With these temporal associations being discovered for the first time in the IA population, it is important to repeat the experiment to achieve consistency of findings which is a key component of the Bradford

Hill criteria (Cox, 2018). The network models that were created here were also utilised using cross-sectional methods, which means that causality cannot be directly inferred from these network graphs. These means that when discussing the associations that were discovered in this chapter, it is important to distinguish that these only represent temporal associations between variables that have potential to extend to causality, but are as of yet only associations.

This study has shown the validity of the information derived from collecting longitudinal data, and also the importance it brings in providing new information that has not been researched before. The existing knowledge from previous cross-sectional studies has been reflected here, affirming the studies' validity and reliability, such as joint stiffness decreasing throughout the day, the associations between physical symptoms and affect. There has been no research in the field of IA that showed the direction of association between negative affect and physical symptoms, and also positive affect and physical activity. It is shown that negative affect significantly influences next period's physical symptoms, and likewise for positive affect and next period's physical activity. These two new findings exhibit the importance of psychological symptoms in patients, not only for improving disease activity such as pain, but also for self-management in physical activity. There needs to be a greater focus on possible negative affect in patients and to identify the main driving force because it may be a sign of future deterioration of physical symptoms. Clinicians also need to be wary of any spikes in negative affect in their patients because it can warn of future spikes in physical symptom. Physical symptoms are significantly associated with negative affect cross-sectionally, but only pain influences negative affect for the next time point. This shows the possibility of studying specific physical symptoms and negative affect symptoms instead of looking at them as a whole aspect. The importance of physical activity for IA patients also mean that future research should focus on how positive affect influences next time period's physical activity, specifically which positive affect. It will also be helpful to explore ways of improving positive affect, with the purpose of increasing physical activity. Network plots have also revealed that the associations between psychological symptoms and physical symptoms vary wildly between how physical symptoms vary in patients. This means that needs to be both targeted and personalised treatment, depending on the variability of the patients' symptoms. The network plot was

also only derived from one participant for each of the varying situations, and thus more research on each of the situations will be needed to ensure accuracy and validity.

7. Impact of COVID-19 & Lockdown on IA Patients

7.1 Overview of Impact of COVID-19 & Lockdown on IA Patients

Building on Chapter 6, this chapter uses data from the same IA-COVID study, but includes both waves of data collected during lockdown and during a period of no restrictions. Due to the COVID-19 pandemic, this study was carried out and presented an opportunity to understand how the implementation of a lockdown affects RA patients. Due to the success of previous chapters in analysing longitudinal data and using network analysis, this chapter uses the same methods in previous chapters and provides a explores how associations and temporal effects change in between waves.

It is important to note that even though one of the waves of data is during a period of no governmental restrictions, IA patients that are involved with this study were still affected by social distancing and social isolation due to shielding. This means that when comparing between waves, it should not be assumed that during a period of no restrictions, participants are experiencing a normal amount of social interactions and no lifestyle restrictions. This was mentioned in Section 6.1, and the possibility of worse mental health derived from shielding was discussed. The need for shielding thus means that it is difficult to generalise the results from this comparison between the two waves to a period after the pandemic where there are no social isolation necessary.

7.2 Background

In December 2019, a new type of pneumonia supported by a novel member of the coronoviridae family named SARS-CoV-2 (severe acute respiratory coronavirus 2 syndrome) developed from Wuhan Province in China. This disease is characterized by dry cough, fever, dyspnea and fatigue (Wu & McGoogan, 2020). Higher age is one of the known risk factors and the clinical course, disease related complications of COVID-19 is more severe in older individuals (Lekamwasam & Lekamwasam, 2020). This is similar to patients with inflammatory arthritis, where the majority of patients are of a higher age. Patients with immune-mediated disease may also be prone to an increased risk of infection and/or more

severe course. Significant comorbidities that are risk factors for a more severe course of COVID-19 are hypertension, diabetes, and cardiovascular diseases. Inflammatory arthritis patients are known to have comorbidities like cardiovascular disease, metabolic syndrome, obesity, and inflammatory bowel disease (Perez-Chada & Merola, 2020). These features show a clear overlap to comorbidities in COVID-19. These show how the COVID-19 pandemic is especially a danger to patients with an existing inflammatory arthritis condition, and thus it is important to see how the symptoms that patients are experiencing have been changed by the ongoing pandemic.

The COVID-19 pandemic has a strong negative impact on human society worldwide. Since the initial outbreak, the epidemic has had a rapid global spread worldwide which led the World Health Organization (WHO) to declare the disease now called COVID-19 a Public Health Emergency of International Concern on 30th January 2020 (WHO, 2020a) and a pandemic on 11th March 2020 (WHO, 2020b). In the UK, the government introduced a national lockdown on 23rd March 2020 where everyone, except for a small group of key workers, were legally obliged to stay at home (GOV.UK, 2020b). This was in place until mid-May at which point social restrictions were gradually lifted. Two further national lockdowns were enacted , with one in from 5th November 2020 and the other form 5th January 2021. During the period up to July 2021 some form of social restrictions were in place.
There are long-term effects of quarantine and social distancing, such as l negative psychological symptoms including confusion, anger, and post-traumatic stress symptoms (Brooks et al., 2020). The impacts of lockdown spread to both physical and psychological health in the general public, and also implemented lifestyle changes which can be felt worldwide (Tommasi et al., 2020). A study carried out in the United States of America using the World Health Organization Five Well-Being Index (WHO-5), which has been found to have good construct validity in measuring depression and well-being (Topp et al., 2015), showed a significant reduced score of 0.085 standard deviation lower for WHO-5 in states that have lockdown measures compared to states that do not have lockdown measures (Adams-Prassl et al., 2020).

The impact is also felt in the United Kingdom, where it has been shown that 29% of adults without a common mental disorder one year before the lockdown were found to screen positive for one in April 2020 (Chandola et al., 2020), and higher levels of post-traumatic stress symptoms, anxiety, and depressive mood was found to positively associate

with the lockdown in Italy (Rossi et al., 2020). It is also shown to affect University students tremendously, with decreased sleep quality, quality of life, and an increase in clinical depression and suicidal ideation (Kaparounaki et al., 2020). The impact of COVID-19 on mental health is also significantly more pronounced in women who reported higher psychological distress of about 13.8%, while men only reported around a 9% increase in psychological distress (Niedzwiedz et al., 2021). There is also a significant increase of domestic violence from 4.4% to 14.8% (Sediri et al., 2020) which could play a factor in why women are more affected by the lockdown than men.

The general impact from COVID-19 and the subsequent lockdown were serious, posing a threat to not just the mental health as previously mentioned, but physical health and other aspects of life as well. COVID-19 infection is significantly associated with muscle pain and also increased sensitivity to pain (El-Tallawy et al., 2020). Those that uses opioid for the chronic conditions were also in danger of opioid addiction because of less access to treatment and less distractions (Silva & Kelly, 2020). There are also cancellations of non-urgent outpatient visits and less admissions which have implications on medical adherence (Palmer et al., 2020). Other general impact such as fewer treatment availability, increased stress due to perceived vulnerability, and delays in diagnosis are also present because of the COVID-19 pandemic and subsequent lockdown. The implementation of lockdown also means that there are restrictions concerning seeing people from outside of the immediate household. People were not allowed to meet in person, and only very small bubbles were allowed to form for people to be able to meet outside. Online interactions provide a different experience for the public as well. Loneliness is recognised as a major public health concern (Bu et al., 2020a), and these restrictions mean that this concern should intensify.

Thus, it is important to see how the changes in social context which should influence loneliness will affect other symptoms. The implementation of lockdown means the closure of gyms, indoor sport complexes and any type of social sports, which should influence the level of physical activity that people can engage in. It is shown that in some population of people, including those over age 55 and those who were highly active before lockdown, the amount of exercise has decreased during lockdown (Constandt et al., 2020). It has also been stated that a decrease in exercise during the lockdown in comparison to before result in worse mood and well-being (Brand et al., 2020). These problems are evident in those with chronic disorders as well. There were concerns with the availability of medications and

follow ups with clinicians, as seen in worsened glycaemic control in diabetes 1 patients (Verma et al., 2020), and a significant decrease on hospital admissions including the paediatric wards (Gavish et al., 2021) and patients with acute myocardial infarction (Mesnier et al., 2020). Patients with chronic pain conditions, such as chronic migraine and small fibre neuropathy, suffered from worse physical health due to the pandemic distress (Consonni et al., 2021) and cancer patients complained of delayed diagnosis, missed treatments and weakened immunity (Moraliyage et al., 2021).

Patients with chronic musculoskeletal disorders, in particular inflammatory arthritis (IA) are also negatively impacted by COVID-19 and the lockdown implemented. The lockdown has an even higher impact on IA patients especially, because around 60% of IA patients are engaged in shielding (Mahil et al., 2021). Those engaging in shielding are involved in the most stringent risk mitigating behaviour, such as social distancing and reducing exposure. This meant that these patients will be even more restricted in terms of social interaction and physical activity. In a study concerning autoimmune arthritis patients, general health which was asked by using a Likert scale to compare change before and after lockdown, is shown to significantly decrease, and patients also have a higher risk of psychological distress (Picchianti Diamanti et al., 2020). The quality of life scale (Burckhardt & Anderson, 2003) was also completed by patients with Rheumatoid Arthritis or ankylosing spondylitis in New Zealand before and after lockdown, and there was a significant decrease that could be predicted by both baseline quality of life and current depression (Johnstone et al., 2021). These negative impact on IA patients were also reflected in the United Kingdom, where a paper produced by the same study that produced both this chapter and Chapter 6 showed that out of 338 participants, 49% met the criteria for depression using the PHQ8 scale, and emotional distress measured using a visual analogue scale (1 to 100) also showed that 58% had more than 10 points increase (Sweeney et al., 2021). IA patients already experienced higher levels of social isolation and loneliness than the general public (Smith, 2017), which means that the restrictions caused by the lockdown will have an even stronger impact on loneliness. Physical activity is often recommended for people with inflammatory arthritis (Plasqui, 2008) as it plays a central role in maintaining muscle strength and function. As mentioned before, the level of exercise and physical activity dropped because of the restrictions, which meant that IA patients will have more difficulty in self-management of disease activity.

Together, these studies demonstrated the potential impact that lockdown may have on psychological symptoms in people with IA, however no studies have shown how specific physical symptoms are affected by a lockdown. Previous studies have also been using only static data before and during a lockdown, which means that any dynamic associations will not be discovered. As mentioned in Chapter 6, symptoms in RA fluctuate tremendously, and thus using intensive longitudinal data will provide a more comprehensive look at the effects of lockdown on IA patients. With the data already collected for Chapter 6 that looked at how symptoms interact during a period of time with less restrictions, it is important to have the same dataset during a lockdown which will provide a comparison between during and before a lockdown. This will allow a more accurate look at how symptoms behave and change dynamically due to a lockdown.

Cross-sectional assessments provide limited insights as they capture current state and cannot account for intra-individual variability in symptoms and how these might be affected by the environmental stressors. During a state of lockdown, people will be at home and have plenty of time and easy access to their computer and/or portable electronic device. This means that much higher frequency of assessment is possible, for example, Ecological Momentary Assessment (EMA). EMA provide fast 'in-the-moment' assessment, reducing recall and desirability bias. Furthermore, since EMA involves repeated sampling in participants' natural environments, ecological validity is maximised. This allows researchers to see how behaviours change in real life contexts and enhances establishment of causal relations between variables. This is also the same methodology used for Chapter 6, and thus collecting these intensive longitudinal data will allow researchers to determine a direction in known associations between symptoms, and delve in more complicated statistical methods which will allow more findings to be revealed.

7.3 Aims and Objectives

The state of lockdown had a negative impact on a lot of people, and the effects were particularly pronounced for those with a chronic condition, such as IA. It was proven in previous studies the impact that lockdown has on mental health for IA patients, however no study has shown how physical symptoms differ. It was also shown that loneliness levels significantly increased during lockdown (Killgore et al., 2020) and physical activity levels

significantly declined (Martinez-de-Quel et al., 2021), two known factors on the psychological and physical symptoms of IA, which meant that the total impact lockdown had on IA must be investigated. Current studies carried out also only looked at two time points, once before lockdown and once during lockdown. As mentioned above, the fluctuations of symptoms in IA mean that a single time point measurement is not accurate enough to gauge how the symptoms really behave during those times. With the presence of a longitudinal dataset before lockdown already present from Chapter 6, there was an opportunity to carry out a similar study during lockdown. This will provide the opportunity to not just evaluate how symptoms change during these two periods, but also if there are any dynamic and causal associations that differ because of a lockdown.

Thus, the main aim of this study will be to understand the impact of lockdown on the quality of life and severity of symptoms in people with inflammatory arthritis, comparing between a wave of data during lockdown, and a wave of data during a period of no restrictions. This will be achieved through the 3 objectives below.

1) What are the main symptom differences between waves?
2) Are there differences between dynamic associations while considering physical activity and social contexts between waves?
3) What are the main differences in symptom networks between during lockdown and after lockdown?

7.4 Methods

7.4.1 Patients and Study Design

This study includes two separate occurrences of data collection, the first in July 2020, during a period of relaxation of social restrictions for most of the country, and the second during the second lockdown implemented in November 2020 and the restrictions of this lockdown can be seen in Table 7.1 below (GOV.UK, 2020a) These two occurrences will be referred to as wave 1 and wave 2 respectively.

Table 7.1: Restrictions in UK: November Lockdown vs No restrictions in July

Lockdown restrictions in the United Kingdom implemented on 5th November 2020.	Restrictions in the United Kingdom implemented in July 2020*
Non-essential shops, leisure and entertainment venues are closed	Non-essential shops allowed to open, some leisure and entertainment venues remain closed
Pubs, bars, and restaurants are closed except for takeaway and delivery	Pubs bars and restaurants are open
Working from home whenever possible	Working from home whenever possible
Staying away from home overnight is prohibited, unless it is for work	Staying away from home overnight allowed
Staying at home during the day whenever possible, unless for work or exercise	Allowed to leave home during the day for any activity
Individuals only allowed to mix with one person from another household	No restrictions on mixing with individuals from another household (rule of six not introduced until September)

*lockdown in England came into force in Leicester area. On 18th July, local authorities in England given additional powers to enforce social distancing. Restrictions were relaxed between the 10th and 15th of July in Scotland. None of the participants were under local lockdown restrictions during the time of data collection and both participants based in Scotland commenced data collection after the 15th of July.

The study design and process of the study for both waves are exactly the same. Participants for the second implementation are recruited from those that have participated in the first occurrence through email, with a total of 19 out of 31 agreeing to continue with the study. The first occurrence of the study is presented in Chapter 6. The sample from that Chapter is recruited from a larger study called the IA-COVID Study (Sweeney et al., 2021). The IA-COVID study is a mixed methods prospective study that recruited 338 patients, from which 328 provided consent to be contacted for future studies. Because the sample for this study during lockdown was derived from the previous sample, it retained the same inclusion

and exclusion criteria. The study procedure also remains the same as the previous Chapter 6, where there are 6 surveys a day. This replication of study design is to make sure that comparable results are achieved, to enable analysis between the datasets.

The comparison between waves will thus be made on datasets that include 30 participants and 19 participants respectively. It is important then to note that this decreased participation count will have an influence on the precision and validity of the findings. This is because the statistical power of the study is dependent on the smaller sample size. However, it should be noted that power is driven by the total number of observations rather than the total number of people, though the within-person association between repeated observations is an influential factor. For example, for a sample of 19 people with 60 observations each (total 1140 observations) and a within-person correlation between observations of r_{ICC}=.5 the effective sample size is 325 and power to detect a correlation of r=.2 is approximately 95% at the 5% alpha level (Snijders, 2005). It should also be noted that although the 5% alpha level is applied here, due to multiple significance testing being performed the true type 1 error rate will be substantially higher than 5%. Given the study is exploratory in nature, and the focus on identifying signals for true effects rather than confirmatory, this higher rate using the traditional 5% level without adjustment is accepted (Lakens et al., 2018). However, this should be noted when interpreting any significant effects.

7.4.2 Measurements

The measurements used in this new data collection during lockdown were exactly the same as the study carried out in July. Physical symptoms such as pain, fatigue, joint stiffness were measured six times a day using a numerical rating scale from 0 to 10, with 0 being none and 10 being extreme. The same scale is also used for psychological symptoms, which his split into positive and negative affect, including symptoms such as content, enthusiastic, cheerful, lonely, anxious, and irritable. Other symptoms that were measured six times a day were highest physical activity and social contact for the past hour. Physical activity was asked by giving a range of options to choose from, ranging from “Resting”, “Sitting”, “Standing”, “Walking Slowly”, “Walking Briskly”, “Moderate Exercise”, and “High/Vigorous

Exercise". Social contact ranged from "None", "Virtually only", "In Person only", and "Both Virtually and In Person".

The rest of the questions were only asked once a day at 8pm. These include daily well-being questions which were scored using the same NRS, including questions about joint and muscle symptoms, problems performing tasks, enjoyment from tasks and also sleep hours and sleep quality the previous night. Participants were also asked if they may have COVID-19, or are experiencing any of the symptoms including fever, difficulty breathing, coughing, headache, and loss of smell/taste. Detailed

7.4.3 Statistical Analysis

The majority of the analysis was carried out on Stata 16.1. The analysis methodology for the first wave of the data were shown in the previous Chapter 6. In order to compare the two datasets, similar codes were used to create several variables such as physical symptom, positive affect, and negative affect. Time variables were also created so as to allow for time series analysis later on. Variables such as physical activity, social support and activities were also re-coded to allow for analysis. Some participants from the first wave of data were also dropped in this study, if they were not participating again in this second wave of data. This is to make sure that the analysis here is based on participants that were in both waves of the study. This means that 12 out of the 31 participants from wave 1 was not used in this study.

The first task carried out was to determine missing data of this new wave of data. Histograms were created to show completion for time of day, and also for each of the 10 days. This was then used to compare with the histogram that was previously created for Chapter 6. Missing data per participant was also investigated to make sure that there were enough longitudinal data for each participant, which was defined to be at least five consecutive days of more than one measurement in Chapter 6.

Descriptive statistics, including mean, within and standard deviation were also calculated. This will show how symptoms vary in between participants and also within a participants' 10-day period. A table was then created to show the descriptive stats for both Waves 1 and 2, and effect size was calculated for each of the differences as well. The effect size is calculated by dividing the difference between the means of the two waves by the standard deviation of the whole study. Effects sizes are reported as standardised mean differences

(i.e, Cohen's *D*), which is calculated and interpreted here as the mean difference divided by the pooled standard deviation. Using Cohen's rules of thumb, a value of 0.2 is considered a small effect, 0.5 is a medium effect and any value higher than 0.8 is a large effect (Cohen, 2013). Following this, a linear mixed methods test was carried out to see if any of the differences are significant. This will cover the first objective to find if there are any differences in symptom severity between waves.

In order to find any causal associations between symptoms, dynamic regression needs to be carried out to ascertain the direction of correlation between symptoms. This means that lagged variables need to be created to investigate how symptoms interact with each other over time. This process is repeated from wave 1 data seen in Chapter 6, besides the inclusion of social contact that was not part of the analysis before. The variables and lagged counterparts were standardized for analysis, and a cross-correlation table was first created to look for any dynamic correlations. Mixed effects regression was then carried out to test for significance between variables and lag-1 variables, and these mixed models were used to account for observations nested within patients. Significant associations were then displayed in an autoregressive cross-lagged panel model. This is then used to compare with the data and analysis from Wave 1.

Last but not least, a symptom network plot was created for both wave 1 and wave 2 data, including physical symptoms, positive affect, negative affect, physical activity, and social contact. Data was first exported from Stata 16.1 into R after the removal of other variables. The package *EBICGLASSO* was then used to create regularized partial correlations to control for other variables while calculating the edges for a network. After the formation of the partial correlation matrix, *Qgraph* was used to plot the network plots. After the two symptom network plots were created, comparisons can be made for how links changed between waves. Model specifications for this Chapter remains as the same as Chapter 6. Centrality values that could be calculated to quantitatively investigate the most influential symptoms of each symptom plot was not carried out here. This is because the purpose of the network plot was to distinguish how connections between symptoms change because of the implementation of the lockdown, thus the influence that each symptom has on the network is not as important.

7.4.4 Ethics

This study received ethical approval from the King's College London Research Ethics Committee (Ref Number: LRS-19/20-18186). Because of the intensive measurements that participants have to go through, the researchers are aware of the burden and have informed participants of their freedom to drop out of the study at any time. They were also informed that a copy of the final version of papers published from this study will be sent to them regardless of completion.

7.5 Results

7.5.1 Demographics

Table 7.2 shows the demographics table for participants involved in both wave 1 and wave 2 data collection. The mean age is 51.2, and that the majority of participants were female. Psoriatic arthritis was the most common IA subtype, followed by Rheumatoid Arthritis. White was the most common ethnicity and the 57.9% of participants had at least an undergraduate level education. 63.2% of participants also never smoked and the average BMI is 28.5, and the average diagnosis year was 2008.

Table 7.2: Demographics of 19 participants involved in both Wave 1 and 2

		N = 19
Age (Mean (Range))		51.2 (41-59)
Gender	Male	5 (26.3%)
	Female	14 (73.7%)
IA Subtype	Psoriatic Arthritis	10 (52.6%)
	Rheumatoid Arthritis	6 (31.6%)
	Spondylarthritis	2 (10.5%)
	Connective Tissue Disease	1 (5.3%)
Diagnosis Year		2008 (2006-2016)
Ethnicity	White	18 (94.7%)
	Mixed	1 (5.3%)
Education	No formal education	2 (10.5%)
	O levels	1 (5.3%)
	A levels	5 (26.3%)
	Undergraduate	8 (42.1%)
	Postgraduate	3 (15.8%)
Smoker	Never smoked	12 (63.2%)
	Ex-smoker	4 (21.1%)
	Current smoker	3 (15.8%)
BMI		28.5 (24.8 – 32.1)

7.5.2 Missing Data

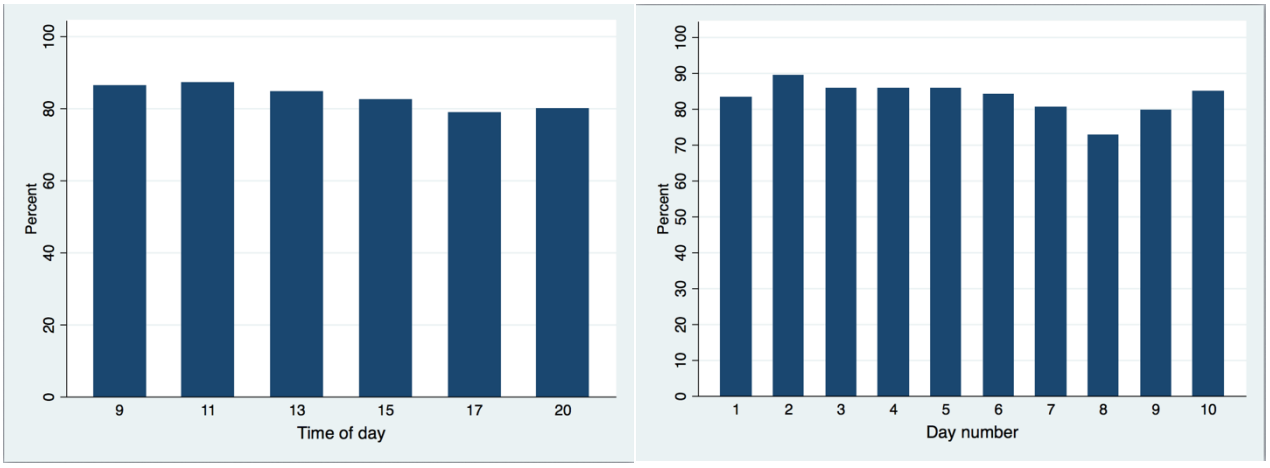


Figure 7.1: Missing data for Wave 1

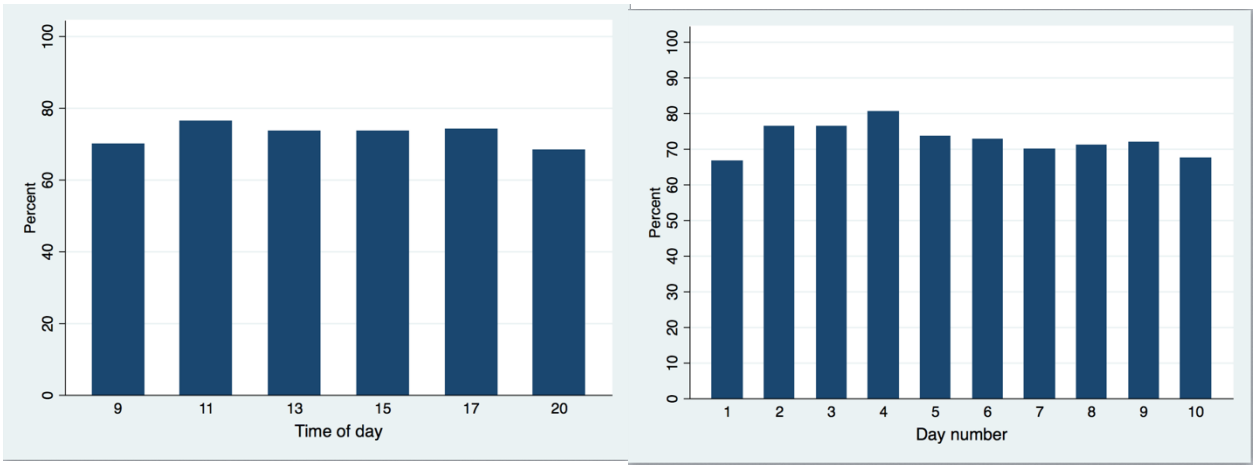


Figure 7.2: Missing data for Wave 2

Figure 7.1 and Figure 7.2 show the amount of data that is completed for waves 1 and 2, separated by time of day (9am, 11am, 1pm, 3pm, 5pm and 8pm), and day number (1 – 10). The average completion rate in Wave 1 for 19 participants out of 60 total surveys each was 83.6%, while the average completion wave for Wave 2 is 72.7%. Completion rates were relatively high for both waves, and there was only a minimal drop off of about 10.9%. There was also no clear time of day effects with completion rates across time relatively constant with each other. The completion rate was also quite constant for each of the study days, with wave 1 not dropping below 70% and wave 2 not dropping below 6.

7.5.3 Mean differences

Table 7.3: Descriptive Tables for both Wave 1 and Wave 2
*These variables are only measured once a day at 8pm

Variables	Wave 1 (953 observations, n =19) *(162 observations, n= 19)			Wave 2 (829 observations, n =19) *(130 observations, n= 19)			Effect Size for mean difference between waves
	Mean	Between S.D.	Within S.D.	Mean	Between S.D.	Within S.D.	
Pain	4.00	2.38	1.22	3.44	2.20	1.11	-0.22
Joint stiffness	4.25	2.02	1.33	3.35	1.69	1.26	-0.39
Fatigue	3.36	2.11	1.62	3.46	1.82	1.60	0.04
Loneliness	0.28	0.37	0.61	0.65	0.66	0.63	0.45
Anxiousness	1.06	1.14	1.28	1.09	1.27	1.12	0.02
Irritable	1.49	1.29	1.53	1.74	1.48	1.54	0.12
Content	5.42	2.25	1.78	5.66	2.31	1.54	0.09
Enthusiastic	4.92	2.08	1.80	5.51	2.27	1.47	0.21
Cheerful	5.55	2.23	1.73	5.69	2.40	1.47	0.05
Physical symptoms	3.87	1.93	1.10	3.42	1.60	1.07	-0.21

Table 7.3: Descriptive Tables for both Wave 1 and Wave 2
*These variables are only measured once a day at 8pm

Positive affect	5.30	2.07	1.54	5.50	2.17	1.31	0.08
Negative affect	0.94	0.77	0.85	1.16	0.99	0.81	0.18
Physical activity	3.14	0.46	1.20	2.91	0.50	1.13	-0.18
Social Contact	1.42	0.35	0.88	1.44	0.44	0.85	0.02
Joint and muscle pain*	4.47	2.20	1.37	3.86	2.35	0.99	-0.25
Difficulty performing task*	4.08	2.48	1.49	3.34	2.66	1.23	-0.26
Enjoyment from task*	6.30	1.38	1.67	5.92	1.76	1.41	-0.18
Satisfaction from social interaction*	6.72	1.74	1.78	6.22	1.81	1.43	-0.21
How supported they feel*	6.70	1.70	1.85	6.09	1.85	1.37	-0.26
Quality of sleep*	5.80	1.52	1.59	5.95	2.05	1.30	0.07

Table 7.4: Linear Mixed models for variables collected six times a day

Symptoms	Coefficient (adjusted mean difference between waves) [95% CI]	p-value
Pain	-0.47 [-0.87, -0.08]	0.019
Joint stiffness	-0.82 [-1.53, -0.11]	0.024
Fatigue	0.21 [-0.93, 1.34]	0.72
Loneliness	0.38 [0.078, 0.68]	0.014
Anxiousness	0.052 [-0.27, 0.38]	0.75
Irritable	0.33 [-0.0085, 0.66]	0.056
Content	0.26 [-0.017, 0.54]	0.065
Enthusiastic	0.19 [-0.27, 0.65]	0.43
Cheerful	0.11 [-0.23, 0.46]	0.53
Physical symptoms	-0.36 [-1.02, 0.29]	0.28
Positive affect	0.19 [-0.13, 0.51]	0.25
Negative affect	0.26 [-0.0014, 0.51]	0.051
Physical activity	-0.45 [-0.85, -0.058]	0.025
Social Contact	0.022 [-0.16, 0.21]	0.82

Tables 7.3 and 7.4 above were designed to investigate if there are any significant differences between waves. Instead of comparing with the entire wave 1 data, only the 19 that were involved in both waves were included because using the same sample of participants would show how symptoms change by the implementation of a lockdown. Table 7.3 shows the mean and standard deviation (both within and between) for the 19 participants involved in both waves of data collection. Within and between standard deviation were both calculated to not just show the variability of symptoms between the 19 participants, but also how symptoms vary throughout the 10-day study period within each participant. The effect size of the mean difference between waves was calculated as well. Table 7.4 showed the result of a linear mixed model carried out on the two waves, and shows the coefficient (the adjusted mean difference between waves) and the p-value of the coefficient. Table 7.3

showed how symptom averages and standard deviation changes between the waves, while Linear mixed models was carried out to investigate if there was a significant difference.

Regarding objective 1, several symptoms differed between waves. Physical symptoms had a lower mean in Wave 2 compared to Wave 1, with a standardised mean difference effect size of d=0.21, which is considered small. Specifically, both pain and joint stiffness were lower in wave 2 with effect sizes of d=0.22 and d=0.39 respectively, while fatigue had a slight increase of d=0.10, with an effect size of d=0.04. Positive affect and negative affect had divergent effects and both increased in Wave 2, and the effect sizes were d=0.08 and d=0.18 respectively. All negative affect and positive affect symptoms showed an increase in Wave 2. Unsurprisingly, loneliness had the largest effect size of d=0.45. Physical activity decreased during Wave 2, with a moderate effect size of d=0.18. The well-being and quality of life questions also all decreased in Wave 2 with effect sizes ranging from d=0.18 to 0.26 which were all small.

Table 7.4 showed that the decrease in total physical symptoms from Wave 1 to Wave 2 is not significant, with a p value of 0.28. However, individual physical symptoms such as pain and joint stiffness had significant decreases in Wave 2, with an effect size of 0.22 and 0.39 for the mean difference in pain and joint stiffness respectively. The difference in fatigue was not significant, and the effect size was also only 0.04, suggesting that the values of fatigue for both waves were similar. Negative affect was low on average across both waves but was slightly higher in wave 2, however this difference was not significant, with a p-value of 0.051. Loneliness is the only negative symptom that shows a significant increase in score, and Table 7.3 also showed that loneliness has the largest increase among negative affect with a large effect size of 0.45. Positive affect also displayed an increasing trend among all the symptoms, however none of the difference was significant, which leads to a non-significant p value for positive affect as a whole as well. Table 7.3 also displayed small differences in between waves, besides enthusiastic which has the biggest increase during Wave 2.

Last but not least, physical activity showed a moderate effect size in Table 7.3 with a decrease from 3.14 to 2.91. This score was also coupled with a significant p-value of 0.025, suggesting that physical activity did significantly decrease during the lockdown during Wave 2. Social contact was found to have no significant difference (p value = 0.82) between waves, with there being a slight increase in Wave 2 compared to Wave 1.It can be seen that

overall, physical symptoms and physical activity both had significant decreases in Wave 2. Psychological symptoms do not have much difference in between waves, beside loneliness which increased with a large effect size.

7.5.4 Lagged variables and Dynamic Regression

Lagged variables were created in order to investigate how symptoms co-vary with each other over time, thus utilizing the dynamic component of the data collected. This will allow for dynamic regressions which show the direction of a correlation present. A lagged variable can be interpreted as a variable at a preceding timepoint, thus a lag-1 variable started at the previous time point, while lag-2 variable started two timepoints before. The use of lagged variables in regression would allow for the direction of a significant association to be revealed. In the event that there is a significant association between variables A and B, dynamic regression between variables and the lagged component of the other variable will show the direction. This is done by exploring the association between variables lag-1 A and B, and between A and lag-1B. If only the association between lag-1 A and B is significant, this means that variable A has a significant association with next time point of B, which meant that the direction of the association would be from A to B. This has been carried out in Chapter 6 as well, but in this paper, social contact will be included as well and temporal associations for both waves will be investigated to see if there are any differences.

For wave 1, the correlation between the variables and lagged components are seen in Table 7.5 below

Table 7.5: Cross-sectional and lagged correlations of variables in Wave 1
Physymp = physical symptom; paffect = positive affect; naffect = negative affect; activity = physical activity; social = social contact; L1 = Lag-1

	Physymp	Paffect	Naffect	Activity	Social	L1 Physymp	L1 paffect	L1 naffect	L1 activity	L1 social
Physical Symptom	1	0.14 (0.001)	0.25 (0.001)	0.04 (0.21)	0.01 (0.70)	0.87 (0.001)	0.19 (0.001)	0.21 (0.001)	0.07 (0.04)	0.06 (0.08)
Positive Affect		1	0.02 (0.62)	0.19 (0.001)	0.04 (0.17)	0.17 (0.001)	0.79 (0.001)	0.11 (0.001)	0.09 (0.010)	0.02 (0.56)
Negative Affect			1	0.01 (0.67)	0.008 (0.81)	0.22 (0.001)	0.11 (0.001)	0.63 (0.001)	-0.01 (0.76)	0.006 (0.86)
Physical Activity				1	0.04 (0.25)	0.06 (0.06)	0.06 (0.06)	0.02 (0.55)	0.20 (0.001)	-0.006 (0.86)
Social Contact					1	0.009 (0.79)	0.02 (0.64)	0.06 (0.07)	0.06 (0.06)	0.30 (0.001)

Table 7.6: Cross-sectional and lagged correlations of variables in Wave 2
Physymp = physical symptom; paffect = positive affect; naffect = negative affect; activity = physical activity; social = social contact; L1 = Lag-1

	Physymp	Paffect	Naffect	Activity	Social	L1 Physymp	L1 paffect	L1 naffect	L1 activity	L1 social
Physical Symptom	1	-0.10 (0.004)	0.40 (0.001)	0.06 (0.081)	-0.14 (0.001)	0.79 (0.001)	-0.07 (0.045)	0.36 (0.001)	0.04 (0.25)	-0.12 (0.003)
Positive Affect		1	-0.05 (0.14)	0.15 (0.001)	0.10 (0.005)	-0.08 (0.029)	0.80 (0.001)	0.04 (0.27)	0.09 (0.014)	0.04 (0.21)
Negative Affect			1	0.04 (0.25)	0.11 (0.001)	0.37 (0.001)	0.009 (0.81)	0.71 (0.001)	0.05 (0.20)	0.10 (0.006)
Physical Activity				1	0.06 (0.065)	0.09 (0.009)	0.05 (0.15)	0.08 (0.02)	0.14 (0.001)	0.03 (0.33)
Social Contact					1	-0.12 (0.005)	0.08 (0.02)	0.10 (0.005)	0.05 (0.14)	0.29 (0.001)

Tables 7.5 and 7.6 show that there was a significant correlation for each variable when comparing between the variable at current time point and previous time point. This meant that all variables are significantly influenced by itself from the previous time point. The correlation between physical symptom and positive affect changed from a significant weak positive correlation to a significant weak negative correlation between Waves 1 and 2. this is also reflected by the change in direction for the correlations between physical symptom and lag-1 positive affect, and the correlation between positive affect and lag-1 physical symptom. Physical symptoms also had a weak but significant negative correlation with social contact and lag-1 social contact in Wave 2, but not Wave 1. Negative affect also develops a significant positive correlation with social support, and lag-1 social support in Wave 2.

These correlations show possible dynamic correlations in each wave, and the potential differences between waves, but significance testing needs to be carried out in order to investigate which dynamic association is significant after controlling for potential confounders. Tables 7.7 and 7.8 below show the coefficient, 95% confidence interval and p-value for each of the variables and lag-1 variables. Figures 7.9 and 7.10 respectively shows the dynamic regression between symptoms and lag-1 symptoms for Waves 1 and 2, while controlling for potential confounders such as age, gender, ethnicity, and the type of IA that the participant is diagnosed with. It can be seen that after controlling for potential confounders, the significant associations for both waves are all present, besides one association in Wave 1. After controlling for potential confounders, lag-1 positive affect is not significantly associated with social support anymore. Although there is a change in interpretation of the significance test, it should be noted that the direction and size of the effect indicated by the coefficients are similar. Figures 7.1 and 7.2 also show the significant associations for each wave, providing an easier look compared to the Tables.

Table 7.7: Dynamic regression between symptoms and lag-1 symptoms in Wave 1

	Physical Symptom		Positive Affect		Negative Affect		Physical Activity		Social Contact	
	Coefficient [95% CI]	p-value	Coefficient [95% CI]	P-value	Coefficient [95% CI]	p-value	Coefficient [95% CI]	P=value	Coefficient [95% CI]	p-value
L1 Physical Symptom	0.48 [0.40, 0.57]	0.001	0.04 [-0.09, 0.17]	0.54	-0.02 [-0.12, 0.08]	0.68	-0.05 [-0.21, 0.11]	0.53	-0.08 [-0.19,0.03]	0.13
L1 Positive Affect	0.06 [-0.04, 0.17]	0.24	0.51 [0.38, 0.64]	0.001	0.14 [0.05, 0.23]	0.003	-0.20 [-0.34, -0.07]	0.003	-0.07 [-0.14, -0.007]	0.03
L1 Negative Affect	0.005 [-0.06, 0.07]	0.88	0.10 [0.04, 0.17]	0.002	0.28 [0.18,0.39]	0.001	-0.03 [-0.13, 0.07]	0.53	0.06 [-0.04, 0.15]	0.24
L1 Physical Activity	-0.009 [-0.04, 0.17]	0.24	-0.05 [-0.07, -0.02]	0.001	-0.006 [-0.04,0.03]	0.75	0.02 [-0.06, 0.11]	0.57	0.03 [-0.03, 0.09]	0.37
L1 Social Contact	0.015 [-0.01, 0.04]	0.29	-0.01 [-0.05, 0.03]	0.58	-0.02 [-0.08, 0.04]	0.52	0.02 [-0.03, 0.08]	0.40	0.15 [0.05, 0.25]	0.004

Table 7.8: Dynamic regression between symptoms and lag-1 symptoms in Wave 2

	Physical Symptom		Positive Affect		Negative Affect		Physical Activity		Social Contact	
	Coefficient [95% CI]	p-value	Coefficient [95% CI]	P-value	Coefficient [95% CI]	p-value	Coefficient [95% CI]	P=value	Coefficient [95% CI]	p-value
L1 Physical Symptom	0.20 [0.11, 0.28]	0.001	-0.04 [-0.08, 0.01]	0.13	-0.02 [-0.11, 0.07]	0.63	0.09 [-0.07,0.25]	0.26	-0.001 [-0.14, 0.14]	0.98
L1 Positive Affect	0.009 [-0.07, 0.08]	0.82	0.23 [0.11, 0.36]	0.001	0.06 [-0.02, 0.14]	0.15	-0.11 [-0.27, 0.06]	0.20	-0.05 [-0.18, 0.08]	0.42
L1 Negative Affect	0.02 [-0.05, 0.09]	0.58	0.07 [0.02, 0.13]	0.009	0.28 [0.14, 0.43]	0.001	0.05 [-0.07,0.17]	0.38	-0.04 [-0.18, 0.11]	0.63
L1 Physical Activity	-0.02 [-0.06, 0.02]	0.37	0.0004 [-0.03, 0.03]	0.98	-0.01 [-0.07, 0.05]	0.68	0.03 [-0.05, 0.11]	0.43	0.005 [-0.06, 0.08]	0.87
L1 Social Contact	-0.05 [-0.1, -0.006]	0.03	-0.03 [-0.07, 0.01]	0.16	-0.005 [-0.05, 0.03]	0.80	0.04 [-0.04, 0.11]	0.33	0.16 [0.06,0.25]	0.001

Table 7.9: Dynamic regression between symptoms and lag-1 symptoms in Wave 1 controlling for confounders

	Physical Symptom		Positive Affect		Negative Affect		Physical Activity		Social Contact	
	Coefficient [95% CI]	p-value	Coefficient [95% CI]	p-value	Coefficient [95% CI]	p-value	Coefficient [95% CI]	p-value	Coefficient [95% CI]	p-value
L1 Physical Symptom	0.47 [0.38, 0.56]	0.001	0.04 [-0.09, 0.17]	0.59	-0.008 [-0.10, 0.09]	0.87	-0.07 [-0.25, 0.12]	0.46	-0.12 [-0.25,0.007]	0.07
L1 Positive Affect	0.06 [-0.04, 0.17]	0.25	0.50 [0.37, 0.64]	0.001	0.13 [0.03, 0.23]	0.01	-0.16 [-0.28, -0.04]	0.008	-0.07 [-0.16, 0.02]	0.13
L1 Negative Affect	0.02 [-0.05, 0.09]	0.58	0.11 [0.04, 0.18]	0.002	0.28 [0.18,0.38]	0.001	-0.009 [-0.11, 0.09]	0.86	0.09 [-0.02, 0.19]	0.10
L1 Physical Activity	-0.01 [-0.04, 0.02]	0.53	-0.05 [-0.07, -0.02]	0.001	-0.003 [-0.04,0.03]	0.87	0.002 [-0.09, 0.08]	0.96	0.02 [-0.04, 0.09]	0.47
L1 Social Contact	0.02 [-0.01, 0.05]	0.21	-0.006 [-0.05, 0.04]	0.79	-0.01 [-0.07, 0.04]	0.	0.02 [-0.03, 0.08]	0.47	0.14 [0.04, 0.24]	0.007

Table 7.10: Dynamic regression between symptoms and lag-1 symptoms in Wave 2 controlling for confounders

	Physical Symptom		Positive Affect		Negative Affect		Physical Activity		Social Contact	
	Coefficient [95% CI]	p-value	Coefficient [95% CI]	p-value	Coefficient [95% CI]	p-value	Coefficient [95% CI]	p-value	Coefficient [95% CI]	p-value
L1 Physical Symptom	0.11 [0.02, 0.20]	0.01	-0.04 [-0.09, 0.009]	0.11	-0.03 [-0.12, 0.06]	0.48	0.09 [-0.07,0.24]	0.27	-0.01 [-0.15, 0.13]	0.86
L1 Positive Affect	0.002 [-0.08, 0.08]	0.96	0.22 [0.09, 0.36]	0.001	0.04 [-0.05, 0.13]	0.37	-0.08 [-0.20, 0.05]	0.23	-0.06 [-0.20, 0.07]	0.36
L1 Negative Affect	0.04 [-0.02, 0.10]	0.23	0.10 [0.03, 0.17]	0.007	0.29 [0.13, 0.45]	0.001	0.04 [-0.08,0.15]	0.54	-0.06 [-0.19, 0.08]	0.41
L1 Physical Activity	-0.02 [-0.06, 0.02]	0.34	0.0002 [-0.09, 0.01]	0.99	-0.01 [-0.07, 0.05]	0.68	0.003 [-0.07, 0.08]	0.95	0.001 [-0.07, 0.07]	0.97
L1 Social Contact	-0.06 [-0.1, -0.007]	0.02	-0.03 [-0.06, 0.01]	0.20	-0.006 [-0.05, 0.03]	0.76	0.03 [-0.04, 0.11]	0.36	0.12 [0.01 ,0.23]	0.03

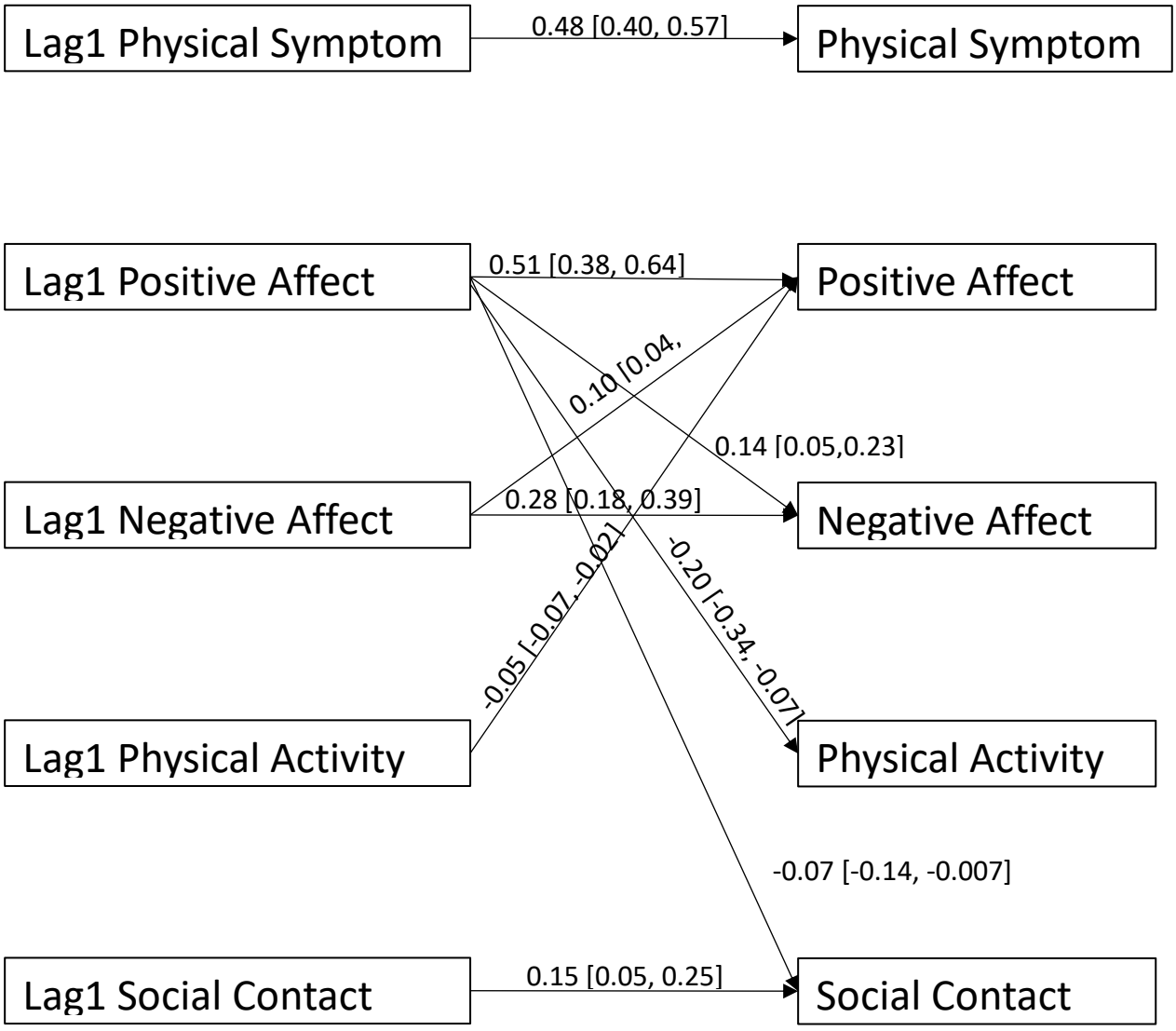


Figure 7.3: Autoregressive cross-lagged panel model for Wave 1

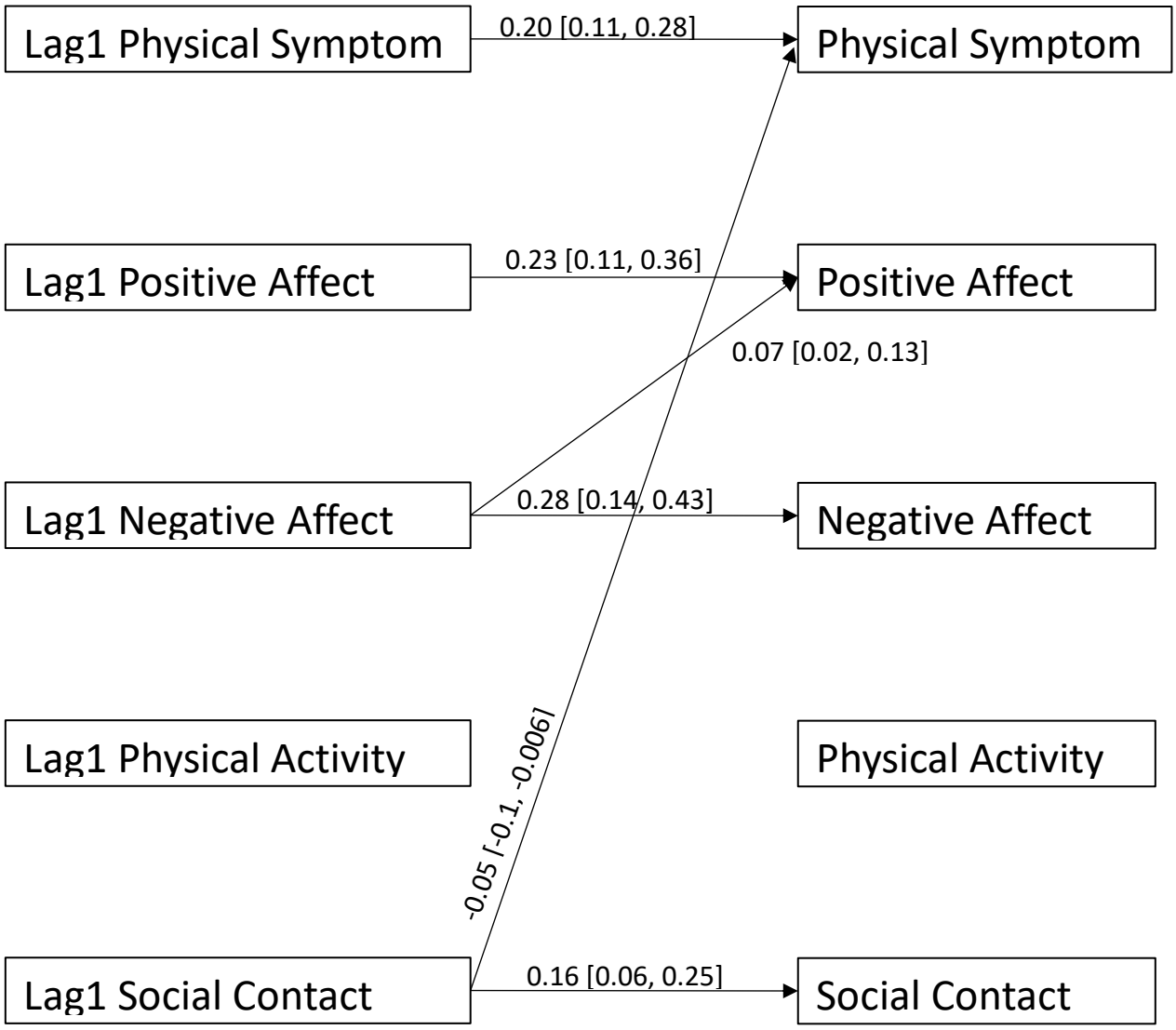


Figure 7.4: Autoregressive cross-lagged panel model for Wave 2

Figure 7.4 shows that there was a significant association (p value = 0.03) between lag-1 social contact and physical symptom in Wave 2, which was not present for Wave 1. This means that social impact has a significant negative correlation with the next time period's physical symptom, where an increase in social impact would lead to a decrease in next time period's physical symptom. The correlation changed direction between the two waves, with Wave 1 having a non-significant positive correlation (p value = 0.29). This showed that in a situation with social restrictions and high loneliness, social contact had a significant association with physical symptom in the next time period. However, this was not a significant difference between the waves, because the 95% confidence interval overlaps ([-0.01, 0.04] and [-0.1, 0.006]).

There were also several differences between the waves for positive affect. The first difference is that positive affect has a significant negative correlation with next time period's physical activity (p value = 0.003) in Wave 1, suggesting that an increase in positive affect will lead to a decrease in physical activity in the next time period. The direction remains the same for Wave 2, however it is non-significant (p value = 0.20). This was not a significant difference between the waves though, because the confidence interval overlaps ([-0.34, -0.07] and [-0.27, 0.06]. However, the same direction for both Waves indicate that the association in Wave 1 where positive affect has a negative correlation with next time period's physical activity is still important. Lag-1 physical activity was also negative significantly associated with next time period's positive affect in Wave 1, which is not present in Wave 2 as well. This shows that there was a much stronger connection between positive affect and physical activity in Wave 1 compared to Wave 2. This is a paradoxical finding however, because as seen in Chapter 6, lag-1 positive affect actually had a positive correlation with physical activity. The other difference in Wave 1, lag-1 positive affect had a negative significant association with social contact. This means that an increase in positive affect would lead to decreased social contact in the next time period. This difference is not significant between the waves, as the 95% confidence interval overlaps ([-0.14, -0.007] and [-0.18, 0.08]). However, the direction remains the same among both waves, and also suggest that in Wave 1 where there were no restrictions, positive affect influences next time period's social contact.

Last but not least, lag-1 negative affect had a significant positive correlation with positive affect, while lag-1 positive affect did not have a significant correlation with negative affect in Wave 2. In Wave 1, there was a feedback loop between positive and negative affect where both variables have a positive significant correlation with each other's lagged component. This shows that in Wave 2 where there was a lockdown, negative affect had a stronger influence on overall mental well-being. However, this difference was not significant between waves ([0.05, 0.23] and [-0.02, 0.14]) but does not discount the possibility that negative affect was the main driver in mental well-being.

None of the differences between Waves 1 and 2 were significant, after comparing the 95% confidence interval. However, there were still novel findings from the dynamic regressions. It could be seen that during a lockdown, increased social contact could lead to a decrease in physical symptoms. Physical activity and positive affect were also more connected during Wave 1, however the direction of correlation is conflicted because it differed from the findings in Chapter 6.

7.5.5 Network Model

Dynamic regressions showed the temporal interactions of symptoms and how these differed in between waves. However, the regression analyses only allowed for the inclusion of a few main variables before it became too difficult to estimate and interpret. Network analysis was used as well to produce symptom network plots for Waves 1 and 2, providing additional information about how every symptom measured six times a day interacted with each other. The symptoms that were included were pain, fatigue, joint stiffness, content, enthusiastic, cheerful, loneliness, anxiousness, irritable, social contact and physical activity. This include all the measurements of physical symptom, positive affect, negative affect, and the lockdown restricted social contact and physical activity.

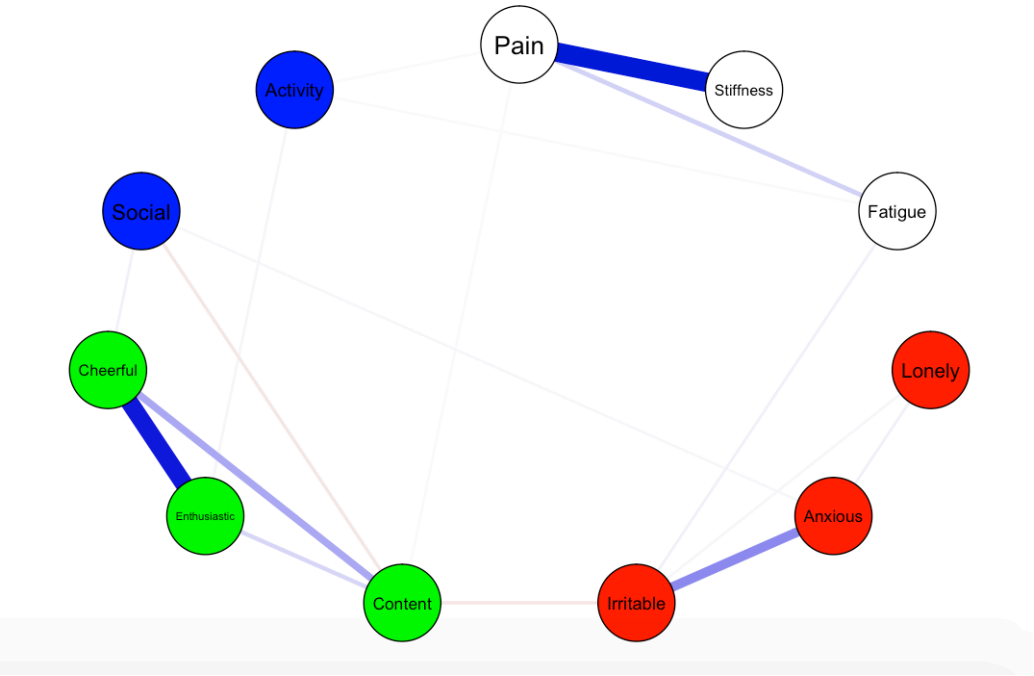


Figure 7.5: Network Plot for Wave 1

Figure 7.5 showed a network plot for data collected in wave 1 during a period of no restrictions. It could be seen that positive affect, negative affect, and physical symptoms are in separate clusters, with social support and physical activity unconnected to most other nodes. Social activity had a negative link with contentedness, and a positive link with cheerfulness, which cannot be explained due to the similarity between cheerful and content.

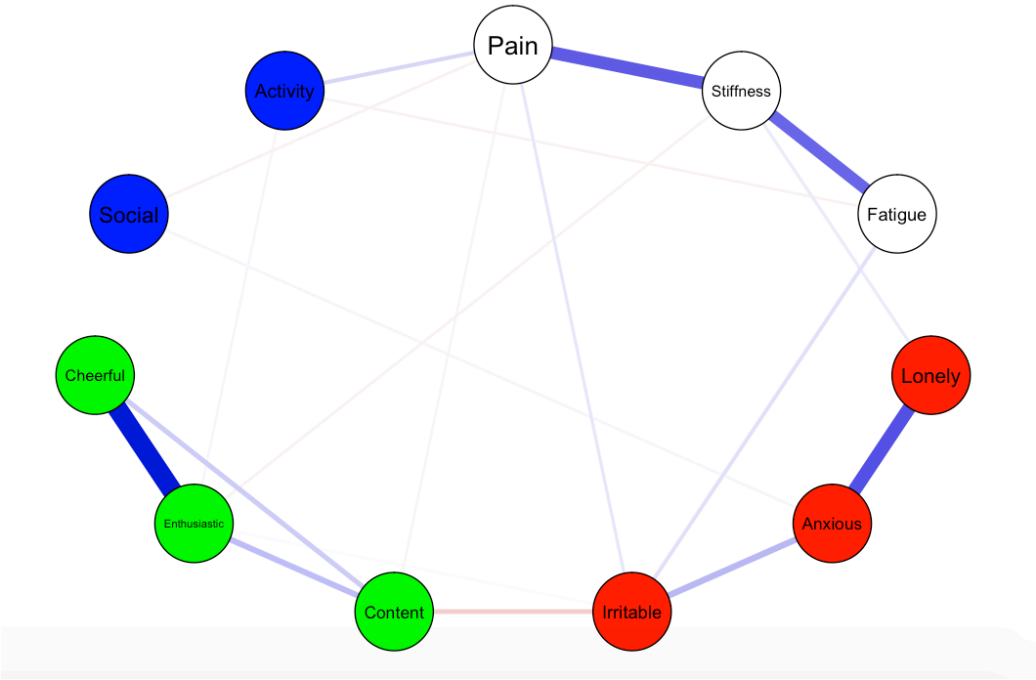


Figure 7.6: Network Plot for Wave 2

Figure 7.46shows a network plot that has more connections between clusters of symptoms. There are additional weak connections between physical symptoms and psychological symptoms, suggesting that a flare in any symptom could potentially result in a flare of the entire symptom network and that the likelihood of this was increased in wave 2. The connection between fatigue and pain has gotten weaker, but there is a strong connection with stiffness in Wave 2. This suggest that in a period of lockdown, fatigue is activated by stiffness as well as by pain. There is also a strong edge linking anxiousness with loneliness in Wave 2, which was absent in Wave 1. This change in wave 2 coincides with the lockdown during Wave 2 that leads to higher loneliness levels, suggesting that there was a change in reason for anxiousness. There is also a moderate link between physical activity and pain in Wave 2 which was not present in Wave 1, which suggests the possibility of physical activity as an external event that activates pain.

Sensitivity Analysis:

In order to ensure the accuracy of the network models, accuracy of the edge-weights will be considered. As there are no centrality indices created, no centrality stability tests are required. A graph for each of the network models will be created, which shows the bootstrap and sample means for each of the edges, alongside the 95% confidence interval. The y-axis represents each of the edges, but they are unlabelled because the purpose of this is to test for the robustness of the entire networks' edges instead of particular edges.

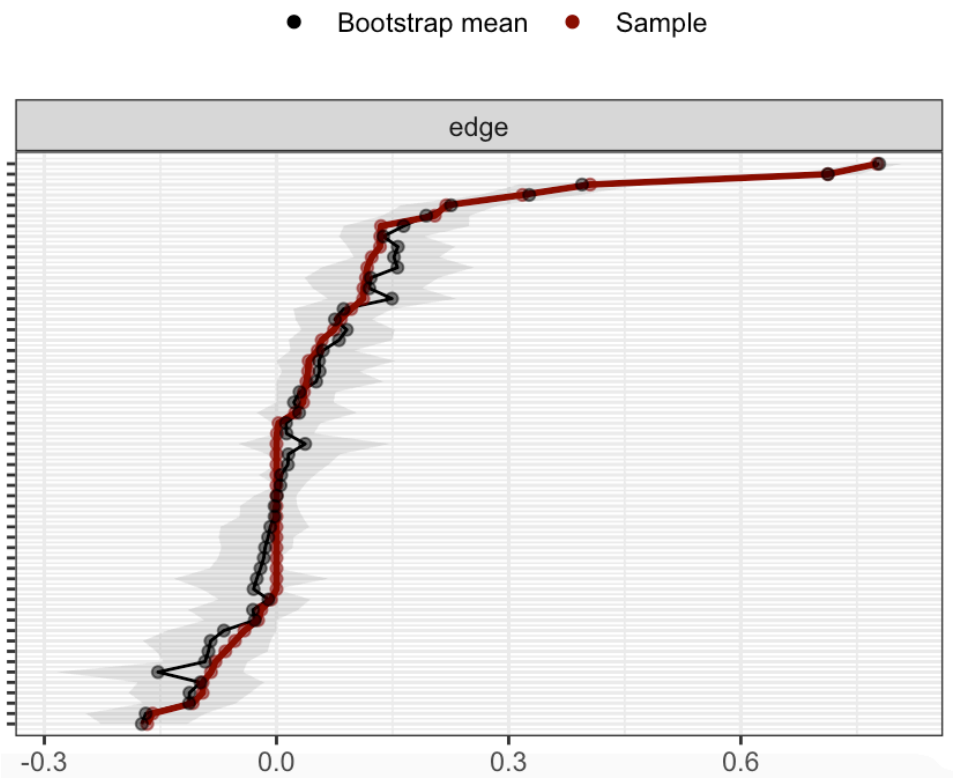


Figure 7.7: Graph for accuracy of edge weights in Wave 1

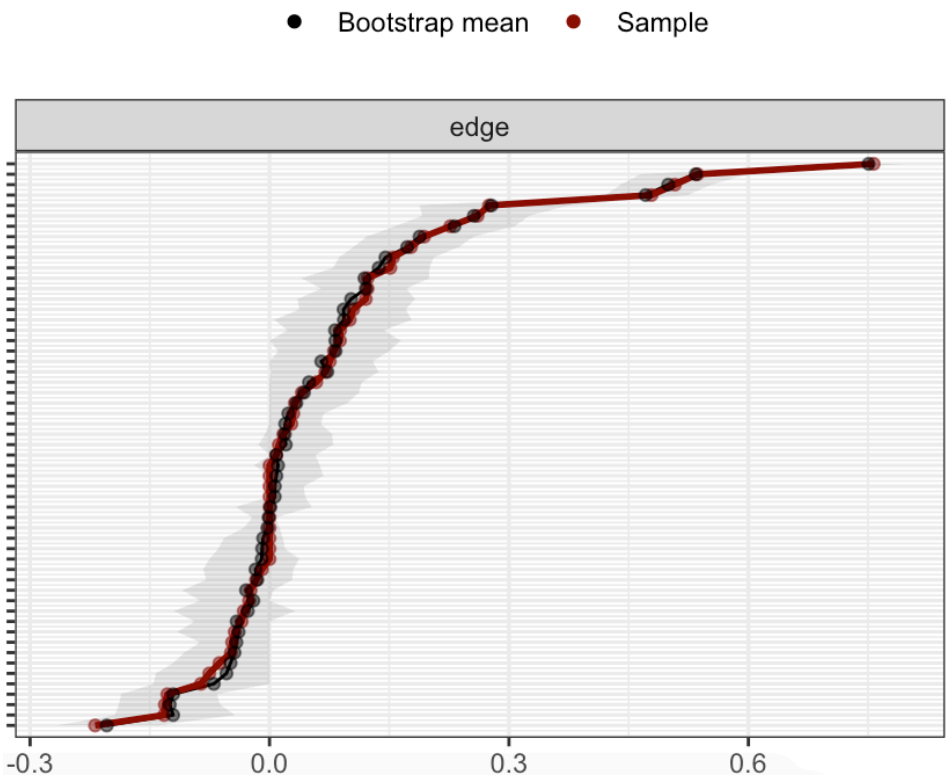


Figure 7.8: Graph for accuracy of edge weights in Wave 2

Both Figures 7.7 and 7.8 showed very close bootstrap and sample means, suggesting that there is not much difference. The 95% confidence interval is also very tight, with the exception of a few edges. There are a few edges in Wave 1 that could be shown in the network graph according to the bootstrap mean, but it is not substantial. This proved that the network models formed for both waves are reliable, and the edge weights are accurate. Comparison between edges can therefore be confidently done.

7.6 Discussion

This study compared data gathered from IA patients between a period of time with no restrictions, and a period of time with lockdown restrictions which provides the assumption that there was less social interaction, and also less physical activity. Using linear mixed models on the data provided, the difference between the two waves were evaluated to observe for any significant differences. Physical activity significantly decreased in Wave 2 with a small effect size of 0.18, however social contact is found to have a slight increase in Wave 2, although this difference is found to be non-significant. This finding is however paradoxical, because both satisfaction from social interaction, and how supported participants feel both decreased in Wave 2 with effect sizes of 0.21 and 0.26 respectively. It was also found that loneliness significantly increased, with the largest effect size of 0.45 among all other variables, which is also paradoxical to the increased social contact score in Wave 2. Physical symptom was also found to significantly decrease overall, in which both pain and joint stiffness follows the same trend, while fatigue had a non-significant increase in Wave 2. Among psychological symptoms, only loneliness had a significant difference. All other positive affect and negative symptoms increased in Wave 2, but not significantly.

Regarding temporal associations, there were similar associations between Waves. However, the dynamic regression showed novel findings in relation to physical activity and social contact. it could be seen that in Wave 2, lag-1 social contact has a significant negative correlation with physical symptom, suggesting that in a period of time with significantly higher loneliness level, an increase in social contact will lead to a decrease in physical symptom on the next time point. There were a significant association between positive affect and physical activity in Wave 1, where positive affect has a significant negative correlation with physical activity in the next time period, and vice versa. This connection disappears in Wave 2, where no lag-1 variable is significantly associated with physical activity. Finally, the network symptom plots showed that in Wave 2, fatigue had a strong connection with stiffness while in Wave 1, fatigue had a strong connection with pain. Physical activity also developed a weak connection with pain in Wave 2, whereas physical activity was isolated in Wave 1. Loneliness also developed connections with anxious and stiffness in Wave 2, while it only had weak connections with other negative affect symptoms in Wave 1.

Physical symptoms, in particular pain and stiffness, significantly decreased in Wave 2. This is a novel finding as no studies carried out on IA patients during lockdown investigated how different physical symptom levels change in comparison to no lockdown restrictions. Similar studies were carried out in other cohorts, for example a study on 150 patients with chronic diseases showed that there were no changes in physical symptoms and pain during a lockdown (Khot et al., 2021). It was also shown in a sample of 63 osteoarthritis patients that pain levels and joint function all significantly worsened during the lockdown (Endstrasser et al., 2020). However, this sample of patients were due for arthroplasty, a surgical treatment to restore function of a joint, which was delayed due to COVID-19. This means that the result is potentially not translatable to this study, where the participants were not included only if they had to delay treatment on joints. A more comparable study concerning IA patients in Germany (Hasseli et al., 2021) investigated differences between the first lockdown in April, to a period of no restrictions in July, and to the second lockdown in November. It displayed a stable self-reported pain score with no significant differences through these three time points, however no other physical symptom was included.

This different result regarding pain levels could be due to the frequency of surveys, where the study referred only asked for self-reported pain scores once a month and this study collected pain scores for six times a day over a period of 10 days. The intensive data collection methodology implemented here could mean that the pain scores are more accurate, while data collection once a month may be inaccurate due to presence of a flare. This significant decrease in levels of pain and stiffness between waves was thus an important finding not only because no other study discovered this, but also because it suggested that in the presence of increased loneliness and decreased physical activity, IA patients experience lower levels physical symptoms. This is paradoxical to what existing literature presents, which meant that it could be other elements of a lockdown that resulted in the decrease of pain and stiffness levels. When comparing between symptom network plots of Waves 1 and 2, there was also a major difference regarding physical symptoms.. Fatigue was strongly connected with pain in Wave 1, but in Wave 2, there was a strong connection between fatigue and stiffness instead. This suggest that in a lockdown situation, fatigue was more likely to be activated due to stiffness than pain, which was not the case in

a situation with no restrictions. No study had proved that the influences of fatigue change in IA patients during a lockdown. Even though this study could not prove a causation between fatigue and stiffness during a lockdown, it created a novel hypothesis that in the situation of low physical activity, fatigue is activated by stiffness rather than pain.

The score for social contact increased in Wave 2, which was opposite to what other literature had about the diminished social support and contact during a lockdown. This information was also paradoxical to other social scores collected in this study, such as loneliness and social satisfaction. This paradox regarding social contact could be due to how social contact is scored in the surveys. The scores range from 0 to 3, with 0 being no social contact, 1 as virtual social contact, 2 as in-person contact, and 3 as both. It does not just measure the amount of social contact, but the mode of social contact as well. This question was scored as such because there is a significantly increased risk of developing depressive symptoms if in-person social contact is decreased, which was not found in online social interactions (Teo et al., 2015), and higher in-person social interaction is also significantly associated with less PTSD symptoms and suicidal thoughts (Teo et al., 2019). This shows the importance of distinguishing between the type of social contact, and in the case of a lockdown which as shown in Table 7.1, has restrictions only on in-person meetings and not online meetings, would definitely play a role in how social contact changes for participant. Thus, the non-significant increase in social contact score does not mean that there is not a significant change in amount of social contact. It is widely acknowledged that lockdown brings about reduced frequency of social contact and insufficient social support (Sommerlad et al., 2021). The decreased social support score in Wave 2, with an effect size of 0.26 supports this finding as well. This established that the assumption this study operated under - where a lockdown leads to less physical activity and social contact - were correct.

Looking at temporal associations, it was discovered in Wave 2, social contact had a significant negative correlation with next time period's physical symptom. This suggested that in situations with reduced social contact and support, an increase in social contact can lead to a decrease in physical symptoms. No study on IA patients during lockdown had this same finding, as most studies on social contact was focused on mental health. However, a study on fibromyalgia patients showed that increased social support were significantly correlated with lower levels of pain (Aloush et al., 2021). A study carried out on hemodialysis patients also showed that a there is a strong negative correlation between

social support and fatigue, suggesting that a high level of social support is linked to a low level of fatigue. None of these studies were carried out on an IA cohort, but provided evidence of the possible association between social support and physical symptoms. The significant association discovered in this study meant that the effect of social contact in IA patients could extend past the mental health which current literature covered, into physical health. This could have important clinical implications because clinicians who were aware of IA patients who suffer from a lack of social contact would need to be more aware of possible spikes in physical symptoms.

The effect of the lockdown could be seen in a significant increase in loneliness with a moderate effect size of 0.45 in Wave 2. An increase in loneliness during lockdown is present in every demographic group, however it is even more severe in those that were already at risk, such as an older population such as this IA sample (Bu et al., 2020b). Loneliness level remains elevated even after the end of restrictions in some populations (Killgore et al., 2020) which points to the danger of lasting effects. These reaffirms the finding from this study that loneliness is significantly increased by the implementation of a lockdown. Loneliness was not evaluated in the dynamic regression that was carried out, but negative affect which was the overall construct was included. It could be seen that in Wave 2 during lockdown, negative affect has a stronger influence on psychological symptoms compared to Wave 1. This is because in Wave 1, the feedback loop between positive affect and negative affect exists, while in Wave 2, only negative affect is significantly associated with positive affect of the next time period. This suggest that negative affect is the main drive of psychological symptoms during a lockdown. No study examined if loneliness affects positive affect during a lockdown, but an EMA study carried out in Germany (Haucke et al., 2021) showed that loneliness increased negative mood. Loneliness is significantly associated with lack of social support (Emmungil et al., 2021), however both symptom network plots created in this study do not show a connection between lonely and social contact. This is most likely due to the scoring criteria of social contact, as described above. However, symptom network plot in Wave 2 showed that lonely has a strong connection with anxious which was absent in Wave 1. In a state of reduced social support, the feeling of loneliness and anxiousness are closely connected, and that an activation of either could lead to a flare in the other. The clinical implication here is that in cases of social isolation in IA patients,

negative affect played a bigger role in patients' mood and loneliness could be the activator for a hike in negative affect.

There was a significant decrease in physical activity in Wave 2 compared to Wave 1, with a small effect size of 0.18. This result is reflected in other studies, where a sample of 204 RA patients showed that there is a significant decrease in physical activity, both in frequency and intensity (Levy-Weil et al., 2021). It was shown in other studies that physical activity could improve mental health and well-being (van Zanten et al., 2020), but this study only discovered a weak association between physical activity and positive affect in Wave 1. The association was negative, suggesting that an increased physical activity led to lower positive affect in the next time period, which was opposite to what van Zanten's study (2020) discovered. Another study (Brady et al., 2021) also discovered that light physical activity could improve both mental and physical fatigue, but both cross-sectional correlation and dynamic regressions do not show any significance between physical activity and physical symptoms. In Chapter 6, lag-1 positive affect was discovered to be positively significant with next time period's physical activity, which was different from the discovery here. This could be because Chapter 6 utilized the full 30 participants dataset in Wave 1, while this was a sub-sample of the dataset in Chapter 6. This could have resulted in the change of direction of association between lag-1 positive affect and physical activity. This hinted at a possible selection bias, and thus the connection between physical activity and positive affect in this study could be inaccurate.

This study showed that there are significant symptom differences between lockdown period a period with no restrictions, but there were including some differences in temporal associations between the two waves. Physical activity decreased and loneliness increased during lockdown, and this was reflected by various other studies as well. This is an important finding because exercise and physical activity are known to help not just cardiovascular health and obesity, but also disease activity in arthritis (Metsios & Kitas, 2018). This significant decrease in physical activity during lockdown is thus a concern for clinicians, and exercise as a self-management tool should be continually pushed. Temporal associations in Wave 2 did not find any significant associations between lag-1 physical activity and other variables, suggesting that it did not play a significant role in other variables. However, because of the reduced sample, there could be inaccuracies. Furthermore, levels of pain and joint stiffness both decreased, which was a novel finding in

the population of IA. This could mean that certain elements of the lockdown helped with alleviating physical symptoms, and one theory that could be derived from this study is that social support could be a factor in determining next time period's physical symptom during lockdown. It is also important to note how physical symptoms change the interaction with each other during a lockdown, with stiffness instead of pain as the main connection within physical symptom. This could suggest that during lockdown, inflammation is the main reason for patient fatigue, which would mean that careful monitoring of inflammation levels could help in reducing fatigue levels. It was also discovered that loneliness, and in turn negative affect could be the main driver of influence for psychological symptoms during lockdown. This could mean that in a period of time with less social contact, loneliness plays an even bigger role in mood for IA patients, which means that in order to regulate psychological symptoms, it is important to have sufficient social support.

Even though this study managed to discover several novel associations, there were a few limitations to the study that prevented these associations from being fully explored. The sample size was reduced from Chapter 6 because of participant drop out, which meant that there was a possibility of selection bias. A sample of 19 also offered insufficient power compared to Chapter 6, which meant that in the case of conflicting information between these two studies, the findings revealed here needed to be verified in future studies. This meant that even though there were clinically important findings from this chapter, more studies with bigger sample size were needed to have a more thorough investigation. There was also a short follow up period, with both studies only carried out over a period of 10 days. This meant that if the participant was suffering from a spike in symptoms due to a flare, the result could be inaccurate. A flare last for more than 1 week in 43% of patients who suffered from a flare (Bykerk et al., 2014), suggesting that a study period of 10 days was not sufficient to take into the account of a flare. The two waves were also carried out in different seasons, with Wave 1 during July and Wave 2 during November. This meant that one was carried out during the warmer season, while Wave 2 was during the colder season. It is known that during the winter seasons, there is a significantly higher level of inflammatory cytokines compared to the hotter seasons (Najim et al., 2021). The difference in season thus meant that the level of inflammation is naturally different, which could play a part in how symptoms severity differ. This could play a role in influencing the significantly different symptoms and temporal associations between waves. Ideally, the two data

collection periods should be closer to each other which would prevent this problem from happening.

As stated above, other studies actually indicated that levels of physical symptoms either remained the same (Hasseli et al., 2021) or worsened (Endstrasser et al., 2020) during the pandemic. This is opposite to what is seen here, with both pain and joint stiffness significantly decreasing during the period of governmental restrictions. It is important to contemplate the contextual variables that are present in this study design that might lead to these different discoveries. As mentioned before, even though there were no governmental restrictions in the first data collection period, IA patients still had to engage in shielding practices which meant that there should still be a limit on physical activity and social contact compared to normal situations. One of the main differences is that during a period of governmental restriction, working from home is necessary. This has a consequence for several variables, such as reducing stress and decrease in physical activity due to the lack of travelling needed to go to work, reduced social contact and increased loneliness due to lack of interaction with colleagues, and a more sedentary lifestyle. These would play a role in the associations between symptoms and thus is a limitation that needs to be noted.

This selection bias can be seen when comparing between demographics of the participants included in this Chapter and those included in the full sample in Chapter 6. Those who completed the 2nd wave of follow-up, and included in the analysis sample in Chapter 7, were in general younger, healthier, more educated and predominantly of white ethnicity compared to the those in the overall sample who did not complete the 2nd wave of the sample. This difference in samples may induce selection bias where these attributes may bias the observed average level of certain symptoms or, if the demographic factor acts as an effect modifier, potential the strength or direction of associations between symptoms. Since the main focus of this study is estimating associations, and where mean differences are considered tests are based on within-person analyses, results are only generalisable under the assumption of homogeneity of the associations between symptoms across demographic factors.

This study has managed to reaffirm several results that are present in the IA community and general public during lockdown,such as the high level of loneliness, lower level of physical activity. There has also been novel discoveries such as the significant decrease of physical symptom severity and the potential beneficial effect on physical

symptoms due to social contact during a lockdown and the strong connection between fatigue and stiffness that developed during a lockdown. Furthermore, negative affect also had more influence on the psychological state of patients during a lockdown. These discoveries were unfortunately not proven, but could be interpreted as novel hypothesis that presents important clinical implications that should be further researched on. This study is limited due to some of the designs as mentioned before, but also by the scoring scale of social contact. Social contact was the only social interaction score that was surveyed six times a day, and the non-significant difference between waves showed that it needed to be changed. Separate scores for both quantity of social contact, and mode of social contact to be asked six times a day would be useful in identifying whether it was the quality or quantity of social contact that affects IA patients the most. Future research could also utilize specific symptoms instead of the symptom construct in dynamic regressions instead, such as pain, stiffness, and loneliness. This will be one of the methods to further the theories that were brought up in this study such as for example which physical symptom does lag-1 social contact have a significant association with. This will provide even greater clinical implication. The symptom network plots also showed how symptom interactions differ between waves, however it does not allow specific symptom interaction, such as how fatigue changed between Waves to be understood. This means that further research would be required to have a full understanding of the change in fatigue during a lockdown.

8. Remote Assessment of RA Patients Starting a New Treatment

8.1 Overview of Remote Assessment of RA Patients Starting a New Treatment

This chapter is based on the APPro study that collected intensive longitudinal data with the help of a wearable device from patients who are starting a new bDMARD treatment. After the previous chapters have established the use of mixed effect modelling and network science in this field, this chapter shows how a new treatment affect patients and provide useful clinical implications for both clinicians and patients. APPro was designed and carried out mostly by the researcher and could be used as a template for future studies that want to collect intensive longitudinal data in the field of RA. This chapter is based on two papers that will be published from the APPro study, and thus will have overlaps in background and methodology with other chapters.

8.2 Background

Rheumatoid arthritis (RA) is an autoimmune chronic inflammatory disorder and generally affects joints in the hands and feet through the inflammation of synovial membrane (Firestein, 2003) (Tobon et al., 2010). It is also the most common form of inflammatory arthritis, and affects about 1% of the global population (Friedewald et al., 2010). The effects of RA are very pronounced, with patients suffering from pain, swollen joints, disability and irreversible joint damage (Smith et al., 2011). There are also extra-articular effects on the heart, lungs and even inflammation of the blood vessels (Cojocaru et al., 2010). According to the NICE guidelines for Rheumatoid Arthritis in Adults (NICE, 2018), the aim of treating RA is to achieve remission, or “treat to target” which means treating to achieve a targeted low disease activity. Clinicians need to measure both the C-reactive protein (CRP) level and disease activity score (DAS28) monthly to see if either remission or low disease activity is achieved. CRP is a biological marker of RA (Chandrashekara & Sachin, 2012) and consistently elevated levels present greater risk for joint deterioration.The DAS28 is a scale that

measures disease activity through combining the scores of 28 swollen and tender joints in the arms, hands and knees, patient's global assessment, and Erythrocyte Sedimentation Rate (ESR). The score ranges from 1 to 9, with a score lower than 2.6 suggesting remission, and a score of 3.2 or lower suggesting low disease activity (Dougados et al., 2007).

Initial treatment plans as laid out by the NICE guidelines stated that conventional disease-modifying anti-rheumatic drugs (cDMARDs) need to be used, and that additional cDMARDs should be used in combination if clinician's disease activity target is not met. If there is still inadequate response to the cDMARDS, biological disease-modifying anti-rheumatic drugs (bDMARDs) are prescribed to the patients. bDMARDs cost considerably more than cDMARDs but is also proven to produce more quality adjusted life years (QALY), which is a measurement that looks at quality of life per year (Doan et al., 2006). This means that bDMARDs is commonly used only on patients with high disease activity. The impact of biologics can be seen in a significantly increased improvement in physical function compared to other treatments (Callhoff et al., 2013), and also significantly reduce joint inflammation and limit erosive damage (Scott, 2012). A review on 32 studies by Almedia and colleagues (2016) also showed a significant improvement in fatigue levels in patients using Biologics, although it is unclear if that is linked to the reduced inflammation. The safety of bDMARDs has also been evaluated, and it is shown to be comparable to cDMARDs and is reasonable especially in light of the benefits that it bring (Ruderman, 2012). Biologics have also been shown to reduce potential cardiovascular complications in RA patients, which in return reduces mortality rate (Mikuls et al., 2011).

RA primarily affects the peripheral joints, but there is also systematic inflammation and extra-articular processes that affects the patients (Turesson et al., 2003). The European League Against Rheumatism (EULAR) highlighted infections, cardiovascular diseases (CVD), malignancy, gastrointestinal disease, osteoporosis and depression as the six main comorbidities in RA (Baillet et al., 2016). These comorbidities have a significant influence on the mortality rate in RA, and thus treatments have to take into account the comorbidities as well (Humphreys et al., 2016). Depression is the most common comorbidity of RA (Baerwald et al., 2019), and a review by Matcham et al (2013) showed that the prevalence of major depressive disorder in RA patients is about 16.8%, while 38.8% of patients have depression according to the PHQ9. These rates are about two to three times higher than the general population (Sheehy et al., 2006), and this comorbidity is particularly dangerous because of

the worsened outcomes. Depression is an independent risk factor for higher mortality rate in RA (Ang et al., 2005), and also leads to higher pain levels, higher disability and also a lower adherence to treatment (Sheehy et al., 2006). This means that when investigating RA, it is important to consider the comorbidity with depression and how the physical symptoms and psychological symptoms interact.

In order to distinguish the underlying structure of comorbidity between RA and depression, there needs to be a model of understanding that allow all symptoms to be included. Network science has been used in a lot of other fields, for example in epidemiology where it is widely used because of its ability to take into account the various types of interactions that may occur between all the nodes (Danon et al., 2011). Network science is a field of study that looks at disorders not as latent variables that causes the various symptoms, but that symptoms are independent variables with causal interactions with each other that manifest into a disorder (Borsboom & Cramer, 2013). This means that disorders can be interpreted as a complex cluster of directly related symptoms and interactions and not a single latent construct (McGrath, 2005). Symptoms in a network are represented with a node, while associations between symptoms are represented with a link or edge in a graphical output which allows for a complete look at the disorder. This concept of network science can thus model comorbidity as a set of direct relationships between symptoms of two different disorders (Cramer et al., 2010). Overlapping symptoms that are linked to both disorders can be interpreted as a bridge symptom, which is crucial to the formation of the comorbidity. When one disorder is active and each of the symptom is activated, the bridge symptom will spread the activation to the other disorders' symptoms which will then manifest into a comorbidity. This concept can be used in looking at both physical and psychological symptoms in RA, where the symptoms are separate into these two main groups and a bridge symptom can be identified. This identifies symptoms that may trigger a spike in physical or psychological symptom, thus providing useful clinical information on what to manage.

RA symptoms are highly fluctuant, and some even varies throughout a day (Evers et al., 2014). This means that in order to have a good understanding of how symptoms interact with each other, it is important to study RA longitudinally instead of cross-sectionally. A review (Vriezekolk et al., 2011) showed that out of 2605 studies including RA and psychological distress, only 19 are longitudinal. This shows a distinct lack of research in

longitudinal designs. Chapter 3 showed that most longitudinal studies do not look at more than 3 symptoms, thus not able to allow all symptoms to be considered in any analysis. This showed that the data collected needs to both cover enough longitudinal range, but also enough symptoms to be able to show a complete picture of RA. In order to satisfy these needs, ecological momentary assessment (EMA) and wearable devices should be used. EMA utilizes repeated sampling throughout a day in real time in order to see how participants' experiences change throughout a day. It is also done in the participants' natural environment so as to ensure ecological validity (S. Shiffman et al., 2008). This means that EMA is uniquely suited to collect data from RA patients which displays day-to-day variability in symptoms (S. Schneider et al., 2012). Collecting data various times throughout a day also reduces recall bias because participant symptoms are collected at the specific times, and thus within participant variability and longitudinal analysis can be carried out with greater accuracy. The scoping review in Chapter 3 also showed that recent studies in high-intensive data collection have also shifted from paper diaries to EMA, suggesting the validity of using this methodology. In order to supplement these patient reported outcomes, remote measurement methods such as using wearables could be used. Wearable devices present the opportunity to collect objective data without any extra burden on the participants. It is also discovered that wearable devices demonstrated good feasibility and acceptability for use in RA patients by Jacquemin et al (2018). Wearable devices have also been used by Gossec et al (2018) which utilizes consumer grade activity tracker on patients diagnosed with RA or spondyloarthritis. It is discovered that the activity tracker which tracks patient activity through steps could detect a flare in disease activity accurately. Chew et al (2019) also showed the feasibility and advantages of monitoring RA patients outside of clinical appointments, which the use of EMA surveys and wearable devices will be able to bring.

It is also shown that the most common symptom that is included is pain, and that psychological symptoms are only classified as depression or anxiety without taking into account the specific symptoms. Utilizing the model of network science enable all symptoms to be considered, and the possibility of a central symptom to be found. Centralities are able to accurately identify the highly influential nodes in a network plot, and a central symptom is most likely to be the one that is in charge of the activation of the disorder network (Lawyer, 2015).There are also no studies that examined how specific physical and psychological RA symptoms change after the prescription of a biologic therapy, which

should ideally show a difference from high disease activity to lower disease activity. This shows the need to design a study that looks at both physical and psychological symptoms in RA that will allow for dynamic analysis, over a period of time that includes both before and after a new Biologic therapy.

8.3 Aims

The main aim of this study is to evaluate the utility of high intensity data collection in monitoring the impact of starting a new biologic treatment on both physical and psychological symptoms. This will be carried out using EMA surveys and a wearable device, FitBit to collect the data. It will address both the lack of study in the change of symptoms after exposure to bDMARDs, as well as the gap of literature in longitudinal studies that look at multiple symptoms that make up RA. This aim will be achieved by completing the following objectives:

1) Is it feasible to recruit and conduct a study involving intensive data collection, including EMA self-reported symptoms and ambulatory assessments with a wearable device, during the initiation of new biologics treatment?
2) Do these methods produce data that could provide opportunities to inspect differences over the 30 days period?
3) What symptom changes can be detected before and after exposure to a new bDMARDs
4) What additional information can be derived from the difference before and after exposure using other analytical methods?

In order to determine the feasibility of the study, the recruitment rate and the completion rate of each participant are calculated to test for willingness to participate in the study and the participant burden that is posed. This is in line with guidance on the conduct of feasibility and pilot studies (Eldridge et al., 2016). The feasibility of the measurements was tested by comparing agreement between the measurements derived for sleep and activity on the FitBit with the self-reported questions. To compare the feasibility of this study, it is proposed that an ideal compliance rate in EMA studies should be at least 80% (Stone &

Shiffman, 2002), while a systematic review showed that average compliance rate in chronic pain patients is around 85% (Ono et al., 2019). Therefore, compliance rates in this study should thus approach these numbers to be considered as a feasible study design with acceptable participant burden.

8.4 Methods

8.4.1 Study Design

NHS ethical approval was obtained from the Riverside Research Ethics Committee (04/01/2020, KCH Ref: KCH20-115). All participants gave informed consent and were sent participation information sheet. The study followed the ethical standards of the Declaration of Helsinki (1964) and its later amendments.

This study is a single arm longitudinal observational study that lasts for 30 days. It collects data through both EMA surveys and a wearable device, FitBit that tracks sleep, heart rate, steps, and physical activity. The participant is expected to wear the FitBit throughout the 30 day study so researchers can get an objective measurement of both sleep hours, nap time, steps, and minutes of intense physical activity. Surveys are sent six times a day for the first 14 days, with the time ranging from 9am, 11am, 1pm, 3pm, 5pm and 8pm. The surveys are repeated for the first five surveys, while the sixth survey at 8pm including additional questions regarding quality of life, sleep, and physical activity. For the last 16 days of the study, surveys were sent only once a day at 8pm, in the exact same format as the 8pm surveys sent on the first 14 days. This means that in total, there will be 100 surveys sent out to the participants over 30 days, with the first 14 days consisting of 84 surveys.

The study starts around three days before the participant starts a new bDMARDs treatment, so that comparisons can be made before and after treatment. There will thus be three days of pre-exposure data, and 27 days of post-exposure data with 11 of those including six surveys a day. The biologics were often mailed to the participants which means that the arrival dates are not always confirmed. This means that the three days of pre-exposure data could vary, depending on the accuracy of the dates that was provided by the

participants. It was not ethical for researchers to request participants to start treatment at a specific date just for the study.

Near the end of the study, participants were emailed to enquire of the interest in a semi-structured interview to provide feedback on the entire study. This interview is carried out on Microsoft Teams, or Zoom if the participant prefers. The purpose of this interview is for the participants to provide information on their experiences in the study and what can be improved. It also provides useful qualitative information regarding the feasibility of the study.

Prior to the recruitment of participants, the entire recruitment and study process were carried out on 3 participants as a pilot test to evaluate if the process runs smoothly. These participants recruited were on a stable treatment plan, and thus were not eligible for the study. This study only commenced after the completion of a pilot test. Initial plans were to allow personal approaches in recruitment where researchers were to meet potential participants in clinics for recruitment purposes. However, because of the COVID-19 pandemic, all recruitment was done by phone and using online forms. Every potential participant was called by the researchers instead of emails or through a nurse, to allow for a more personal approach. Furthermore, all these researchers were trained and highly informed about the study and study design. Participants were also given the FitBit that were used during the course of the study as incentives, thus fulfilling the recruitment strategy stated above.

8.4.2 Participants

Participants were recruited from came from the Rheumatology Clinics in King's College Hospital (KCH) that is situated in Denmark Hill, London from February 2021 to September 2021. Because of the COVID-19 pandemic, it is not feasible to recruit participants when they come in for their structured clinic appointments. This means that in order to recruit potential participants, researchers sit in on weekly Biologic meetings where rheumatologists and their multi-disciplinary teams discuss which RA patients require a new biologic, and what is the ideal biologic to prescribe.

Considering that the main study objective is to test for the feasibility of an intensive data collection methodology in patients undergoing a new bDMARDs treatment, power calculations to determine the sample size are not appropriate and sample size justification should be based on the precision with which key parameters of interest are estimated (Billingham et al., 2013). The sample size here was partly based on feasibility of recruitment given the limited resources available and based on previous pilot and feasibility studies having median sample sizes of between 30-36 (Billingham et al., 2013). In the case of this study, a sample size of 30 is sufficient because of the large amount of datapoints that each participant contributes for the analysis of the collected data. Furthermore, recruitment rates can be estimated to within a 95% CI of approximately +/- 9-10%, assuming a 30% recruitment rate (i.e. 100 people have to be approached to recruit 30 people). This is sufficient to inform the feasibility of future research and identify whether additional research to understand willingness to participants and the acceptability of intensive designs are needed before progression to a larger study. All eligible patients were approached, and recruitment will stop after the sample size of 30 was achieved.

8.4.3 Materials

Baseline Survey:

Participants were sent a baseline survey as part of the consent process for the study. This survey asks for basic demographic information from the participants, including age, gender, disease duration, and highest education level attained. The survey also asks for some basic clinical information using the Musculoskeletal Health Questionnaire (MSK-HQ) (Hill et al., 2016), PHQ2 (97% sensitivity 67% specificity) (Kroenke et al., 2003) and the GAD2 (86% sensitivity, 83% specificity) (Kroenke et al., 2007) which are all shown to be valid and reliable scales.

EMA Surveys:

There are two parts to the EMA survey. The first part includes 11 questions including 3 on physical symptoms, 4 on positive affect, and 4 on negative affect. This survey was sent 5

times a day at 9am, 11am, 1pm, 3pm, and 5pm for the first 14 days. These questions were scored on a numerical rating scale (NRS) ranging from 0 to 10.

The second part of the EMA survey is sent at 8pm for the full 30 days. This survey includes the afore-mentioned 11 questions, but adds additional questions that asks about the participants' physical activity throughout the day, sleep quality and hours for last night, quality of life through the day, and usage of FitBit.

FitBit:

Each participant is given a FitBit Charge 4 at the start of the study so that objective measurements of sleep and activity can be taken. According to a study that compares between a previous FitBit product, FitBit Flex and a validated wearable tool for measuring physical activity in RA patients named SenseWear (Feehan et al., 2014), it is found that patients rated the experience with FitBit 4.7 out of 5, suggesting satisfaction with using FitBit. However, It is found that FitBit Flex overestimates step counts compared to the validated tool. A newer and more powerful version of FitBit in Charge 4 should provide a better and more accurate read, however no study has been released regarding Charge 4. An old systematic review carried out on 67 studies regarding the accuracy of FitBit devices on step counts (Feehan et al., 2018) shows that there is consistent evidence that FitBit devices provide acceptable accuracy for step counts. Another review focusing on 22 studies (Haghayegh et al., 2019) compared FitBit to polysomnography and found that FitBit manages to distinguish between sleeping and waking times at a accuracy level between 0.81 and 0.91. This justifies the use of FitBit Charge 4 in this study to extract objective information regarding physical activity and sleep.

8.4.4 Measurements

Following the success of the COVID-IA study where it can be seen that there is at least a completion rate of 75% across all times, the EMA survey questions can be shown to be feasible for participants to be completed. This is why elements of the previous study has been implemented here as well, with the same physical symptom being chosen. Pain and fatigue has been chosen in the majority of longitudinal studies in musculoskeletal disorders

according to the previous scoping review (Tung et al., 2021). The positive and negative affect symptoms were kept as well, but instead of three symptoms each they were expanded to four symptoms each. This is done so that there will be an equal number of low and high valence symptoms in both affect. Negative affect included the symptom of "Sad" which is included to even up the number of low valence symptoms, and also a direct interpretation of low mood which was not covered before. Positive affect included an extra symptom of "Relaxed" in order to have two low valence symptoms as well. These 11 symptoms are all rated using a Numerical Rating Scale (NRS) that ranges from 0 to 10, with 0 labelled as none, 5 as moderate and 10 as extreme. The NRS scale is used because it allows participants to complete the questions quickly, thus increasing the completion rate. It is also validated for use in self-reports of pain studies (Hjermstad et al., 2011) and even in even in children as young as eight years old (von Baeyer, 2009) (von Baeyer et al., 2009), suggesting that the use of NRS is both reliable and simple. These questions are included in every survey sent to the participant.

There are additional questions sent on all the 8pm surveys, which is sent every day. These questions include daily well-being questions which were scored using the same NRS, including questions about joint and muscle symptoms, problems performing tasks, enjoyment from tasks and also social interactions and support available throughout the day. Participants were also asked about the highest level of activity that happened on the day. This is because physical activity is vital to manage the disease course of RA, and is found to improve muscle function without affecting inflammation or joint damage (Plasqui, 2008). Fitbit also measures minutes of intense physical activity, so the measurement of highest activity level in surveys will provide a subjective contrast. There were also questions regarding hours of sleep and quality of sleep, which can also be compared with the FitBit data. Sleep is important when discussing RA symptoms because it is shown that in cases of sleep loss in RA patients, mood and pain levels deteriorated (Irwin et al., 2012). The end of the survey asked participants if they removed the FitBit during any exercise, so the researcher will be able to know if any possible discrepancy between FitBit and survey data is caused by this. The measurements derived from the FitBit are FitBit sleep, FitBit activity, and FitBit steps. FitBit sleep is measured by the number of hours that the participant is asleep each day as calculated by the FitBit based on readings of movement, heartrate and temperature following the proprietary methodology. Similarly, FitBit activity is measured by

the number of minutes each day that FitBit shown the participant as “Fairly Active” and “Very Active” based on readings of movement and heartrate. FitBit steps are the number of steps that the participant has walked each day as shown by the FitBit readings of movement.

8.4.5 Procedure

The study’s participants are recruited from the Rheumatology Clinics from King’s College Hospital. Because of the restrictions from the COVID-19 pandemic, recruitments could not be done in person. This means that researchers have to attend a Biologics clinic attended by Rheumatologists and multidisciplinary team and identify potential patients that are diagnosed with RA and about to start a new biologic treatment. Upon identification of these potential participants, the name and NHS ID was collected so the researcher could use EPR to get contact information. Telephone numbers are the priority, and in case of missing numbers, emails were collected.

Researchers call the potential participants in order to receive informal consent over the phone. The study only progresses if the participant indicate interest, and wants to receive the participant information sheet and consent form that will be sent through email. Upon completion of the consent form which is designed using Qualtrics, participants are also directed to a baseline survey that is part of the consent process. Participants are only fully consented and included in the study after completion of both consent form and baseline surveys. After formal consent is achieved, researchers will remind participants that the study has to commence three days before the new biologic treatment and that upon receiving news from the nurse or pharmacist, participants should email the researcher of the start date. Because of the possibility that participants may forget, researchers still contact the participant at least once every fortnight to enquire about the status of the new biologic treatment.

After receiving a concrete start date for the new treatment, researchers contact the participants and enquire about the preferred mode of set up, either through email instructions, phone call or video call. Researchers need to set up the FitBit with custom log

in details so as to extract data, and also provide a link to SurveySignal which will sign the participants up for the survey study. The set-up needs to happen one day before the commencement of the study, because the surveys are sent one day after registration, and the Fitbit needs to record the night's sleep before the first day of survey as well. Surveys are sent six times a day for the first 14 days, at 9am, 11am, 1pm, 3pm, 5pm and 8pm. For the last 16 days, surveys are only sent once a day at 8pm. At the end of the study, the data are extracted from Qualtrics, and FitBit data is extracted using the API in order to get both intra-day data and inter-day data.

Participants are also contacted near the end of the 30 days to enquire about interest and availability for a semi-structured interview. Those that accepted were interviewed over Microsoft Teams or Zoom, and the meeting was recorded and transcribed. The interview follows a topic guide that can be seen in Appendix D. The topic guide is just a guideline for the interviewer to follow, and that participants have the freedom to control the flow of the interview.

8.4.6 Statistical Analysis

The survey data that was downloaded from Qualtrics was first converted into a format that is readable on STATA, and additional information such as IP address was removed. Once opened in STATA, some of the variables are recoded so that it appears in a format that could be used for analysis. There were no missing data because the survey questions all had to be filled in for it to be submitted. Time variables are also created so that dynamic regressions can be carried out. Some duplicates was also discovered and removed, the duplicates was likely to have been caused by server problem with SurveySignal that means the same survey was sent multiple times, resulting in repeated answers. The first input of the duplicate was kept. 3 new variables; physical symptom, positive affect, and negative affect were created by using the average of the sum of each of the symptom constructs. This is to enable easier analysis between the types of symptom and allow associations to be created between physical and psychological symptoms.

In order to complete the first objective which is to evaluate the feasibility, the total number of participants approached, the total number of participants recruited and the reasons for why each potential participant was not recruited was investigated. This creates

a table and flowchart that shows the rate of success in recruitment, and the percentage of participants that were not able to participate in this study due to various reasons. The next step is to then gauge the feasibility of the data for analysis of the difference before and after biologics. A descriptive table including mean, within and between standard deviation of all the variables was first created to show the spread of data. After that, the completion rate of the surveys were shown using histograms. Histograms for surveys completed over the first 14 days was shown by using completion rate per time point, and also completion rate for each time point over all 14 days. Histogram for the last 16 days was also shown by looking at the completion rate per day.

After establishing the feasibility of both the study and the dataset, change in symptom severity before and after the exposure to new biologic treatment can be discovered. Codes were first written in STATA in order to separate the data into exposed and unexposed. Following that, mixed effects model were carried out on each of the 11 symptoms scores and also the overall physical symptom, positive affect and negative affect. Physical activity and sleep scores for both FitBit and Survey data were included as well. The first step was to create a line plot for the change in severity scores for the entire study. After that, the margin scores for before and after exposure was compared to see if there is a significant change in severity score after exposure to a new biologic therapy. Last but not least, the average change each day in symptom severity score after exposure was also investigated. These steps will show which symptom has a significant change in score after exposure, and also the trend of these changes. These steps were also carried out for physical activity and sleep, but only after correlations were carried out between the data derived from survey and data extracted from the FitBit. This will allow not just the investigation of change in activity and sleep after biologic, but also allow for the validation of objective and subjective measurements.

Dynamic multilevel models utilise only main symptom constructs of physical symptoms, positive affect, and negative affect instead of individual symptoms as stated before. One of the main reasons why main constructs are used is to prevent the cluttering of analysis results. If every symptom is included, there will be 11 symptoms and the lagged components included in the dynamic panel model, creating a complicated picture that is difficult to interpret and to extract useful information from. Furthermore, the estimation of such a model is complex and problems with convergence typically encountered, particularly

under scenarios where there is likely to be a high degree of multicollinearity due to theoretical overlap between variables. Using the overall symptom constructs allows for models to be estimable and results in a clearer understanding of the temporal associations that can be easily derived from models. However, naturally this aggregation loses information. This is specifically the point of symptom network analysis, which allows for the inclusion and graphical summary of the associations between not just a handful but large numbers of symptoms, thus and allows for a clearer interpretation of different associations between symptoms across the network.

In order to accomplish the final objective, there will be two main analysis applied on this longitudinal data. The first will a dynamic regression to see how symptoms interact with each other over time. The first step is to create lagged variables, which is simply the value of the variable at a preceding timepoint, thus a lag-1 variable is the value at the previous time point, while lag-2 variable is the value two timepoints before. This was carried out for the main symptom construct of physical symptoms, positive affect, and negative affect. This is because the previous analysis has already looked at the symptoms in depth, so a look at how the entire component changes with another will provide novel information. A cross-correlation between these 3 symptoms and the lagged counterpart was first carried out to investigate any potential temporal correlations. After that, dynamic regression was carried out to investigate the associations. They are then drawn in a cross-lagged dynamic panel model for easier viewing. This will show potential causations between symptoms by showing the direction of the associations. This is done for both before and after exposure, so as to establish if the temporal associations change after exposure to a new biologic. The next step will be to create network plots of the symptoms for both before and after exposures as well. This is done by first exporting the data from STATA into R. After that, the data is transformed into a regularized partial correlation using the package *EBICGLASSO*. The formation of this package will then allow the matrix to be calculated into a symptom plot using the package *qgraph*. The network plots will then be evaluated for differences, and then centrality values, including degree, closeness, betweenness, bridge, and expected influences will be calculated. This is to provide both a quantitative and qualitative look at the network plots.

The lagged analysis is conducted through all data collection points without considering the differences in the timings between assessment differing throughout the

day. For most observations the differences is consistent, however, this means that the effect of previous evening symptoms on current morning symptoms will be included in assuming the strength of the association is the same as the current mornings symptoms on the assessment 2 hours later. With the evening symptoms measured at 8pm and morning symptoms measured at 9am, there is a 13 hour difference between these two lagged periods. This variability in time difference may pose as a problem because some symptoms may not have an effect after a night's sleep, and even if this is not the case it would be expected that the correlation would reduce with time. It is not straightforward to allow for different lengths of time between lagged observations so this is something that will need to be considered when interpreting effects. Specifically, the lagged association will be underestimated for the first observation of the day and slightly underestimated for other lagged associations.

8.5 Results

8.5.1 Recruitment Rate

Upon discussion of the patients in MDM meetings, the names of potential participants are noted down. The contact details are searched on the Electronic Patient Records (EPR), and are called within a week. The average time from MDM meeting to recruitment is about 5 days. Upon recruitment, it ranges from one day to two months for participants to begin the study, depending on when the new biologic treatment starts, with the average being around three weeks.

74 potential participants have been listed down and contacted, and 25 have been successfully recruited. This is a 33.8% success rate in recruitment. Out of those that did not consent (n=49), table 8.1 shows the reasons and quantity of participants in each group. Elaborations for each reason is below the table.

Table 8.1: Reasons that participants declined to participate (n = 49)

Reason	Number of Participants (%)
Did not complete consent	9 (18.4%)
Biologic date missed	5 (10.2%)
Wrong contact information	7 (14.3%)
Did not want to take part	8 (16.3%)
Did not speak/read English	4 (8.2%)
Did not pick up the phone	10 (20.4%)
Did not have required technology	3 (6.1%)
Problems with FitBit	3 (6.1%)

Out of the 49 patients that were not recruited, 17 of the patients were not contactable. Seven of them had wrong contact information (phone numbers) on the Electrical Patient Records (EPR) and phone calls were not able to be put through. The number was called on at least three occasions, on varying days and times to ensure that the number was incorrect. For the other 10 patients, the number was valid but no one picked up the phone. All participants were called on at least 3 different instances, with at most a week in between each call. Calls were also made on each day at different hours, accounting for the possibility of participants being out of home, or busy at work. It was decided that after three weeks of attempts to stop contacting the potential participants, because of the average three weeks biologic treatment commencement wait time as mentioned above, and the inconvenience posed to the participants from all the calls.

32 potential participants picked up the call and was willing to talk about the research project. Out of the 32, seven was not able to proceed with the project because they were not eligible due to the exclusion criteria. Four of the participants either did not speak English or read English at a level comfortable enough to read the participation information sheet and surveys that will be sent daily. The other three patients did not have sufficient technology to commence the project, where a smartphone with internet access is needed. Two of the three did not have a smartphone and thus cannot access the surveys on the go, and the last one did not have internet access.

The patients eligible for the project was gauged for interest on the project, and an informal consent was sought on the phone. Eight patients declined to proceed with the project and was not interested. Nine patients were initially interested and provided us with their email address to get access to both the participation information sheet and consent form, but did not finish the consent process. These nine patients were contacted at least once a week after the initial phone call to remind them of the study.

The last eight participants that did not participate in this study completed formal consent for the study. However, three of these could not proceed because they had issues with the FitBit. Two participants had skin problems which would interfere with wearing Fitbits, and the last one had lymphedema which meant that the wrists are too swollen to wear FitBits. This means that these 3 patients had to withdraw their consent in this study. The last 5 participants were also unable to commence with the study because of a missed Biologic date. The EPR system does not show the start of new Biologic treatment date, thus participants were called or emailed often to remind them to inform researchers of their new treatment date.

This showed that only 14.3% of patients not participating were unable to participate due to the exclusion criteria, which means that the criteria is not too strict. Due to the COVID-19 pandemic, recruitment plans changed from in-person at the clinic to phone calls. This could decrease the amount of patients that could not be contacted, which stands at about 34.7% of those not participating. Only 1/3 of the patients that are not participating in this study due to their disinterest in the project, suggesting that the study design and the burden on patients is acceptable. These can be seen in Figure 8.1 below.

Only 25 were successfully recruited instead of the target sample size of 30, mainly because of the delay in recruitment due to the COVID-19 pandemic. Recruitment was delayed because ethics approval was initially granted in late 2020 and then further affected by the Christmas lockdown, and only 3 pilot participants tested prior to the study being paused to recruitment as part of the prioritisation of COVID-19 research. Recruitment was restarted in March 2021 with insufficient time to recruit to the initial target sample size of 30 by the latest time that this analysis was undertaken to allow for completion of the thesis. However, recruitment will continue target. Out of the 25 recruited, only 12 participants has completed the 30 days study period, and thus only those are included in that element of the study. This means that the results gathered regarding the feasibility of this study is a

preliminary analysis based on a subset of the final sample size. The final analysis submitted for publication will include a total of 30 participants both for the estimation of the recruitment rate and the analysis of the longitudinal data.

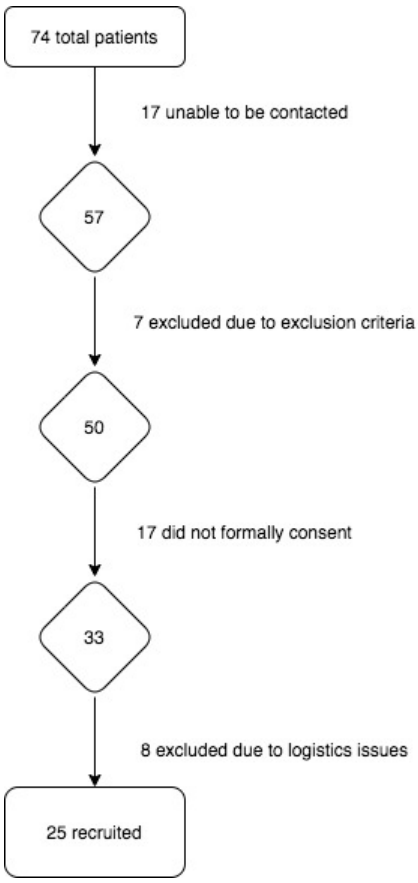


Figure 8.1: Flowchart of recruitment of participants

8.5.2 Descriptive & Completion Rate

Table 8.2: Descriptive Statistics

Variables	Number of participants (average number of assessments)	Mean	Between S.D.	Within S.D.
Pain	12 (88.75)	3.92	2.08	1.44
Joint stiffness	12 (88.75)	3.62	1.66	1.43
Fatigue	12 (88.75)	3.66	1.67	1.58
Sad	12 (88.75)	1.65	2.00	1.02
Loneliness	12 (88.75)	1.50	1.98	0.927
Anxiousness	12 (88.75)	2.13	1.89	1.22
Irritable	12 (88.75)	1.97	2.09	1.19
Relaxed	12 (88.75)	3.97	2.14	1.47
Content	12 (88.75)	4.57	2.29	1.47
Enthusiastic	12 (88.75)	4.10	2.16	1.40
Cheerful	12 (88.75)	4.335	2.31	1.51
Joint pain effect	12 (26.58)	3.87	2.05	1.63
Difficulty performing task	12 (26.58)	3.31	1.95	1.68
Enjoyment from task	12 (26.58)	4.55	2.06	1.32
Satisfaction from social interaction	12 (26.58)	5.44	2.41	1.49
How supported they feel	12 (26.58)	5.69	3.14	1.16
Hours of Sleep	12 (26.58)	6.41	1.09	0.792
Physical Activity	12 (26.58)	3.73	0.988	0.903

Fitbit Sleep	12 (85.75)	6.62	0.932	1.17
Fitbit Activity	12 (91.1)	36.8	26.2	37.0
Fitbit steps	12 (91.1)	8790	3900	3410

Table 8.2 above shows descriptive statistics for all of the symptoms measured. Both within and between standard deviation are shown, because within standard deviation examines how the symptoms change over time within each participant, while between standard deviation examines how the symptom score varies between participant. It can be seen that for physical symptoms, positive affect and negative affect, there is a larger between standard deviation than within, suggesting that it varies between participants more and are rather consistent within each participants' study period. The only symptoms that varies more within each participant are the FitBit data for Minutes of Activity and Hours of Sleep.

Table 8.3: Percentage of completion rate and number of days pre-biologic per participant
*Because of a server outage with SurveySignal, these participants missed days 15-18.
These missed surveys are included in the missed completion rate

Participant ID	% of completion rate	No. of days pre-biologic
35220	100	3
41117	88	3
43403	88	1
45217	96	3
51337*	92	2
59478	89	2
76072	84	2
84451	83	3
85007	93	3
88412	94	3
94057	87	3
95815*	71	4

As seen in Table 8.3, the completion rate of participants are mostly above 80%, with only one at 71% and it ranges to 100%. The average completion rate is 88.75%. Majority of the participants also have three days of pre biologic data which is part of the study design. There was one with four days, one with one day and three with two days of pre-biologic data.

Figures 8.2, 8.3, and 8.4 below will show a close look at completion rates for each time and each day. Figure 8.2 shows the completion rate for each time of day over the first 14 days. The first day has relatively worse completion rate, while it starts to get much more complete at the start of the fifth day.

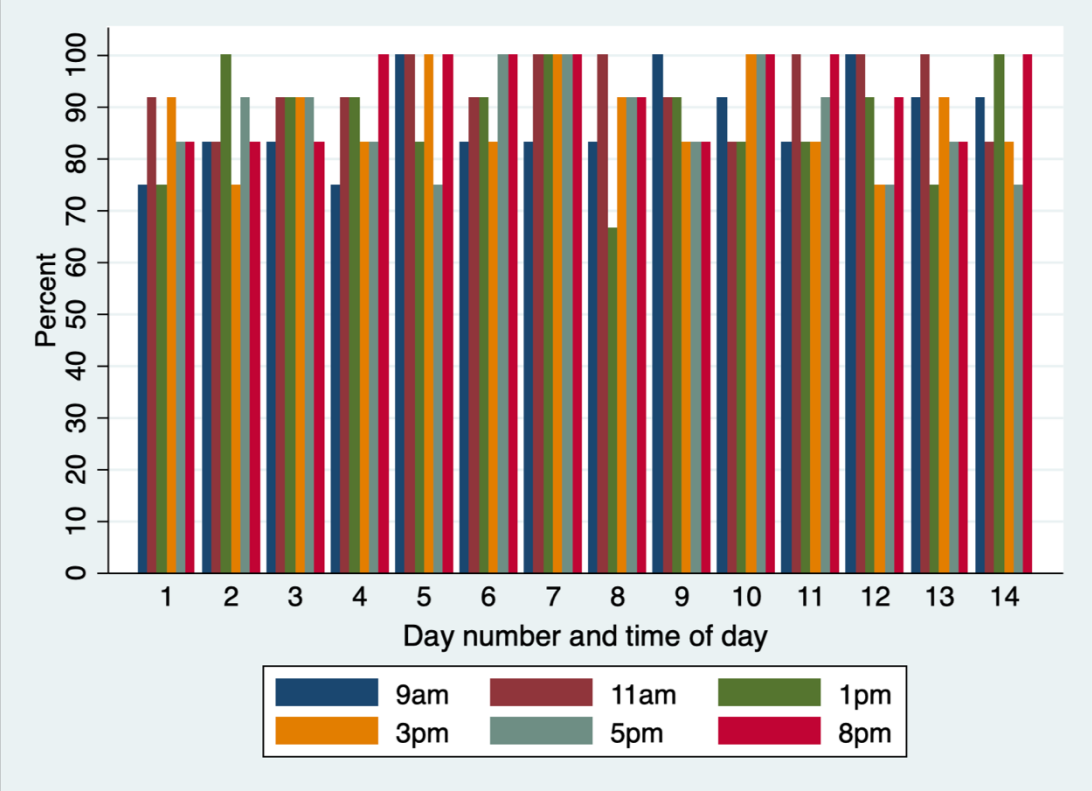


Figure 8.2: Completion rate of each time for each of the first 14 days

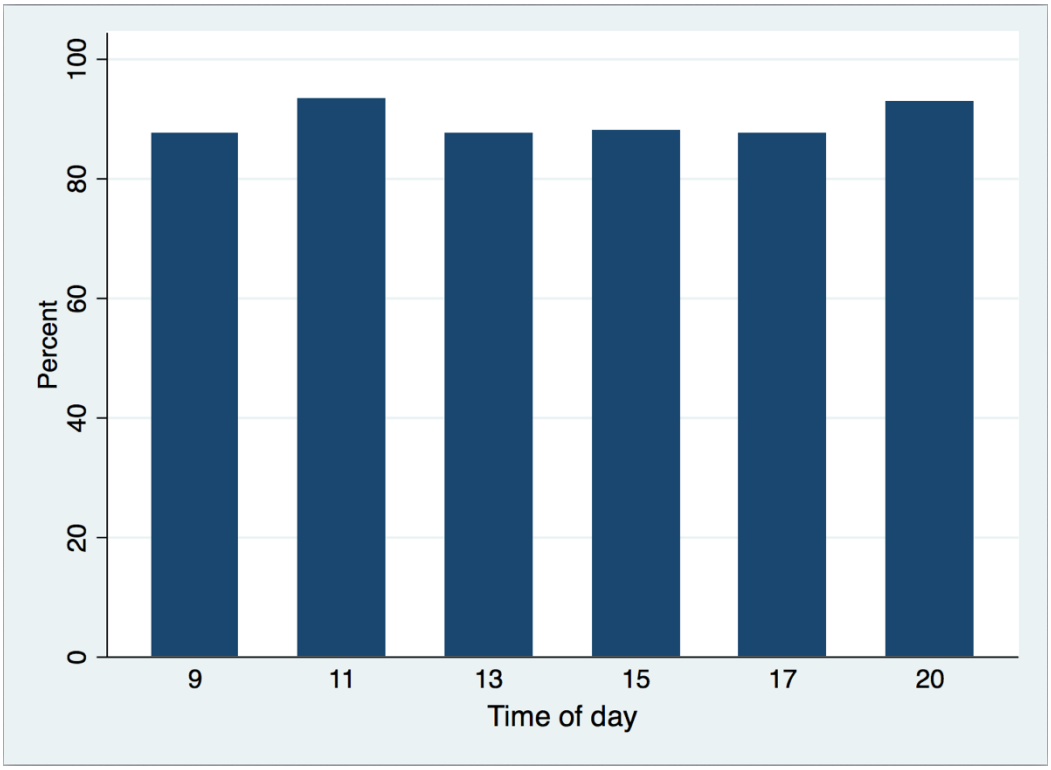


Figure 8.3: Completion rate of each time over first 14 days

Figure 8.3 is a simpler look at the completion rate of first 14 days. It can be seen that 11am and 8pm has the highest completion rate of about 90%, but other times are all around 85% at least. This shows that both 9am and 8pm time points are not too early or late respectively, and that the gap in between each time point is acceptable.

Looking at Figure 8.4 below shows the completion rate for the last 16 days. There is only one data collection per day, so the percentage of completion each day is lower, since the absence of one survey will mean that it is 0%.

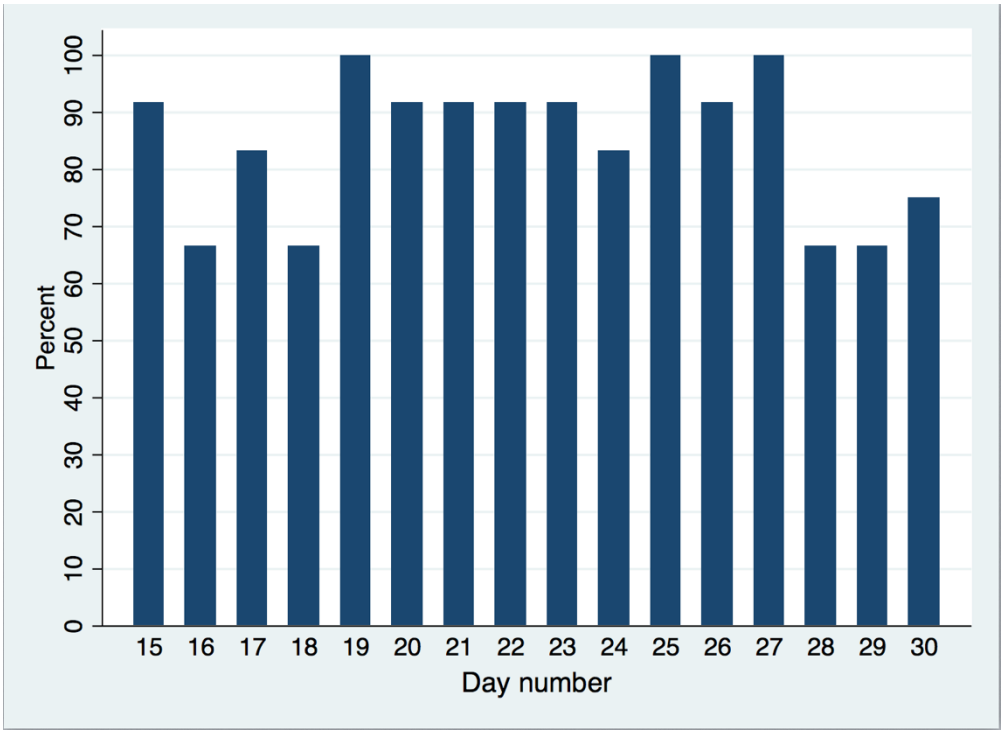


Figure 8.4: Completion rate of the last 16 days

It can be seen that the completion rate of every participant is relatively high. There is an average of 88.75% completion rate for each participant, and that the completion rate of each time point over the first 14 days are all satisfactory. There also seems to be not much drop off for any day, besides a slight drop off on the 28th and 29th day which increased again on the last day. 33.8% of the patients that researchers attempted to contact were recruited as well, with only 1/3 of the patients not recruited showing a lack of interest in the study. This means that the recruitment rate of a study that uses similar study design should be even more successful in recruitment with a slight change of recruitment method.

8.5.3 Mixed Effects Model for Difference

Having established the feasibility of both recruitment of participants for this study and the data, it is important to see what novel information this data can provide. According to Table 2, all participants have at least one day of data collection before biologics, thus providing the opportunity to inspect differences before and after biologic. Using mixed effects model,

each symptom is looked at to see if there are any significant changes after the commencement of a new biologic treatment, which will be termed as day 0. It is also investigated if there are significant changes when comparing between exposed and unexposed. Day 0 will not be treated as an exposed or unexposed day, it will be disregarded from analysis when looking at difference. This means that exposed days will be any day starting from Day 1, the day after biologics infusion, and unexposed days are any days before Day 0.

Table 8.4: Mixed effects model for difference before and after exposure to bDMARDs

Symptom	Coefficient [95% CI) for unexposed vs exposed	P-value for unexposed vs exposed?
Pain	-1.32 [-1.54, -1.10]	0.001
Fatigue	-0.519 [-0.777, -0.261]	0.001
Joint Stiffness	-0.975 [-1.20, -0.754]	0.001
Sadness	-0.0357 [-0.211, 0.139]	0.689
Loneliness	0.0743[-0.085, 0.234]	0.361
Anxious	0.204 [0.0007,0.407]	0.049
Irritable	-0.281 [-0.486, -0.076]	0.007
Relaxed	-0.50 [-0.740, -0.260]	0.001
Content	-0.538 [-0.781, -0.296]	0.001
Enthusiastic	-0.207 [-0.444, 0.030]	0.087
Cheerful	-0.492 [-0.743, -0.240]	0.001
Physical Symptoms	-0.940 [-1.13, -0.749]	0.001
Positive Affect	-0.436 [-0.644, -0.228]	0.001
Negative Affect	-0.0106, [-0.143, 0.122]	0.875
Physical Activity	0.216 [-0.147, 0.579]	0.244
Sleep	0.0927 [-0.228, 0.413]	0.571
Fitbit activity	-13.8 [-20.1, -7.47]	0.001
Fitbit steps	-1120 [-1690, -560]	0.001
Fitbit sleep	-0.0802 [-0.286, 0.125]	0.445

Table 8.5: Mixed effect model for average difference per day after exposure
*value is left blank if linear model was chosen

Symptom	Coefficient [95% CI] of linear component	P-value for linear	Coefficient [95% CI] of quadratic component*	P-value for quadratic*
Pain	-0.114 [-0.178, -0.0499]	0.001	0.00222 [0.00077, 0.00367]	0.003
Fatigue	-0.0473 [-0.0794, -0.0152]	0.004	-	-
Joint Stiffness	-0.0445 [-0.0947, 0.00571]	0.082	-	-
Sadness	-0.0208 [-0.0413, -0.000232	0.047	-	-
Loneliness	0.0374 [0.00907, 0.0657]	0.010	-0.00196 [-0.00316, -0.000762]	0.001
Anxious	-0.0158 [-0.0423, 0.0108]	0.244	-	-
Irritable	-0.0147 [-0.0353, 0.00587]	0.161	-	-
Relaxed	-0.0808, [-0.131, -0.0304]	0.002	0.00407 [0.00232, 0.00583]	0.001
Content	-0.0378 [-0.0955, 0.0198]	0.199	0.00250 [0.000802, 0.00421]	0.004
Enthusiastic	0.0284 [-0.00301, 0.0599]	0.076	-	-
Cheerful	0.0224 [-0.0220, 0.0668]	0.322	-	-

Physical Symptoms	-0.0894 [-0.137, -0.0413]	0.001	0.00171 [0.0005, 0.00294]	0.007
Positive Affect	-0.0389 [-0.0876, 0.00978]	0.117	0.00267 [0.00122, 0.00412]	0.001
Negative Affect	-0.0142 [-0.0307, 0.00238]	0.093	-	-
Physical Activity	0.00131 [-0.0143, 0.0169]	0.869	-	-
Sleep	0.0155 [0.00388, 0.0271]	0.009	-	-
Fitbit activity	0.0432 [-0.477, 0.563]	0.871	-	-
Fitbit steps	8.19 [-42.9, 59.2]	0.754	-	-
Fitbit sleep	0.200 [-0.00242, 0.0424]	0.080	-	-

Table 8.4 and 8.5 shows 2 different significance tests being carried out. Table 4 looks at if there is a significant difference between unexposed and exposed, and the coefficient is also shown to demonstrate the direction of the difference. The average change per day is also calculated and shown in Table 5, and it is carried out in both linear and non-linear models. The preferred model is then chosen by the lower Bayesian Information Criterion (BIC) score.

The study duration ranges from -4 to 28, with the negative numbers representing the unexposed dates, and day 0 being the day of treatment. Exposed days will thus be from day 1 to day 28. There is only one participant with 4 days of pre-biologic data, and thus the "-4" data is based only on that dataset, likewise with day 28 which is the only based on the participant with 1 day of pre-biologic data.

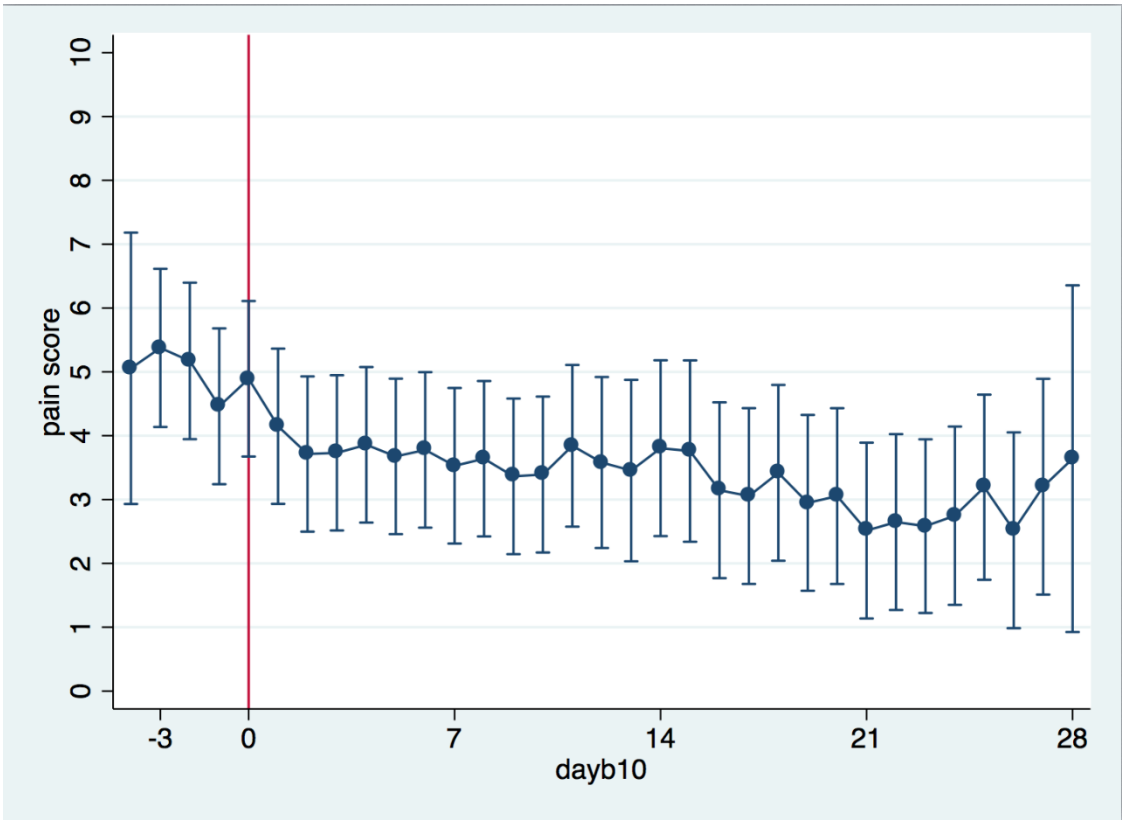


Figure 8.5: Line plot for Pain

Figure 8.5 shows the line plot for pain severity levels throughout the study. It can be seen that there is an immediate decrease after day 0, and then a gradual decrease until the end where there is a sudden hike in pain severity levels. This is reflected by the significant value (p value = 0.001) of -1.32 when comparing between unexposed and exposed. There is also an average of 0.114 decrease after exposure at a quadratic rate of change, which means that there is a larger decrease in score right after exposure which tapers off at the end.

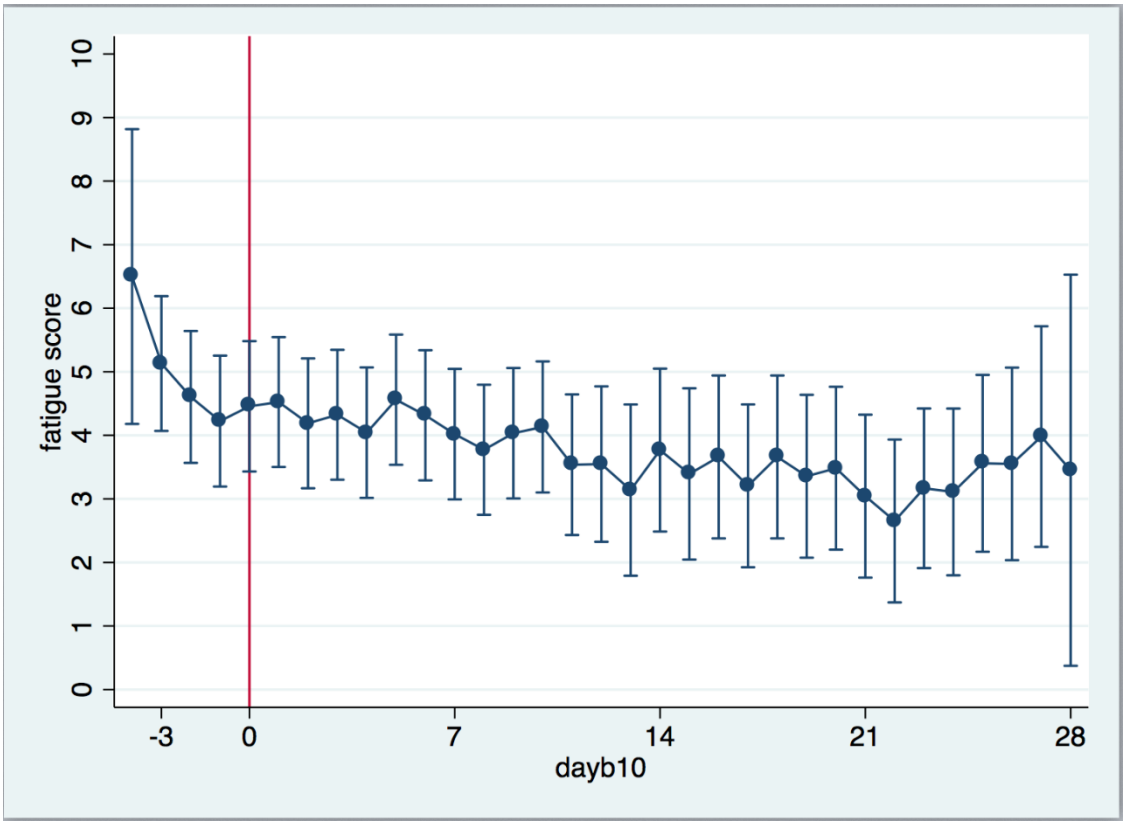


Figure 8.6: Line plot for Fatigue

The line plot in Figure 8.6 shows that fatigue levels dropped before exposure to biologics, and it stayed consistent for a few days before dropping after exposure. It reflects a significant (p- value = 0.001) difference between unexposed and exposed, however with a lower value than pain of -0.519. The significant linear average change after exposure is only -0.047, suggesting that there is a consistent decrease of fatigue daily but at a small level.

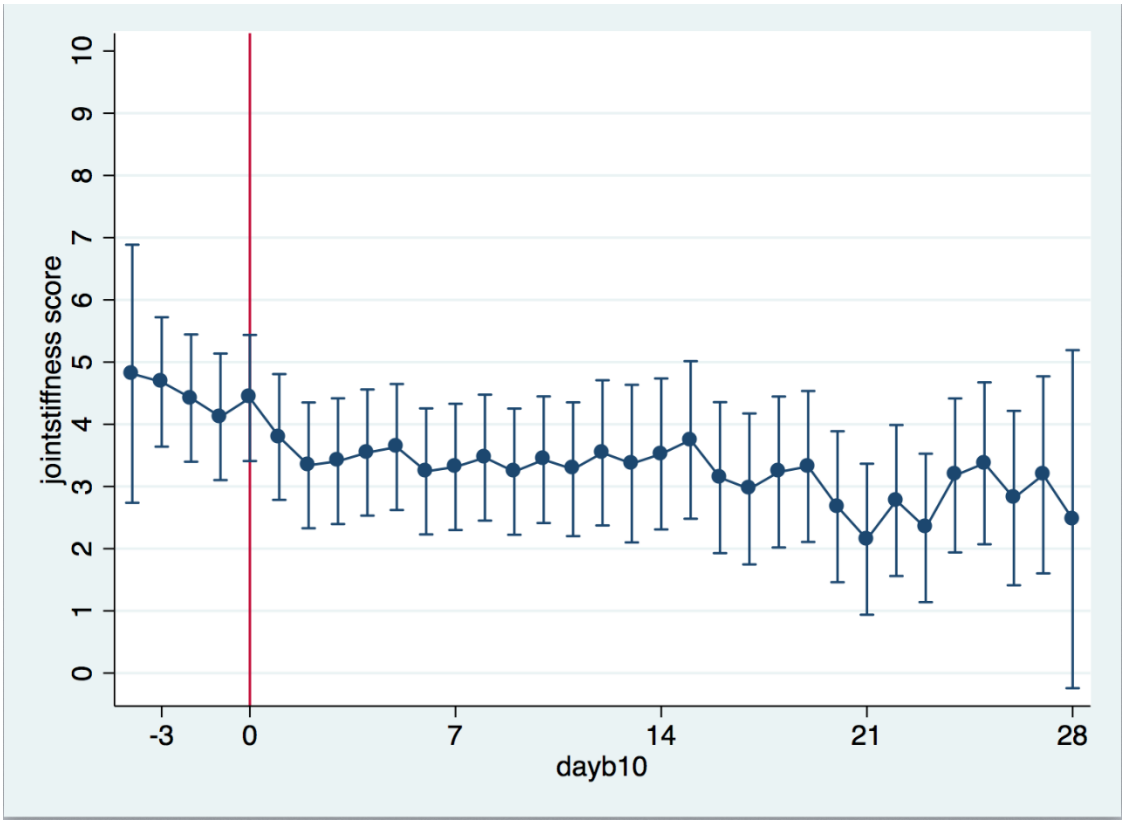


Figure 8.7: Line plot for Joint Stiffness

Figure 8.7 shows an immediate decrease of joint stiffness scores after exposure, which maintained the same for around two weeks, before another period of decreasing scores. There is a significant (p value = 0.001) difference of around -0.975 between exposed and unexposed, however the average linear change for each day after exposure is not significant. This means that there might be fluctuations of scores after exposure which means that the average change is not significant, but the overall difference is still significant.

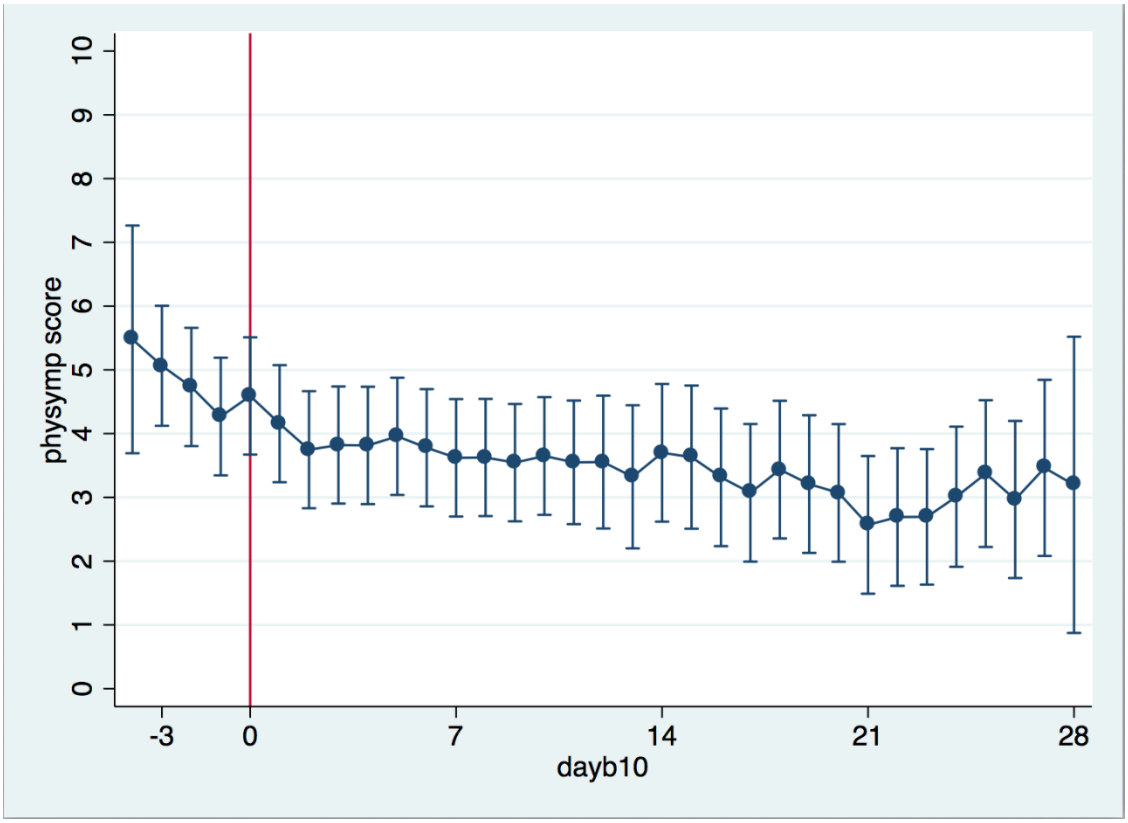


Figure 8.8: Line plot for Physical Symptoms

Figure 8.8 shows the line plot for average of the three physical symptom scores. It can be seen that there is a constant decrease before exposure, and also a constant decrease after the exposure. At around the 14 days mark, there is some fluctuation but the overall trend is still decreasing. This is reflected by the significant value of -0.940 between unexposed and exposed, and also the significant quadratic rate of change which suggests a larger decrease initially after exposure and then remaining constant for the last week. This suggests that after the new biologic treatment, participants experience an immediate decrease in physical symptom for two weeks, until it plateaus at a constant level.

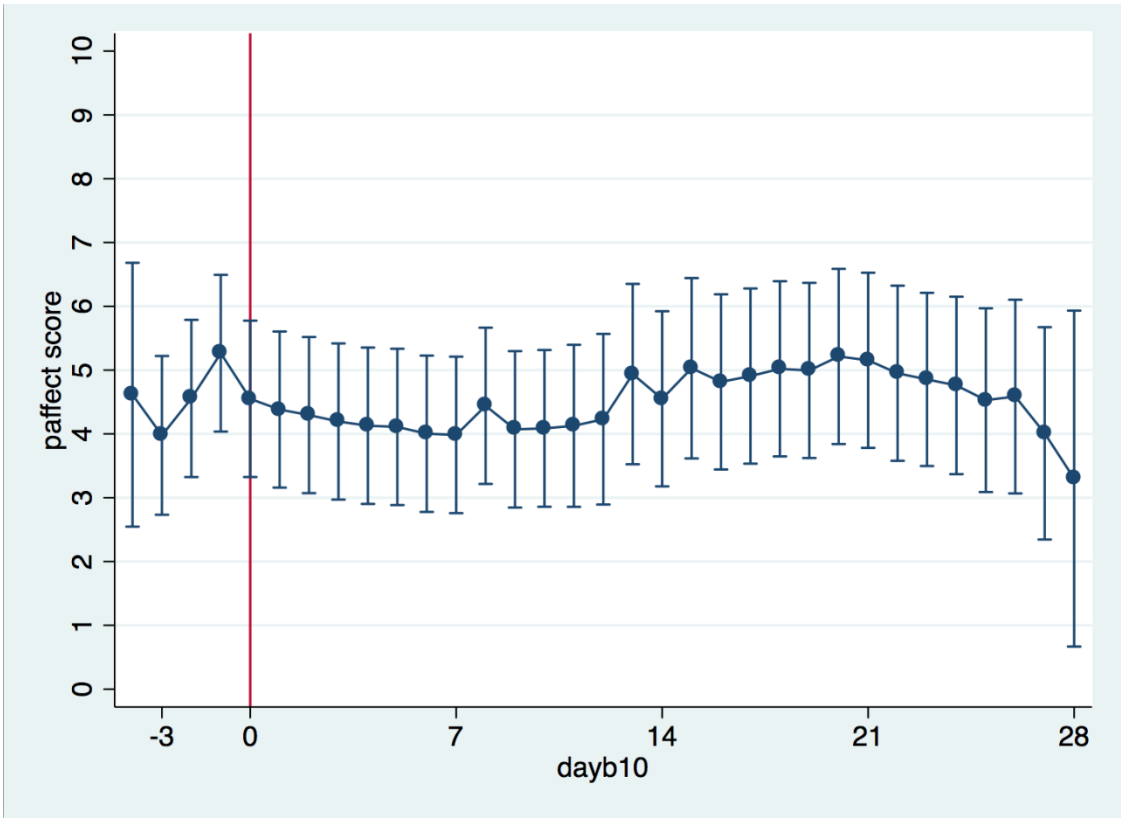


Figure 8.9: Line plot for Positive Affect

Figure 8.9 shows the line plot for overall positive affect, which includes relaxed, content, enthusiastic and cheerful. Because of the similarity of positive affect symptoms, it has been decided to be included as a single construct to better compare between other symptom constructs. It can be seen that positive affect has a rather fluctuant line plot, with a slight decrease after exposure leading to a gradual increase in the second and third week, and then a decrease in the last week again. This is reflected by the non significant negative quadratic average change. However, there is also a significant difference between unexposed and exposed of -0.436, which suggests that exposure to a new biologic treatment will decrease positive affect overall. This can be partly explained by the fluctuant positive affect symptoms of the first four days.

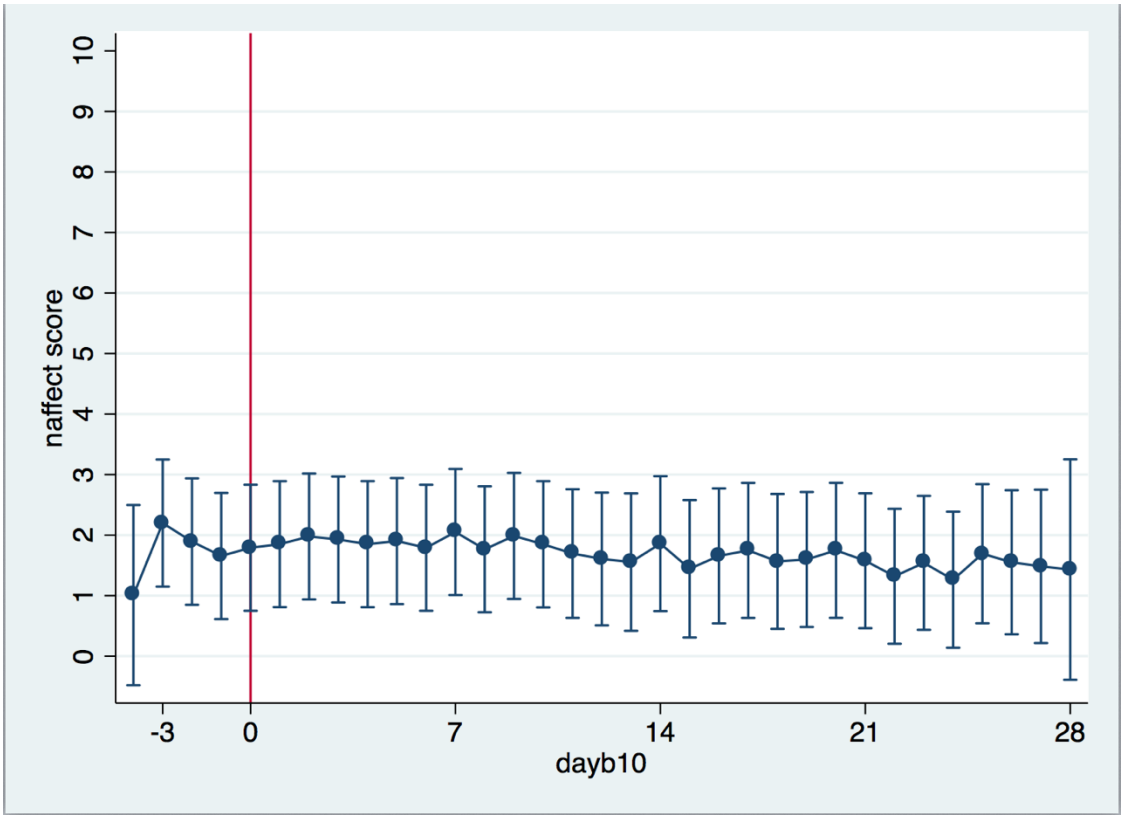


Figure 8.10: Line plot for Negative Affect

Figure 8.10 shows the line plot for negative affect, which shows a constant level throughout the study. There is a outlier on the first data point, which could be due to the fact that it is based on only one participant. There are no significant difference between exposed and unexposed (p value = 0.875), and the average change daily is not significant as well, however showing a negative direction which means that there is a very slight decrease in negative affect each day (-0.0142).

Physical activity is measured by both the survey and Fitbit, and thus the line plots below will reflect both of these measurements. FitBit measures both activity and steps, and the correlation between the three elements are in Table 8.6 below:

Table 8.6: Correlation of physical activity measured by surveys and Fitbit

	Physical activity	Activity Fitbit	Steps Fitbit
Physical activity	1	0.420	0.477
Activity Fitbit	0.420	1	0.710
Steps fitbit	0.477	0.710	1

All of the correlations are significant, and it can be seen that there is a moderate correlation between the survey data and Fitbit data. The Fitbit steps and activity counter have a strong correlation with each other.

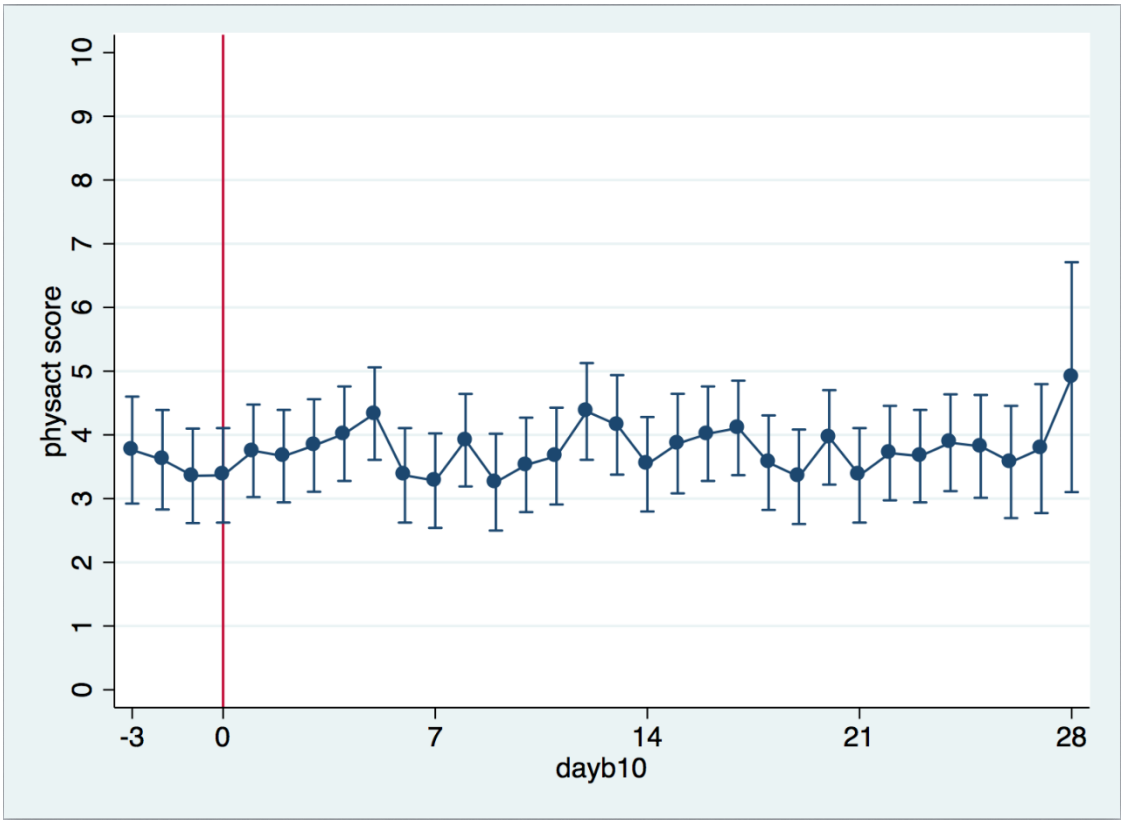


Figure 8.11: Line plot for Physical Activity

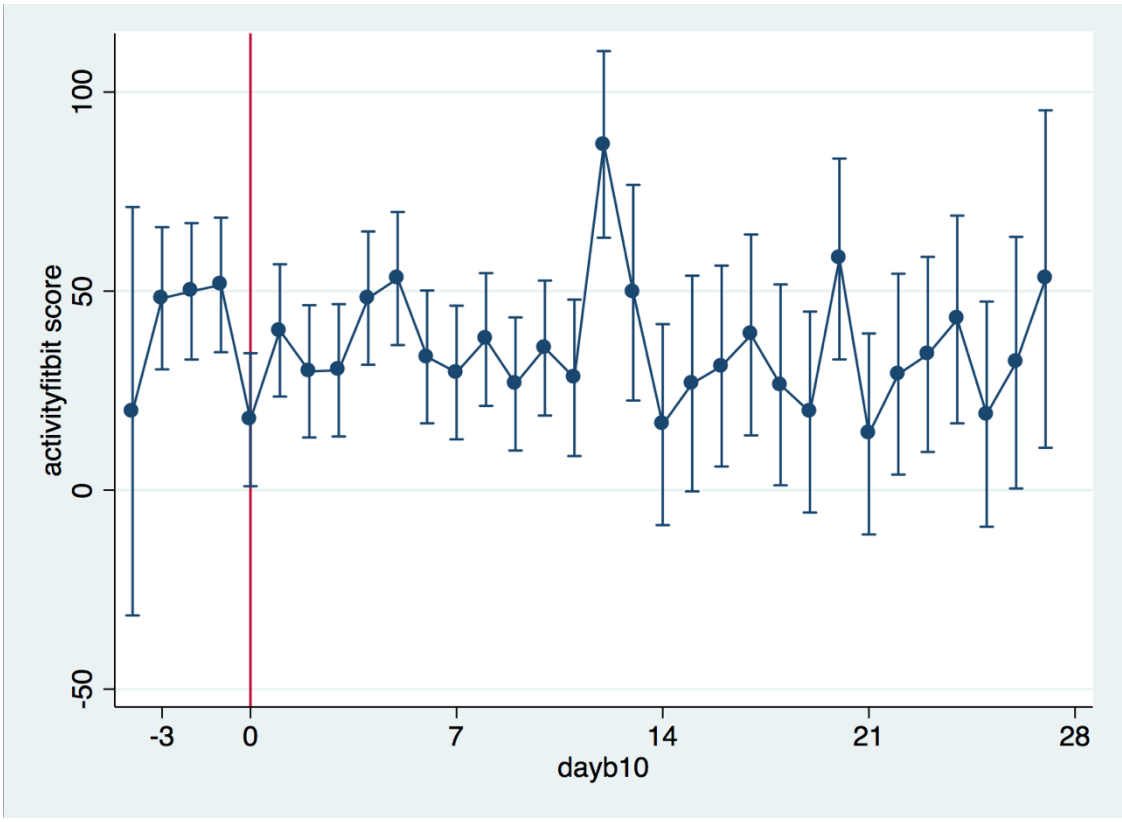


Figure 8.12 Line plot for FitBit Activity Minutes

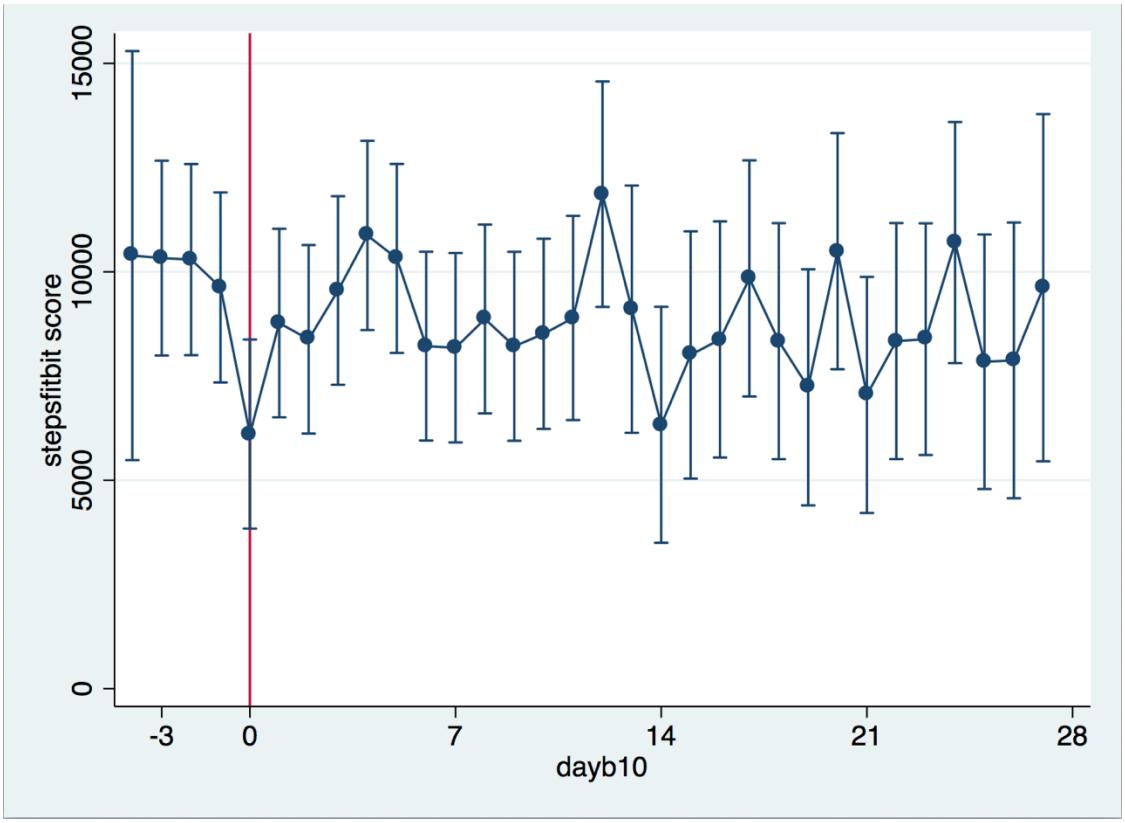


Figure 8.13: Line plot for Fitbit steps

Figures 8.11, 8.12, and 8.13 show the line plots for physical activity on both survey data and Fitbit data. It can be seen that the line plots are very fluctuant for all three, with no trends throughout the study period. Figures 8.12 and 8.13 showed a hike in activity on day 12, and a drop in activity on the day of exposure. However, this is less pronounced on Figure 11 based on the survey data. It was shown that physical activity based on survey data shows no significant differences between unexposed and exposed, however analysis of the Fitbit data shows significance decrease of both activity and steps when exposed to a new treatment. However, the linear rate of change for all three measurements are positive, albeit insignificant. This means that there is an overall decrease in activity according to the FitBit, however there is also a small big insignificant increase on average everyday, which agrees with the fluctuant nature of the line plots.

Sleep is measured using both the Fitbit and survey data as well. The correlation is seen in Table 8.7 below:

Table 8.7: Correlation of sleep measured by surveys and Fitbit

	Sleep	Fitbit sleep
Sleep	1	0.688
Fitbit sleep	0.688	1

There is a significant and strong correlation between the Fitbit and survey data of sleep. The line plots are seen in Figures 8.14 and 8.15 below.

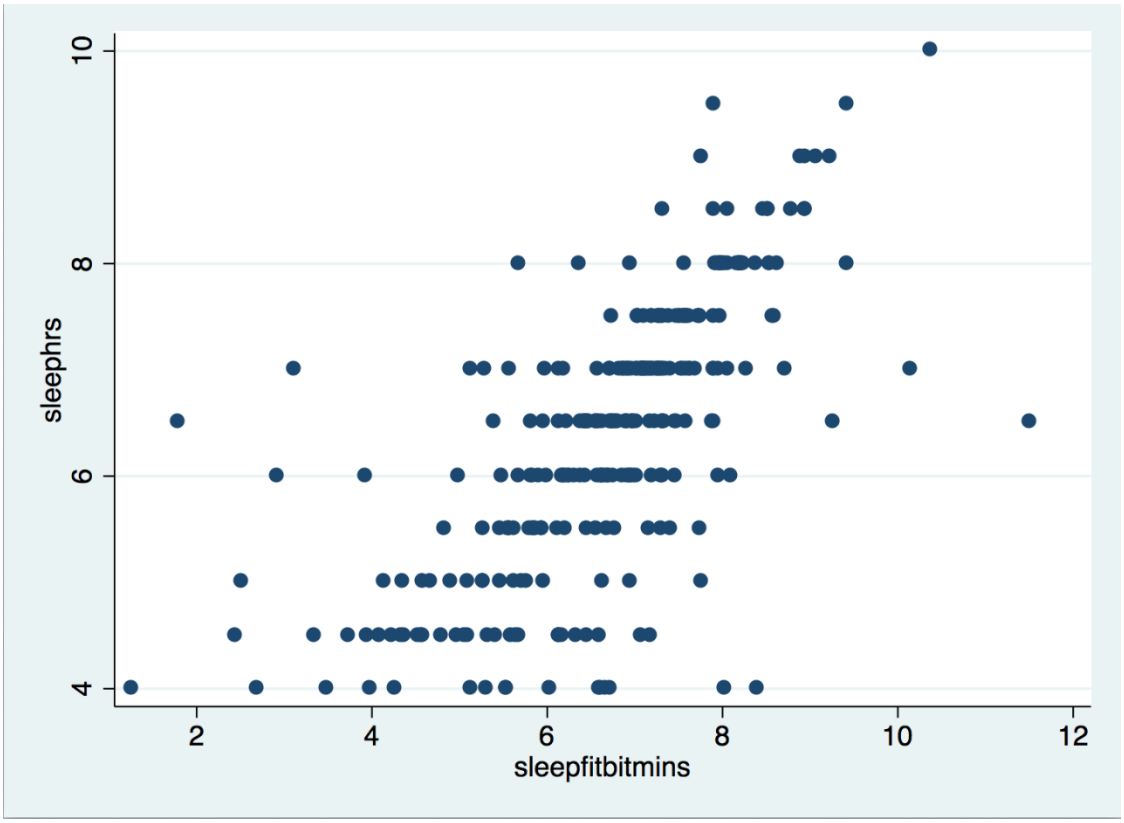


Figure 8.14: Scatterplot of Sleep vs FitBit Sleep

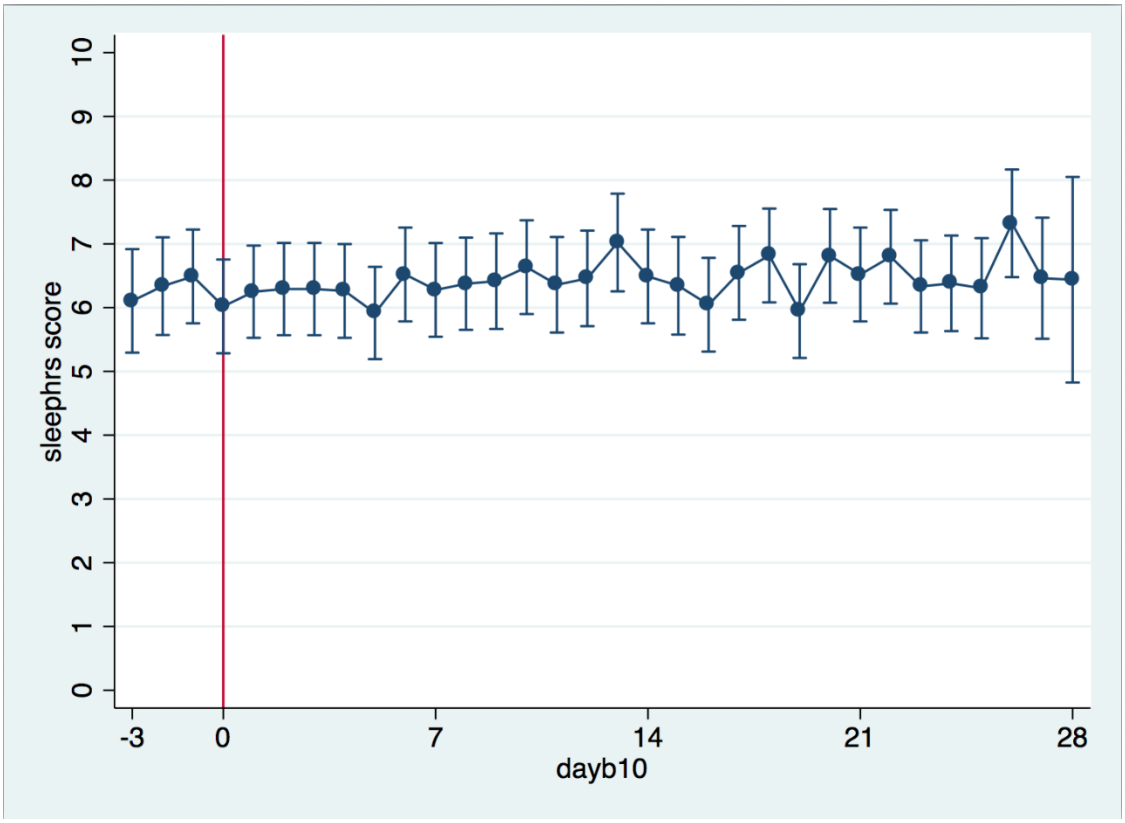


Figure 8.15: Line plot for Sleep

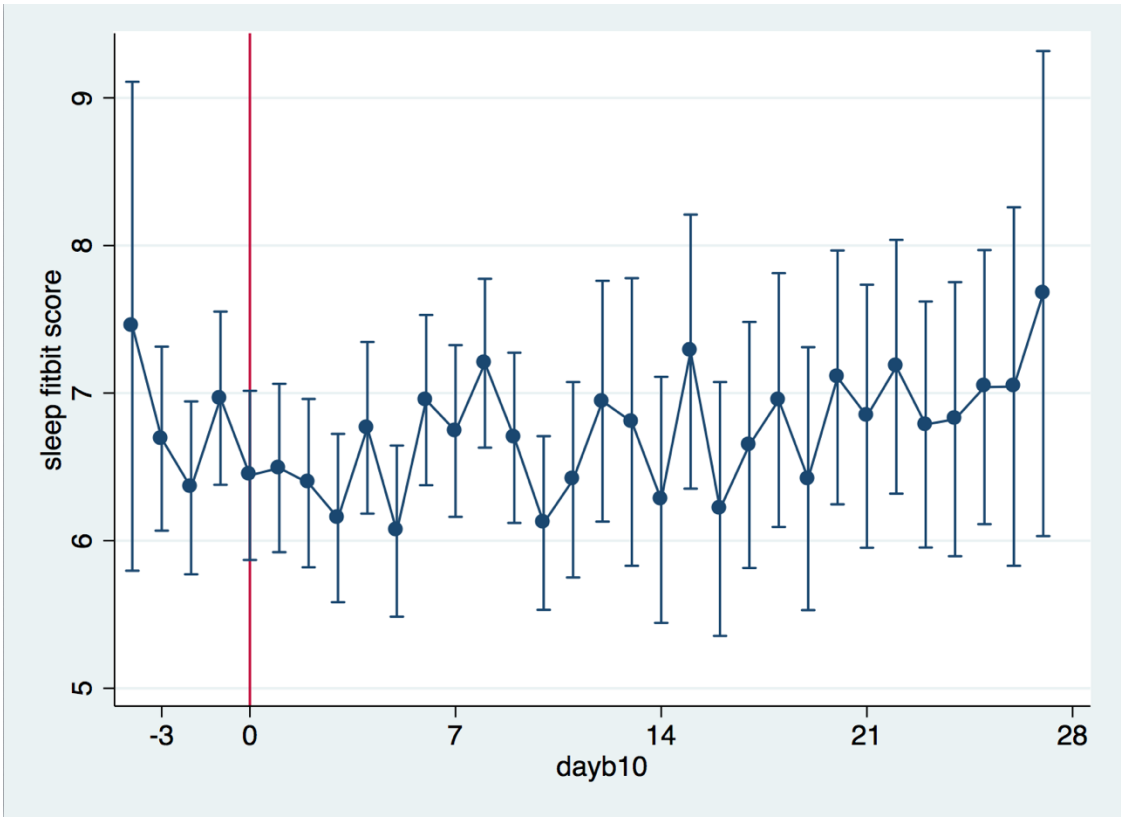


Figure 8.16: Line plot for FitBit Sleep

Figure 8.14 shows the scatterplot of the survey data and Fitbit data on sleep. It can be seen that it is generally correlated, however there is a greater discrepancy when it comes to either extremes. Survey data's lowest entry for sleep duration is 4 hours or less, and thus it will not be able to identify those that had less than 4 hours of sleep apart from those with 4 hours. Figures 8.15 and 8.16 show the sleep duration data derived from both survey and Fitbit respectively. Because the scale for the Y-axis is different, it showed that the data from FitBit is more fluctuant. However, a closer look suggest that line plots for both FitBit and Survey ranges from around 6 to 7.5, suggesting a similar range of fluctuation. Significance test for difference between unexposed and exposed shows that survey data shows that sleep duration is increased by 0.0927 in those exposed, while Fitbit shows that sleep duration is decreased by 0.0802. Both are not significant, however it shows a difference in direction between the two types of data. This does not align with the strong correlation between them. However, both follows a positive linear average change after exposure, and it is significant for the survey data. This shows that both data agrees that there is a small increase in sleep duration score each day after exposure.

8.5.4 Lagged Correlations and Dynamic Modelling

Having looked at the differences before and after exposure to a new biologic treatment, the next step is to utilize the longitudinal data and look for any potential associations across time. Dynamic regression will be carried out for before and after exposure as well, to see if there are any dynamic differences after a new biologic treatment. Symptoms included will be the sum of physical symptoms, positive affect and negative affect instead of the individual items so to allow for an overall look. Lag-1 elements of these 3 symptom constructs are created to allow for dynamic regressions to be carried out. A cross-correlation of the symptoms and the lag-1 counterparts are shown in Table 8.8 below:

Table 8.8: Correlation of physical symptom, positive affect, negative affect and lag-1 components

	Physical Symptoms	Negative Affect	Positive Affect	Lag-1 Physical Symptom	Lag-1 Negative Affect	Lag-1 Positive Affect
Physical Symptoms	1	0.431	-0.212	0.879	0.418	-0.187
Negative Affect		1	-0.250	0.410	0.940	-0.221
Positive Affect			1	-0.181	-0.235	0.897
Lag-1 Physical Symptom				1	0.431	-0.212
Lag-1 Negative Affect					1	-0.22
Lag-1 Positive Affect						1

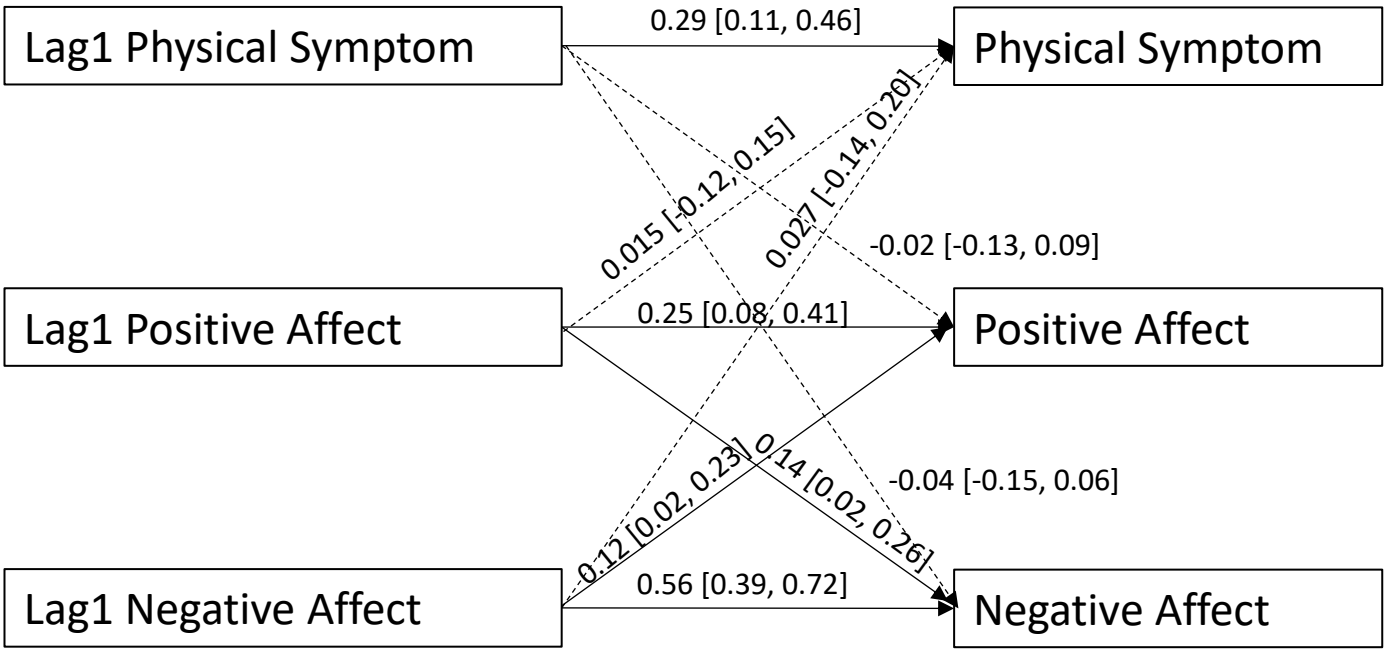


Figure 8.17: Dynamic panel model for unexposed

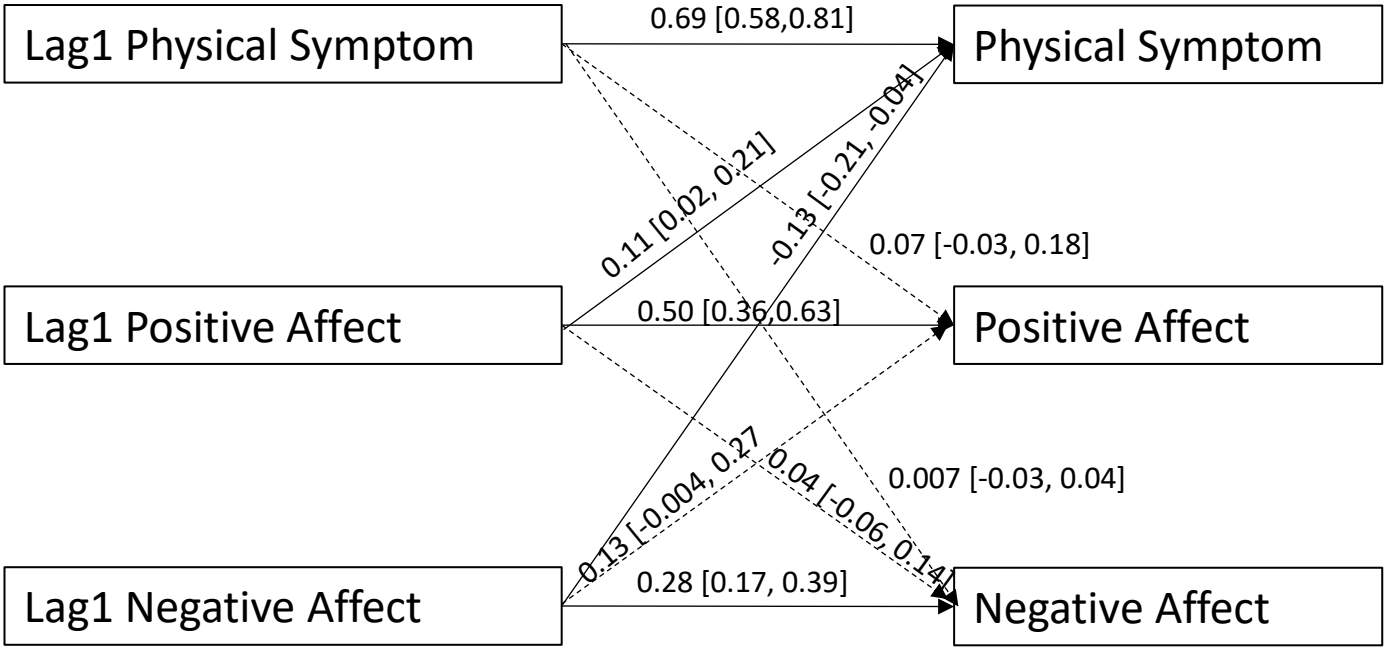


Figure 8.18: Dynamic panel model for exposed

Figures 8.17 and 8.18 show the dynamic panel mode for both unexposed and exposed days of physical symptoms, positive affect and negative affect. Every coefficient and 95% confidence interval was shown, but the significant associations were drawn in solid lines, while non-significant ones were dashed. The directions were all from lag-1 to current. It can be seen that in the unexposed model, physical symptom is only significantly associated with lag1 physical symptom, suggesting that any change to lag1 physical symptom will lead to a change in current physical symptom. The only cross associations were between positive affect and negative affect, where both lag1 positive affect and negative affect has a significant association with current positive and negative affect. As mentioned before, there is a significant decrease of physical symptom after exposure, which means that physical symptom score is higher in the unexposed group. Coupled with this finding suggests that in high physical symptom score states, positive affect and negative affect are more susceptible to fluctuations, and that it is led by more of a temporal association between the psychological symptoms rather than physical symptom.

Figure 8.18 shows that after exposure to a new biologic treatment, current physical symptom has a significant association with lag-1 physical symptom, positive affect and negative affect. The temporal associations present in Figure 8.17 between the psychological symptoms has disappeared as well. This means that physical symptom is more vulnerable to fluctuate due to influences from psychological symptoms in a lower physical symptom severity state. However, none of these difference in associations between pre-exposure and post-exposure had a significant difference, because the 95% confidence interval overlapped with each other.

8.5.5 Network Modelling

Having established the dynamic associations present between the three big symptom constructs, it is also important to have an in-depth look at each of the symptoms interact with each other before and after exposure to the new biologic. This will be done by creating a network plot for before and after exposure, and centrality will also be calculated to find out the most influential symptom in the respective network plots. Figures 8.19 and 8.20 below will show the network plot for before and after exposure respectively.

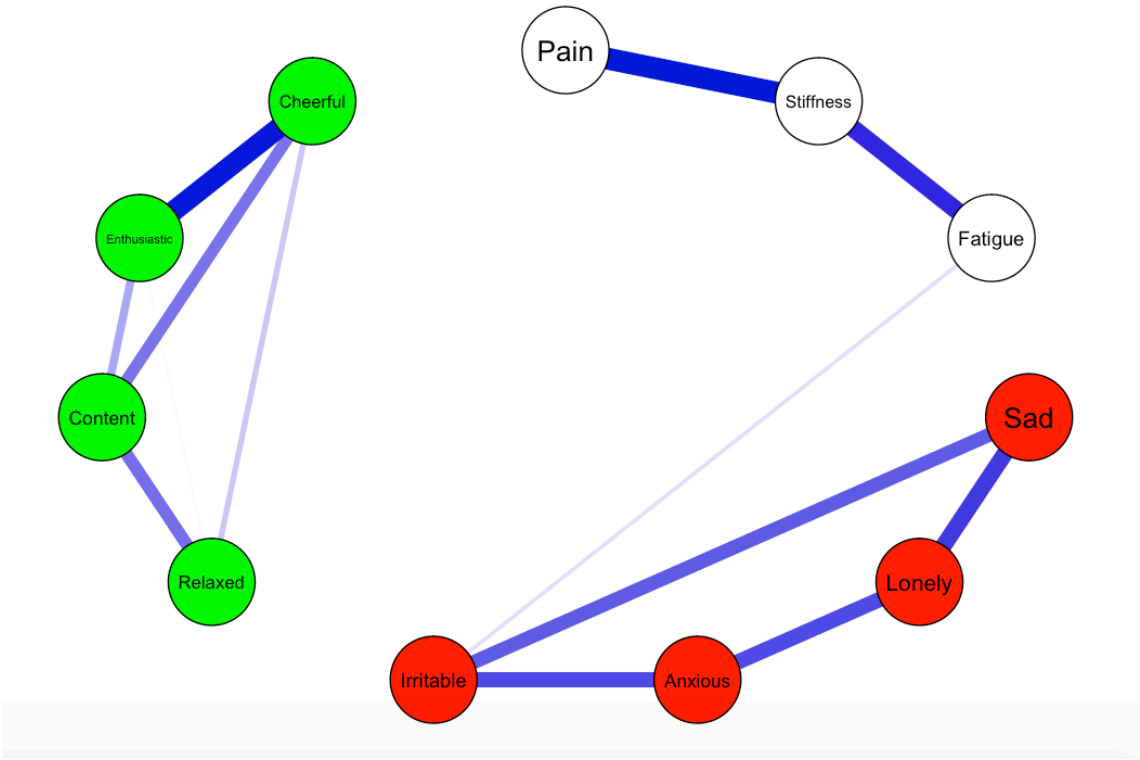


Figure 8.19: Network Plot before Biologic

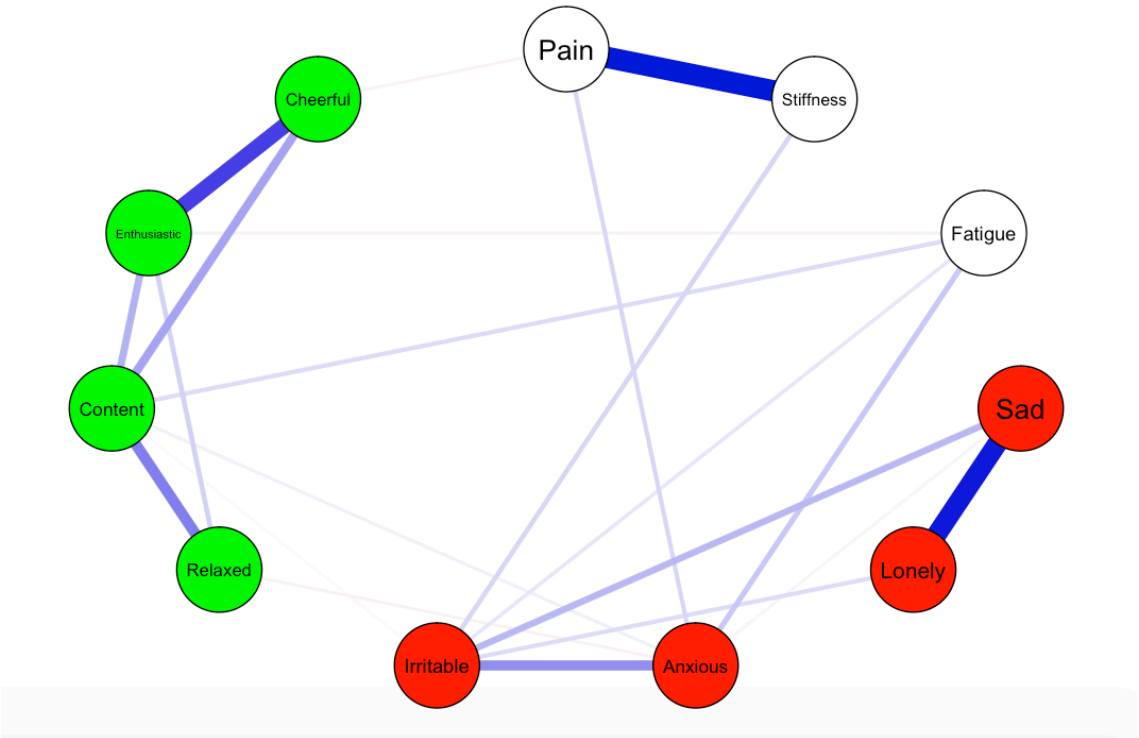


Figure 8.20: Network Plot before Biologic

Both network plots show a strong correlation between each of the constructs of physical symptoms, positive affect and negative affect. In Figure 8.20, the connection between the physical symptoms is weaker than before, with fatigue having a weaker connection to the physical symptoms and a stronger association with the psychological symptoms. It is also seen that negative affect after exposure have elements that are more closely associated with physical symptoms such as irritable and anxious, while positive affect is still quite separated. After exposure, positive affect has less of a connection with negative affect, but a more significant association with fatigue. This shows that before biologic, where physical symptom scores are higher, physical symptoms are not as affected by psychological symptoms, while after exposure where there is a significant decrease in physical symptom scores, positive affect is more associated with pain severity, while negative affect is associated with fatigue more. In a lower physical symptom score state, fatigue is also disconnected from other physical symptoms and can be regarded as more of a psychological symptom.

Figures 8.21 and 8.22 below will show the centrality tables for network plots in Figure 8.19 and 8.20 respectively. The exact centrality values can be seen in Appendix D. Degree, closeness, betweenness centrality, and expected influence will be shown in these tables. The values are standardized because the raw value is not as important as the relative importance between each symptoms. The centrality tables will allow a more quantifiable manner of looking at which symptoms are more important in the respective network plot.

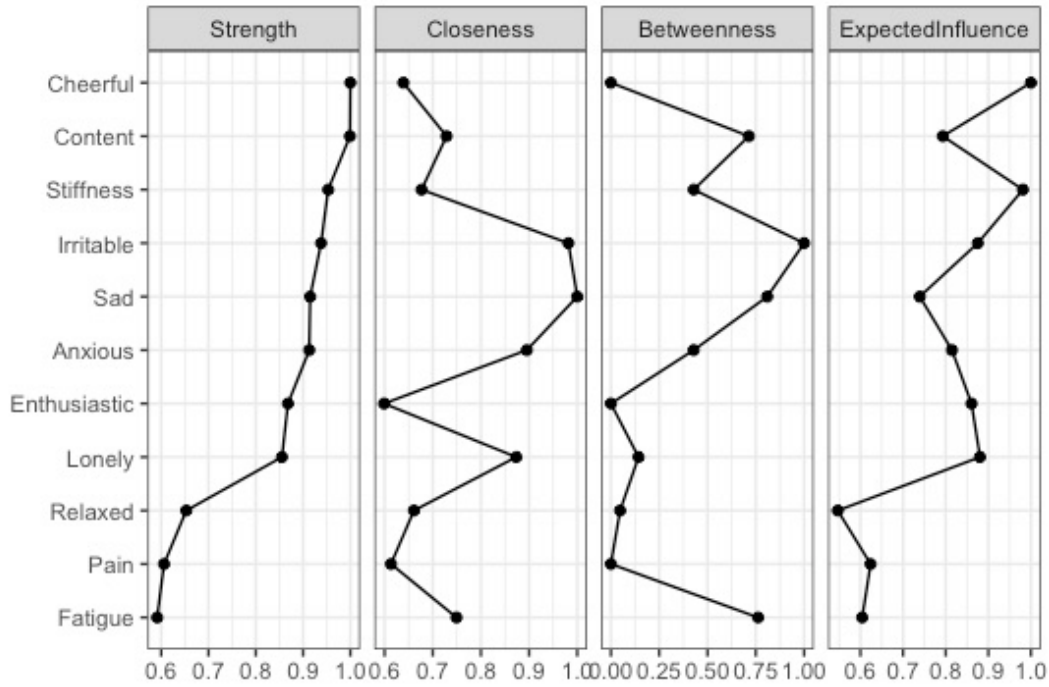


Figure 8.21: Centrality Table for Before Biologic

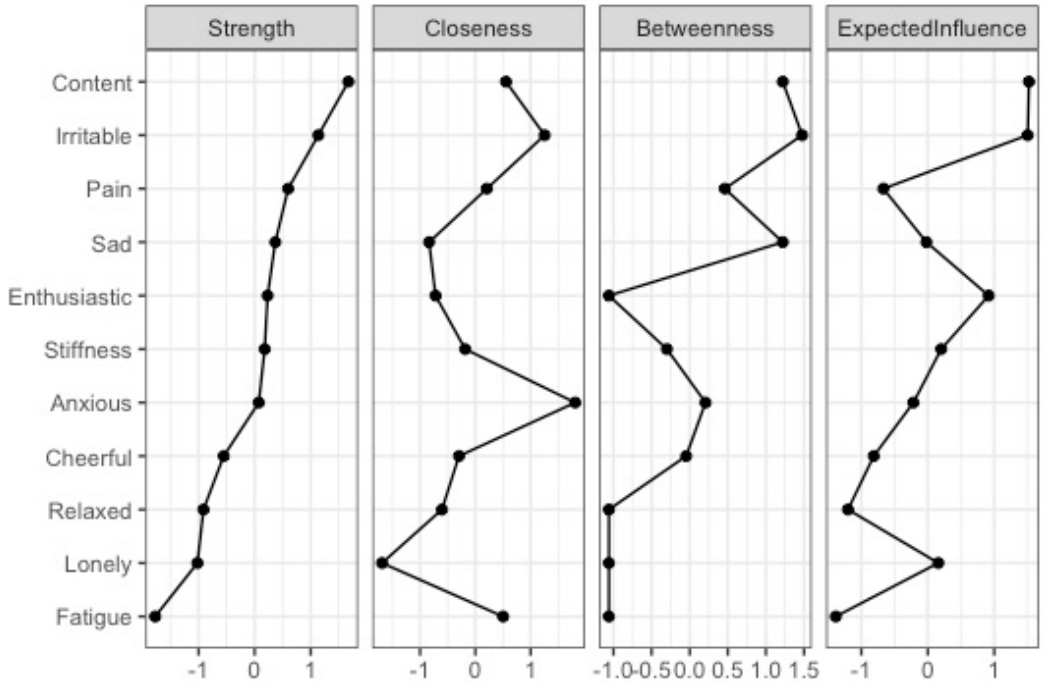


Figure 8.22: Centrality Table for After Biologic

Looking at degree centrality (strength), it can be seen that positive affect tops the table for both before and after exposure. This phenomenon is more pronounced before exposure, where the second highest is a positive affect symptom as well, whereas after exposure irritable is the second highest degree centrality. It is also shown that the most

influential physical symptom in regards to degree centrality changes from stiffness to pain severity after exposure. Because of the negative edges present in the network plot, expected influence will allow for a more comprehensive look at strength of each node. It can be seen that stiffness is joint top with cheerful for before exposure, while after exposure physical symptoms have much lower expected influence. Both content and irritable have the highest expected influence after exposure, which suggests that psychological symptoms as a whole has a much higher influence.

Closeness table is similar in both before and after exposure, where the highest scores are all negative affect symptoms. This reflects what the network plot shows, as negative affect is in between physical symptom and positive affect. It can be seen that fatigue is the only symptom that is comparable with negative affect in Figure 8.22, as it has been disconnected slightly from the physical symptoms cluster. Betweenness centrality again shows irritable as the most influential symptom before and after exposure, suggesting that it plays a part in a lot of symptom interactions. The major difference is that fatigue has a high betweenness score for before exposure, while pain severity has a high betweenness score for after exposure, suggesting the change in influence in the physical symptom cluster. Overall, it can be seen the massive influence that psychological symptoms have in a RA symptom network, which shows how important it is to understand the connection between the two major clusters. The below tables will show the difference in bridge expected influence for before and after exposure, which shows the most important symptom that connects the two clusters.

Sensitivity analysis:

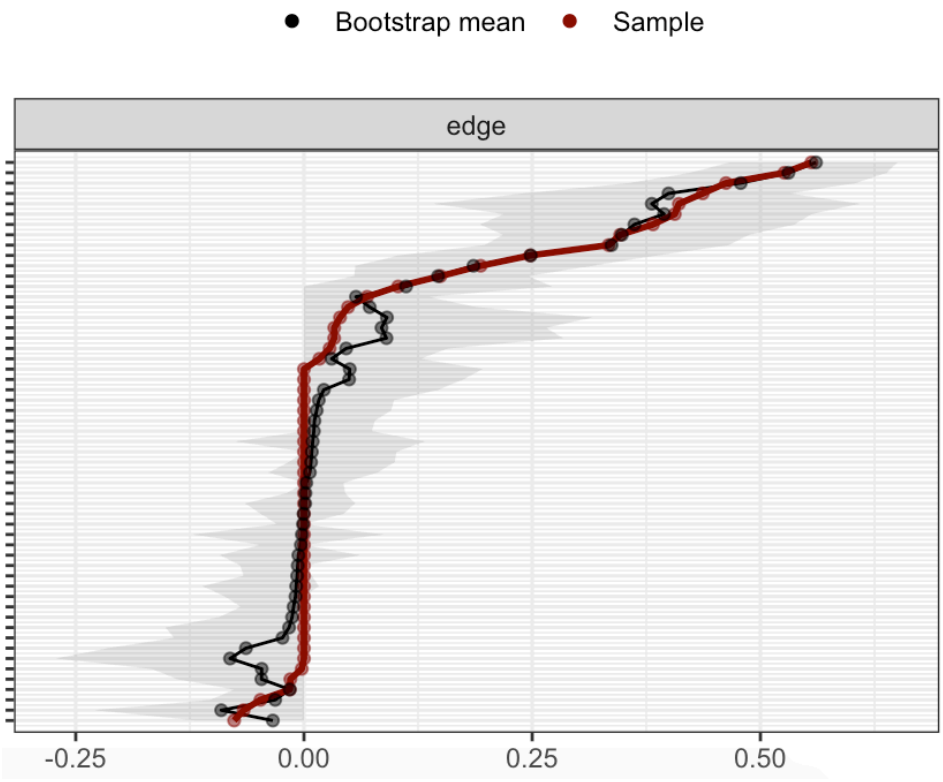


Figure 8.23: Graph of edge-weight accuracy Before Biologic

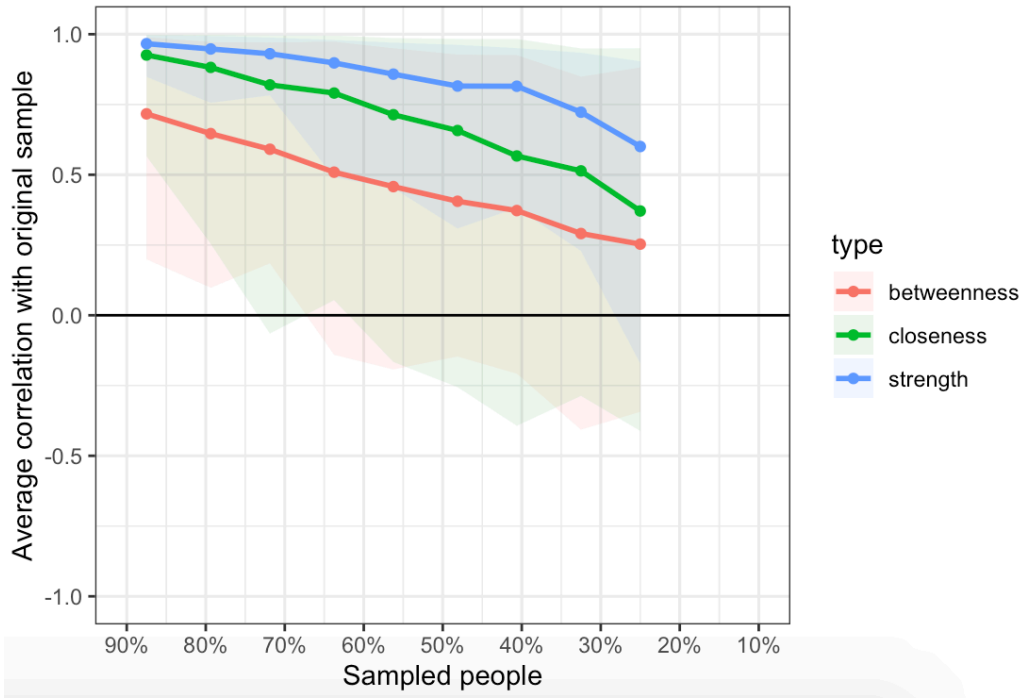


Figure 8.24: Graph for centrality stability Before Biologic

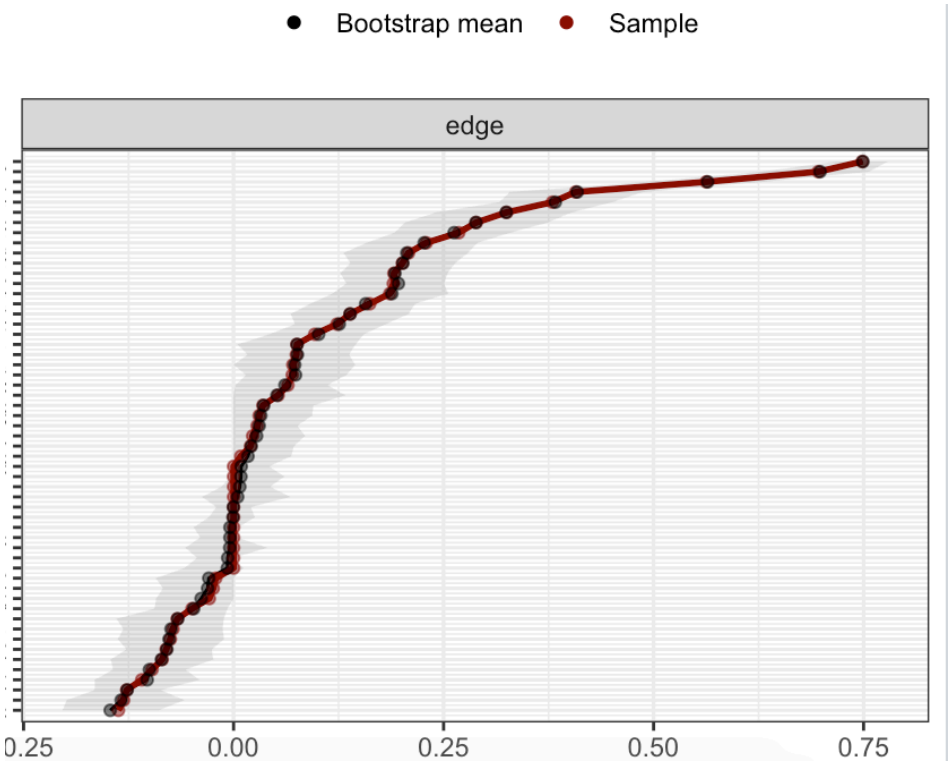


Figure 8.25: Graph of edge-weight accuracy After Biologic

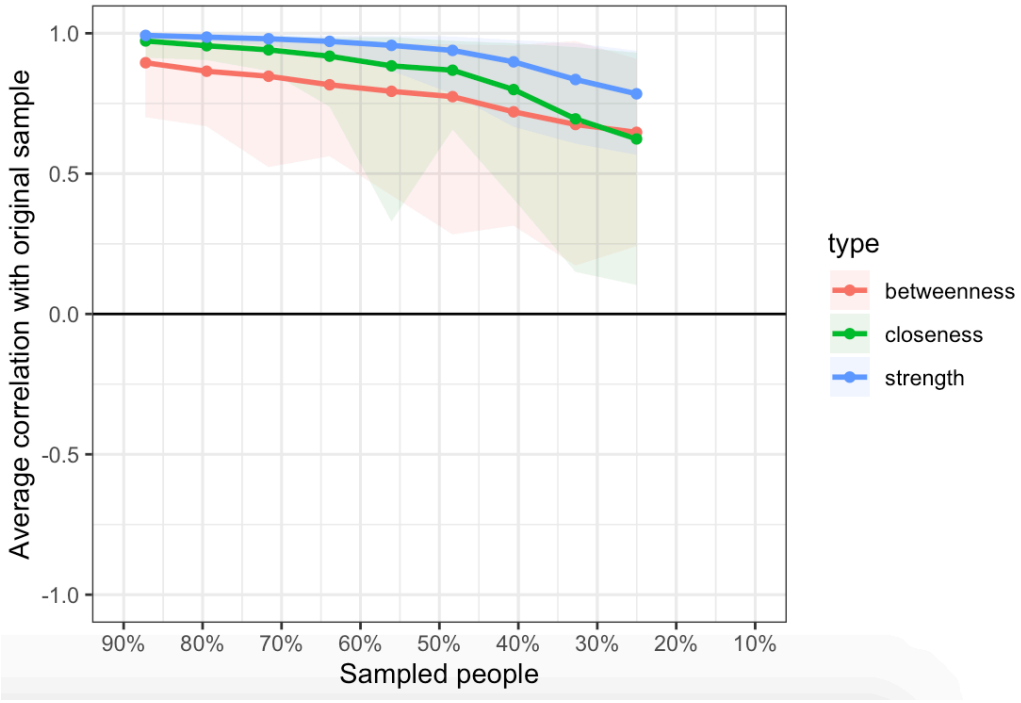


Figure 8.26: Graph for centrality stability After Biologic

Figures 8.23 to 8.26 look at both before biologic and after biologic network plots, and evaluate the accuracy of the edge-weights and also the stability of centrality values. Figures 8.23 and 8.25 evaluates accuracy of edge-weights by first comparing the bootstrap means and sample means, and also by looking at the width of the confidence interval. The X-axis is the edge strength, and any link that has a value other than 0 should appear on the network plot. Y-axis represents each of the edges between all the nodes, but they are not labelled in this situation because the purpose of the stability analysis is to evaluate the accuracy of all the edge-weights of the model, instead of any particular ones. Figures 8.24 and 8.26 look at centrality stability by comparing the correlation of centrality values of subset of cases with the original samples' centrality values. The purpose is to find the correlation stability coefficient (CS-coefficient), which is a measurement that calculates what is the maximum proportion of cases that could be dropped such that there is still a 95% probability that the correlation between original sample centrality and subset sample centrality is at least 0.7.

For the network model before biologic, Figure 8.23 showed that bootstrap and sample means are quite close, but some edges were estimated to be 0 by the sample when bootstrap estimated it to be different from 0. This meant that some more edges should be present in the network model. The 95% confidence interval is quite tight, and thus overall, the edge-weights could be interpreted accurately, and difference between edges were reliable. Figure 8.24 showed the correlation, and the CS-coefficient is 0, 0.125, and 0.281 respectively for betweenness, closeness and strength. Only strength is above 0.25, which meant that betweenness and closeness centralities were not stable, and comparing between nodes could be difficult. Strength centrality is not above 0.50, which also meant that any interpretations need to be made with care.

For after biologic, Figure 8.25 showed that the bootstrap means and sample means are very close together, with almost no difference at all. The 95% confidence interval is also very tight, which meant that all the estimates do not lead to much variation. The edges in this networks are thus very accurate, and any differences between edges can be interpreted confidently. Figure 8.26 showed the correlation of centralities. The CS-coefficient values are 0.205, 0.517, and 0.594 respectively for betweenness, closeness, and strength. Betweenness value is below 0.25, thus it is not stable enough to differentiate between each node. However, closeness and strength are both above 0.50, and thus both values could be

interpreted with confidence. Any difference between nodes could also be interpreted as significant.

It could be seen that both network models have accurate edge-weight, with after biologic's network model being the most accurate. Centrality stability is also more stable for the after biologic network model, with both closeness and strength centrality having a CS-coefficient value of higher than 0.5, which is optimum (Epskamp et al., 2018). This meant that both network models and the subsequent centrality values can be used for analysis, but with the slightly less accurate model for before biologic, any result derived should be re-tested. The main reason why the network model for after biologic is much more stable and accurate is because of the quantity of data, where it has around 11 days of data compared to three days of before biologic.

8.6 Discussion

This study showed that there is a 33.8% success rate in recruiting RA patients with high disease activity for an intensive longitudinal project that includes wearables. Out of those that refused, only 35% were due to a lack of interest in the study. Of those recruited, 12 has finished data collection and because of time constraint, were the only ones that were included in this study. The completion ranges from 71% to 100%, with 88.75% as the mean completion rate. Physical symptoms including pain, fatigue and joint stiffness all significantly decreased after exposure to a new biologic treatment, while only high valence negative affect such as irritable and anxious changed significantly. Negative affect as a whole did not have a significant change after exposure, while positive affect does, and the only positive affect symptom that did not significantly differ from before exposure was enthusiastic. Both physical symptoms and positive affect as a whole significantly decreases after exposure, while negative affect decreases as well but is not significant. FitBit data and survey data also have a moderate correlation for both physical activity and sleep duration (0.420 and 0.688 respectively). However, FitBit step count and activity both significantly decreased after exposure, while activity data from survey had a non-significant increase. Comparing temporal associations before and after exposure shows that prior to a new biologic treatment, physical symptoms are not significantly affected by the past time point's psychological symptoms. This shows that at a high physical symptom severity state,

psychological symptoms do not have much impact on the next time period's physical symptoms, while in low physical symptom severity state, positive affect and negative affect both have a significant correlation with next time point's physical symptom. Network plots before and after exposure also showed a distinct difference in how physical symptoms interact, with fatigue being disconnected from the physical symptom cluster and have more associations with psychological symptoms. It is also seen that after exposure, the links in between the clusters are weaker as well.

The research team attempted to recruit 74 patients, and 25 (33.8%) was successfully recruited over the period of about five months. Previous studies concerning RA and intensive longitudinal data collection do not provide the success rate for recruitment, but problems with recruitment is a major problem for clinical trials and more than 50% of studies require funding extensions due to recruitment (Williams et al., 2014). This shows that in order to evaluate the feasibility of this study, the recruitment rate needs to be investigated. Out of those that were not recruited, 17 (35%) of them could not be contacted due to either wrong contact information or non-responsiveness to phone calls. This study was carried out during the COVID-19 pandemic which restricted the possibility of recruitment in person. This means that these participants could have been successfully recruited if recruitment could happen face to face. Approximately 7 (14%) of those unsuccessful were rejected due to the inability to understand English competently, or lack of a smartphone to answer survey questions. Technology usage could be an issue because of the generally older population that RA samples are derived from, but smartphones are predicted to have around 6.3 billion users in 2021, and the older population of 51 years and above use smartphones around 100 minutes a day (Andone et al., 2016). The rate of smartphone usage should only increase, and with recruitment centred in the UK, recruitment rates should not suffer much due to the exclusion criteria of competency in English. 8 (16%) potential participants could not join because of logistical issues, ranging from an inability to use the FitBit to the new Biologics treatment date starting too early. Only 17 of the 49 (35%) participants, or 23% of the population were fully eligible and declined to participate. This means that the study design and burden is generally acceptable for potential participants, and in ideal situations with face to face recruitment, the recruitment rate could increase to 50%.

Following the feasibility of the study to recruit participants, it is also important to see the data quality from those recruited. There is no studies that have shown the required response rate to an EMA study, but a couple of studies in self-reporting intensive longitudinal studies have proposed a compliance rate of 80% as acceptable(Stone & Shiffman, 2002) (Jones et al., 2019). According to a meta-analysis on chronic pain patients (Ono et al., 2019), the average completion rate 85%. This means that the completion rate of this study which is 88.75%, is higher than both the recommended compliance rate for general EMA use, and also in chronic pain patients. Another review by Wen and colleagues (Wen et al., 2017) showed that there is a slight, but insignificant drop of compliance rate from 77.4% to 73% when EMA is combined with a wearable device. That is demonstrated here that even using a FitBit device for a whole month, the response rate is still above average. Histograms were also created to show completion rate for each time of day and each day. It can be seen that for the first 14 days, the completion rate is at least 85% for all times, and the 8pm survey has the highest rate. Figure 4 also shows that response rate is quite consistent among the last two weeks, before a drop on the last three days of the study. These coincide with a study that looks how time affects EMA compliance rates (Courvoisier et al., 2012) which shows that compliance rate is better in the evening compared to the morning, and that it drops near the end of a study.

The last stage of feasibility is to compare the objective and subjective measurements (FitBit and Survey data). It is shown that sleep duration has a correlation of 0.688, and physical activity has a correlation of 0.420 with minutes of activity on FitBit and 0.477 with steps on FitBit. This shows that there is at least a moderate correlation on activity and a strong correlation for sleep duration. This is reflected by a study that compares FitBit data and self-report data (Thota, 2020) reports consistency between FitBit data and self-reported sleep data, and also another study in Type 2 diabetes patients (Weatherall et al., 2018) which show a strong positive association for both physical activity and sleep between FitBit and self-reported data. These show the feasibility of recruiting high disease activity RA patients who are about to start a new biologic treatment to a high intensive data collection study. It also shows the possibility of using FitBit to record some data, especially sleep which could save on the patient burden and replace sleep questions on surveys to other relevant questions. The high response rate on remote measurement methods such as wearables and smartphone surveys also show the possibility of monitoring patients outside of structured

clinical appointments. This is important because of the severity of RA flares which could happen anytime even in those who have inflammation under control (Hewlett et al., 2012) and the substantial role it plays in increasing risk of a cardiovascular disease comorbidity in RA (Myasoedova et al., 2016). According to the scoping review in Chapter 3, this study fills the gap in literature regarding more than 3 symptoms in an intensive longitudinal study for RA, and also addresses the need for a study that looks at how symptoms change dynamically before and after exposure to a new bDMARDs.

The comparison before and after exposure to Biologic shows that physical symptom significantly decreased after exposure to a new bDMARDs. Pain has the largest decrease, followed by joint stiffness and fatigue. It is also shown that the average change per day after exposure is linear for fatigue and joint stiffness, but quadratic for pain. This means that pain has an initially larger decrease in score which then evens out near the end of the study, while fatigue and joint stiffness has a more consistent decrease throughout the study. Looking at this difference, it is important to consider the potential placebo effect that may take place here after the initiation of a new treatment. In a meta-analysis that compares six different biologics with placebo effect (Singh et al., 2009), it is shown that biologics lead to a significantly decreased disease activity using the ACR50 scale. ACR50, or the 50% improvement in patient and physician-reported criteria of the American College of Rheumatology distinguishes disease activity through patient assessment, physician assessment, pain scale, function scale, and inflammation through ESR or CRP. This coincides with the result of this study, however the effects of biologics are normally only experienced after a few weeks, while this study showed an immediate change in physical symptom scores as seen from the line plots for pain and joint stiffness. This suggest the possibility of a placebo effect, especially as it has been shown that placebo effects are very common in measurements of pain, in up to 40% of pain studies (Holmes et al., 2016) and could even induce a decrease in fatigue levels (Piedimonte et al., 2015). This means that the significant decrease should be considered carefully, but the rate of decrease after exposure could still provide interesting information. No study has been carried out to investigate how symptoms change in relation to time after exposure, but this study provides preliminary information with how pain has more immediate effect than the linear rate that stiffness and fatigue decreases at. Placebo responses are common and expected in this setting, and as this is an observational study it is not possible to determine what this is as. However, based

on other research (Bechman et al., 2020), the effects seen here seem plausible and are in line with likely patient expectations regarding the effectiveness of treatment.

Positive affect significantly decreased after exposure to biologic as well, while negative affect decreased non-significantly. This means that psychological symptoms overall worsened after exposure to biologics, suggesting that depressive symptoms increased after the prescription of new bDMARDs. Pain and mood are very strongly linked in RA, and the presence of pain greatly increases the prevalence of depression (Goldenberg, 2010).This is a contrast to the finding in this study because there was a significant decrease in physical symptoms, in particular pain, which should lead to an increase in positive mood, but the opposite was discovered here. It has also been shown in a longitudinal study concerning psoriasis (Strober et al., 2018) that biologics lead to a decrease in depressive symptoms while compared to cDMARDs. However, no study has been carried on RA that looks at positive and negative affect specifically after biologics, and this study is the first that looked into the effect of a new biologic treatment on affect in patients. This is especially important because it has been discovered that symptoms of depression at the start of a new biologic treatment will lead to worse treatment response (Matcham et al., 2018). This means that it is important to track the trajectory of patients' emotions and affect before and after biologic treatment in order to make sure that the new bDMARDs is not affected. The discovery of decreased positive affect in this study is thus important because it means that clinicians need to be aware of the possibility of a development of depression in patients that were starting a new treatment. Positive affect decreased significantly after the treatment and the average difference each day for both after exposure is a quadratic change. This was similar to the quadratic change in pain, which means that symptoms change drastically more immediately after exposure, and the change over time is in a decreasing trend. This reinforced the suggestion of the effect of placebo over certain symptoms, such as pain and positive affect.

FitBit data has been proven to have at least moderate correlation with self-reported patient data. Sleep duration data from both methods have shown to not have significant difference after exposure. However, activity data from FitBit showed that there is a significant decrease in both minutes of intense activity and steps. There has been no study that evaluates the difference in physical activity after a new biologics treatment, however it has been shown that less arthritis pain should lead to an increase in physical activity (Knittle

et al., 2011). Pain severity has been shown to have the largest significant decrease, but physical activity decreased according to the FitBit data. This could hint that physical activity is not entirely dependent on physical symptom, and that the decrease in positive affect has an impact as well. This is reflected by the finding in Chapter 6 that showed positive affect having a significant association with next time period's physical activity.

No significant temporal differences were discovered between before and after exposure, however the significant associations that were discovered for each panel model still provided useful information. Dynamic regressions were carried out to investigate how symptoms affect next time point's symptoms. It is discovered that the major difference between exposure is the connection between physical symptom and psychological symptoms. It is found that prior to exposure, or in a high physical symptom severity state, psychological symptoms do not have a significant correlation with next time point's physical symptoms. This correlation however is found to exist after exposure to biologics. It can also be seen in Figure 18 that physical symptoms do not impact next time period's psychological symptom, thus this association's direction is established. This means that when RA patients are experiencing severe physical symptom, the impact of psychological symptoms are not as pronounced. No study has established how the susceptibility of physical symptoms change according to its severity state, and this study establishes the possibility of the impact of psychological symptoms varying according to the severity of physical symptoms. This means that more care should be given towards psychological symptoms and depressive mood after biologic, because it plays a larger part in the disease and could have a significant impact on later physical symptoms.

This coincides with the conclusion from a study that looks at depression and biologic treatment in a UK cohort (Matcham et al., 2018) which states that depression should be managed as part of routine care in order to make sure that treatment for RA is optimized. It was also discovered in Figure 8.17 that there are temporal associations between positive affect and negative affect, in how both affects the next time point's positive and negative affect. This is a reflection of the network model of depression, in how a disorder starts. An activation in one of the affect symptoms spreads to the other, which in turn spreads back to the original node, forming a loop that reinforces the disorder. These dynamic models show that in decreasing the physical symptom, the temporal associations between psychological

symptoms disappear in Figure 8.18, suggest the close knit relationship between physical and psychological symptoms.

Last but not least, two network plots for before and after exposure was created. It was discovered that fatigue was strongly connected to other physical symptoms before biologics, but after biologics fatigue is disconnected from physical symptoms and formed multiple links with psychological symptoms, as seen in Figure 8.20. This means that in low physical symptom severity states, fatigue is more closely connected to psychological symptoms and does not have much of a relationship with physical symptoms. This has clinical implications on how to improve fatigue in patients, and how it depends on the severity of pain and stiffness. This disconnection between fatigue and other physical symptoms have not been noticed before in RA, suggesting another avenue of research that could provide novel insights. Centrality tables also attempt to show the most influential symptom in both symptom plot, and it can be seen that psychological symptoms rank highly for both plots. This provides evidence for the importance of psychological symptoms in RA, especially in after exposure to a new bDMARDs. One of the reasons for this could be that there are three physical symptoms and eight psychological symptoms involved in the network, which provides more influence for affect. However, it can still be seen that influence of joint stiffness decreased drastically between network plots, showing that in low physical symptom severity states, stiffness does not have strong associations with the disorder as a whole.

Even though this study has produced some novel results, there are still some limitations that could be improved. It has been addressed that placebo could be the reason for the significant decrease in physical symptoms after exposure, especially considering how symptom scores seem to be affected significantly within a day of exposure. This means that in order to have an accurate look at how symptoms change after biologics, the duration of the study should be extended. This study only contains around three weeks of post-biologic data, however some patients only experience the effect after four weeks. Extending the study to include more time after biologics will ensure a more accurate read without placebo effects at how symptoms change after exposure. The three weeks of data pre-exposure will allow researchers to have a more accurate estimate of average symptom severities and variances due to larger amounts of data available. This also potentially allows for removal of not just the day of biologic infusion but a few days before, which may not be ideal days to

consider as a baseline level, for example anxiety levels may be heightened in expectation of a medical procedure potentially not experienced prior. The 5 weeks post-exposure data will allow researchers to have a more accurate estimate of the true effects of the new biologics treatment, which could take up to a month to fully work. This will also allow participants' symptoms to even out after treatment and provide a more accurate estimate of the average of symptom levels after the new treatment. However, this added burden on patients may mean it is hard to keep up with the response rate. This means that there will need to be a pilot test to ensure that completion rate is still above the 80% that is a benchmark for EMA studies. Possible ways to ensure a higher completion rate while having a longer study period is to restrict surveys to once a day for the majority of the study, and have only a shorter period of time with multiple surveys a day. It is also possible to restrict the number of questions per survey, however it is important to be able to measure symptoms covering a range of experiences in RA, thus it will be difficult to choose which symptoms to drop. Because of time constraint, this chapter only utilized 12 participants out of the ideal sample size of 30 in the analysis because the rest of the participants have not finished the study yet. This means that more analysis could have been carried in this study, particularly analysis to see how symptoms interact throughout a day instead of just between two time points. The FitBit also produces intra-day data accurate to the minute for both physical activity and sleep duration. This data was not used in this study yet, and could provide an even more in depth look at whether the objective and subjective measurements for activity and sleep correlate, which could increase the feasibility of using wearables in a longitudinal study. Network approach also provide the opportunity for longitudinal networks to be created, which can show how temporal edges may be created from exposure to a new biologic, suggesting new influential points to the network.

This study is the first of its kind to consider intensive longitudinal data is collected around the time of biologic initiation during the pandemic, and has implication for the post-pandemic period from RA patients that are starting a new biologic treatment. There are some potential barriers, such as people needing to have access to a smartphone to receive texts with link to EMA surveys, and also need to be able to install and operate the FitBit Application on the phones. Researchers also need to help set up the FitBit and manually download data for each participant which is time consuming and not scalable. However, many more clinical appointments are done remotely now with the situation likely to

continue. This places less burden on healthcare system and the patient, but also means that remote monitoring of symptoms is needed. As a result, participants and clinicians may have greater motivation to have access to this kind of data. Another facilitator to recruitment is keeping the data collection protocol as streamlined as possible with minimal patient burden, as this will help to retain high levels of patients over several weeks.

This study proved feasibility for not just intensive follow up with wearable devices, but also the recruitment of patients with high disease activity. It showed how study protocols could be improved to increase the success rate of recruitment, and also provides a template for EMA studies in patients starting a new biologic. It also proposes new study durations to negate the impacts of placebo. Novel findings were also derived from the dataset, in particular that pain severity has a more immediate impact from Biologics compared to other physical symptoms and physical activity having an association with positive affect. Temporal associations also showed how physical symptoms are more influenced by psychological symptoms when in lower severity states, and that fatigue could be the reason why since it is disconnected to other physical symptoms in that state. It also affirms current knowledge of the close association of physical and psychological symptoms, and the importance to treat depressive symptoms together with physical symptoms, especially after the prescription of biologics in order to maintain a high quality of life for RA patients.

9. Discussion

9.1 Overview of the discussion

This chapter summarises the findings of Chapters 5, 6, 7, and 8 concerning the feasibility of high frequency follow up methodology, use of network analysis in the field of RA and depression, and associations between the physical and psychological symptoms under different situations. These findings from the empirical chapters are discussed in the context of the aims that were set out in Chapter 2. Following this, a discussion on the strengths and limitations of the thesis's methodology and analysis are laid out. Finally, the clinical implications of the results are shown that are beneficial to patients and clinicians are shown, along with possible future studies in the field of RA and depression, and the use of network science in this field.

9.2 Overview of the aims and objectives

Chapter 1 established the common comorbidity of depression in RA and the dangers that it posed to the patients. The severe negative impacts that RA had on patients' health and quality of life, and the fluctuant nature of the symptoms was also discussed. The scoping review in Chapter 3 showed that there was a lack of studies in this field that utilised longitudinal data in multiple symptoms, which meant that most findings were derived from data collected from a single point in time. The lack of longitudinal data meant that the variation of symptoms over time were disregarded. Several studies covered in the scoping review utilised the EMA design to collect intensive longitudinal data, however a major limitation of these studies was the inability to incorporate more than three symptoms in the analysis and the lack of temporal associations discovered.

A theoretical model, the network approach, was discussed in Chapter 1 which illustrated the importance of individual symptoms and its interactions in the study of depression and comorbidity instead of the latent variable approach. This model was utilised for each of the empirical chapters, and each of the symptoms that were include in each chapter was considered as a node in the network. The use of this model would thus consider multiple symptoms and every interaction between each symptom, which differed

from what current literature showed. This meant that novel connections could be made in the symptom networks which could provide new clinical implications that were undiscovered.

Based on the gap in literature shown in Chapter 3 and the advancement of network analysis, three main aims were presented: 1) To test the feasibility of high-frequency data collection methodology along with the use of a wearable; 2) To discover novel associations between symptoms and important variables in RA; and 3) to investigate the feasibility of usability of network analysis in RA and depression. The remainder of this section will address how each of these aims were completed, and how each empirical chapter contributes to it.

9.2.1 Feasibility of high-frequency data collection methodology

The scoping review in Chapter 3 showed the current literature in the field of musculoskeletal disorders that utilized high-frequency data collection to look at symptom variability in patients. It also displayed the gap in literature concerning longitudinal data in this field and could be used as a framework when designing studies that utilise high-frequency data collection. It showed that the no study in this field had used longitudinal data to look at more than three symptoms, and that most of the studies focused on pain. It was also revealed that none of the studies looked at how symptom variability affects symptom severity and there was an insufficient amount of research on how within-individual variability across symptoms interacts with each other. The identification of these gaps shaped how the longitudinal studies in this thesis was designed.

In Chapter 8, the data was collected using an EMA methodology that sends surveys to participants six times a day for the first two weeks, and once a day for the last 16 days. This adds up to 100 in a month. In IA-COVID study shown in Chapter 6, a cohort of IA patients were also recruited to complete 60 surveys over 10 days. The surveys were substantially longer including questions regarding social contact and physical activity, and only 31 out of 218 (14.2%) of participants agreed to participate in the study. The completion rate of the 28 participants that provided usable data were around 83.3% which was acceptable. Because of the high completion rate, this survey was used as a framework to be

adapted to Chapter 8. The study period of Chapter 8 was longer, because of the need to have a longer period after a new treatment to track how symptoms change over time. This longer study duration meant that it was not feasible to have the same number of questions and still maintain a similar completion rate, thus minor changes were made to the questions and frequency of survey. The number of questions in each survey were decreased, and the last 16 days of the study also included just one survey a day.

The participants were also expected to use a wearable device, specifically a FitBit during the period of the study to provide the researcher with data regarding sleep and physical activity. The wearable device was used as part of the remote measurement methodology that would allow participants' data to be tracked, as the FitBit was shown to be the most accurate device to detect moderate to vigorous physical activity (Rosenberger et al, 2016), and also showed good sensitivity in distinguishing between awake and asleep states for participants (Haghayegh et al., 2019). The purpose of the wearable device is to lessen participant burden, for the participants only had to wear the FitBit and data could be collected automatically. However, no study was carried out to compare between the objective measurements of sleep and activity from the FitBit, to the subjective self-reported scores from RA patients. Thus, the surveys in this study also included questions on sleep and physical activity, and to test the feasibility of using FitBit in similar studies in the future. The entirety of the study in Chapter 8 was carried out by the researcher, and thus the recruitment methodology could also be considered as part of the feasibility test. This feasibility of collecting longitudinal data in a RA cohort including the use of a wearable, could be used as a format in future studies that are interested in looking at the variability in symptoms in RA.

The first objective to complete this aim was to consider the recruitment methodology of the study. This was important because the COVID-19 pandemic resulted in a shortened recruitment period for the APPro study, and thus a high success rate would mean that sufficient participants could be recruited before the end of the study. The study in Chapter 6 only had a success rate of 14.2%, however the participants were recruited off via email from a pool of participants that were already in the main study. In comparison, RA patients that were recruited in Chapter 8 were participants that were approved through the clinical team to be starting a new biological treatment and not involved in another study. In order to optimise the recruitment method, this study utilised key recruitment strategies

that were successful in previous studies such as running pilot tests, personal approach, trained research staff, and incentives (Nicholson et al., 2011). These recruitment methods were described in Section 8.4.1, and out of the 74 participants, 25 participants were successfully recruited, resulting in a 33.8% successful recruitment rate. Out of the 49 that were not recruited, 17 (34.7%) were due to an inability to contact the participants which could be alleviated if the recruitment was done in person. This meant that these 17 could have been recruited outside of pandemic times. Furthermore, only 17 (34.7%) out of the 49 participants were eligible for the study and refused to participate, which suggested that the study design and recruitment methodology was acceptable. It was discovered that in stroke patients, the recruitment rate was around 29.1% in a cross-sectional study design (Polese et al., 2017), which was lower than the 33.8% present in the study in Chapter 8. Furthermore, a longitudinal study that included a longer study duration, and featuring RA participants starting a new biologic should have even lower rate, which suggests that the recruitment methodology present in this study was efficient.

Having established the feasibility of the recruitment methodology, the feasibility of the study design was evaluated. Only 12 of the 25 participants were considered, because the rest of the participants were still completing data collection due to the delays caused by the COVID-19 pandemic. Out of the 12 participants, the completion rate ranged from 71 to 100%, with an average rate of 88.75%. As stated in Chapter 8, this rate was higher than proposed rate of 80% in self-reporting longitudinal studies (Stone & Shiffman, 2002) (Jones et al., 2019) and the 85% seen in a meta-analysis on chronic pain patients (Ono et al., 2019).This high rate was even more impressive in the context that using a wearable alongside EMA surveys would result in a slight drop in compliance rate normally (Wen et al., 2017). The compliance rate was also consistently high throughout the first two weeks, and the survey at 8pm that contained additional questions had the most response. The last 16 days with only one survey a day were also active on average, with a slight decrease in the last three days. These showed that even though there were an increase in number of measurements compared to Chapter 6, the average completion rate of 88.75% in this study was even higher than before and proposed numbers by existing literature. A similar study (Brannon et al., 2016) that included 4 surveys a day for 20 days and two wearable devices that measured sleep and physical activity showed a compliance rate of 81%, which was still lower than the 88.75% rate in this study. The four surveys contained 36 questions for the

first three, and 47 on the last survey. This study was also carried out on adolescents between 13-18 years old and were in good general health. This meant that a similar study design in a RA cohort starting a new biologic treatment would likely decrease the completion rate tremendously, suggesting that a design similar to Chapter 8 in this thesis would most likely be more viable.

The data collected from the FitBit also showed that there was a correlation coefficient of 0.688 between survey and FitBit data for sleep, and a correlation coefficient of 0.420 and 0.477 for physical activity. There were a strong and moderate correlation respectively, which showed the feasibility of using FitBit to measure these variables even with some issues with the methodology as covered in Chapter 4.

The 33.8% recruitment rate and 88.7% compliance rate from the study carried out in Chapter 8 showed the feasibility of collecting high-frequency longitudinal data from a RA cohort that was about to start a new treatment. It also established that the study design, which included the use of a wearable, was sufficient to ensure a high compliance rate. The robust correlation coefficient between FitBit and self-reported survey data also revealed the possibility of using wearables in the future. Compared to the sub-study in Chapter 6, the study design and recruitment methodology here showed great improvement and could be a possible template moving forward for studies that wants to incorporate wearables with EMA

9.2.2 Association between symptoms and important RA variables

After the feasibility of the intensive longitudinal study was established, the next step would be to analyse the collected data in order to reveal novel information that were not available in current research. Chapter 3 showed the lack of research carried out on longitudinal studies, and also the limited number of symptoms that were included. This would be addressed in Chapters 6, 7, and 8, where longitudinal data were collected and analysed, and multiple symptoms that addressed different aspects of a RA patients' experiences were covered. The four objectives also considered additional important quality of life variables such as physical activity and social contact. Because of the COVID-19 pandemic and the ensuing lockdown, data was collected during this period that created an opportunity to observe how symptom interactions change due to the lockdown. It was stated in Chapter 1

that patients have to try multiple dMARDs in order to achieve disease remission, which means that it is important to discover how starting a new treatment affect patients. This will provide clinically important information that help clinicians and patients to achieve better treatment outcomes.

9.2.2.1 Diurnal variations throughout the day

The first task was to investigate how symptoms of RA changed during a day and was carried out in the IA-COVID study in Chapter 6. It was important to observe diurnal variations because it would show how symptoms change throughout the day which is important information for both clinicians and patients. Current literature showed that joint pain is fluctuant (Zhang et al., 2015) and both pain and stiffness in RA were higher in the morning (Cutolo et al., 2003) and that this circadian rhythm was actually evident as well in inflammation levels calculated by power doppler ultrasonography (PDUS) which decreases throughout the day (Semerano et al., 2011). Fatigue (Pietrowsky & Lahl, 2008) decreased throughout the day for both physical and mental aspects, positive affect was shown to increase throughout the day and negative affect was more variable throughout a day without a clear pattern (Peeters et al., 2006). These are not all carried out on an IA sample, and thus this objective also served to look at whether the trends in the general population were similar in the field of IA.

It could be seen that physical symptoms such as pain and fatigue decreased in severity as the day goes on, with stiffness having the most evident drop with an effect size of 0.43 . Positive affect also increased throughout the day with an effect size of 0.43, while negative affect only had a slight decrease at the end of the day but with no substantial variation. This reflected current literature that was shown earlier for the general population, and established the diurnal variation that exists in RA. There was also no existing research that investigated diurnal variation of affect changed in IA. Furthermore, it could be seen that most symptoms vary throughout the day which gave impetus to the fact that longitudinal data were required to have a full picture of symptom interactions because of this variability in symptoms.

9.2.2.2 Associations between physical symptoms, psychological symptoms, and physical Activity

The IA-COVID study also included physical activity as one of the main variables that were measured from the cohort. By looking at associations between symptoms and physical activity, it was possible to look at how physical activity could influence patient symptoms and how patient symptoms could potentially have an effect on the level of physical activity. This is also the first time that a dynamic regression model was carried out in this thesis, and thus possible associations between physical symptoms and psychological symptoms are investigated as well.

A mixed-effect dynamic regression model was carried out and showed that there was a significant positive association between lag-1 negative affect and physical symptoms, meaning that an increase in negative affect would cause an increase in physical symptoms in the next time period. This suggested a direct connection from negative affect to physical symptoms which no current literature in the field of IA had showed before. A study carried out on the general population showed that negative affect predict pain in the next time point (Feeney, 2004). This established the importance of tracking depressive symptoms in IA patients because of the potential influence on next time period's physical symptoms.
This finding between lag-1 negative affect and current physical symptoms is important because it reveals the possibility of decreasing physical symptoms by focusing on certain psychological factors. In the wider musculoskeletal and rheumatic disease literature, there are some evidence of this phenomenon as well. A study carried out on 55 fibromyalgia patients showed that pain-related negative affect is one of the main predictors of pain as measured by VAS (Staud et al., 2003). Other rheumatic diseases such as psoriatic arthritis and ankylosing spondylitis also showed that psychological factors play a major role in health-related quality of life and fatigue levels of patients (van Middendorp & Evers, 2016). In the field of RA itself, it is also shown that illness perception could be related to longer morning stiffness, optimism related to lower pain and social support related to lower fatigue levels (Treharne et al., 2005). Even though there are some current evidence regarding psychological factors on physical symptoms in similar fields, it is important to note that these studies do not utilise intensive longitudinal data and only use either cross-sectional data or routinely collected data of a few time points. This means that the direction

of association discovered cannot be determined and the impact of psychological factors are uncertain as well. This reinforces the novel impact that this thesis provides in the field of musculoskeletal disorders and shows the importance of using longitudinal data.

Furthermore, it was shown that the only lag-1 variable that was significantly associated with physical activity was positive affect, with a significant positive association suggesting that an increase in positive affect would increase physical activity. As mentioned above, physical activity was an important method of self-management for patients and thus increasing physical activity should be a priority. A cross-sectional correlation between positive affect and physical activity were shown before, however no studies had shown a possible causal relationship between positive affect and physical activity. The lack of current literature to back this finding meant that more research is needed, in particular to investigate which aspect of positive affect in particular had this temporal effect with physical activity.

Chapter 6 was the first time mixed effect regression was used to investigate potential temporal associations between symptoms in this thesis, and it produced two novel findings that were not discovered before in the field of IA. Both findings had current literature backings in other populations or other types of data, but it was the first time these findings were revealed in the field of IA. It was also clinically important because it showed that the development of depressive symptoms could cause more severe physical symptoms, and that in order to increase physical activity in patients, the impact of positive affect cannot be discounted. It also provided a template for the rest of the thesis in how to carry out dynamic regression analysis on longitudinal data.

9.2.2.3 Difference in associations between lockdown and period of no restrictions

The IA-COVID dataset provided a perfect opportunity to study how lockdown affected IA patients because of the two waves of data that were collected. Lockdown impacted on both physical and psychological aspects of health, and also implemented lifestyle changes such as reduced social contact (Tommasi et al., 2020), and thus it is important to investigate how such a major change affected IA patients. With social contact one of the main influences on the management of depression and psychological symptoms (Zyrianova et al., 2006), the inclusion of social contact as one of the variables to compare with IA symptoms would allow

for more insight in how symptoms interact with each other. Comparing between lockdown and a period of no restrictions would thus mean that the level of physical activity and social support would be different, which adds an extra dimension to 9.2.2.2.

Physical symptoms specifically pain and stiffness significantly decreased during lockdown. This was a novel finding in the field of IA during lockdown, but contradicted similar research in other fields or with different study designs, for example an IA research study in Germany (Hasseli et al., 2021) showed stable self-reported pain levels in participants during and after a lockdown. However, the difference was that there were only three measurements of self-reported outcomes compared to the potential 60 measurements in this study. This exhibited how utilising longitudinal data could provide novel information that cross-sectional data could not. This deterioration of physical symptom during a lockdown is particularly important because there were less clinical visits because of the restrictions imposed.

The other significant differences between the two periods were a significant increase in loneliness level and a significant decrease in physical activity. These two differences were expected as during a period of lockdown, there were restrictions regarding in-person social interaction and activities outside the house, as shown in Chapter 7. This meant that when comparing associations between the two periods, it could be assumed that the associations that were discovered during Wave 2 (period during lockdown) were in a situation where there were decreased physical activity and increased loneliness.

Mixed effects dynamic associations showed no significant differences between temporal associations discovered in Waves 1 and 2, however different waves displayed different associations that could still provide important clinical implications. It was discovered that during Wave 2, there is a significant negative association between lag-1 social contact with physical symptoms, which was absent in Wave 1 which had an insignificant positive association between lag-1 social contact and physical symptoms in Wave 1. This meant that in a situation where there were increased loneliness, an increase in social contact would lead to a decrease in physical symptom. As noted in Chapter 7, social contact was scored by mode of social contact instead of frequency, which meant that instead of increased social activity, an increase in social contact score meant more in-person social contact compared to virtual social contact. This meant that more in-person social interactions that a RA patient with high loneliness score would mean a decrease in physical

symptoms in the next time period. It was shown in Chapter 7 that in-person social contact provided more benefits than virtual social contact, and this finding further illustrates this and provides evidence for it in an IA cohort.

Furthermore, lag-1 positive affect also had significant negative associations with physical activity and social contact in wave 2, suggesting that an increase in positive affect would lead to a decrease in physical activity and less in-person contact for the next time period. It showed a contradictory effect between positive affect and physical activity from the discovery made in Chapter 6, which could be due to the decrease in the sample size to 19 for the analysis in this study. The decrease in sample size resulted in less power and opened up the potential for biases that a larger sample size would have avoided. However, even with the smaller sample size, it could be seen that positive affect had more influence on other variables and symptoms during a period of no restrictions, than compared to a period of lockdown. This meant that in Wave 2, where there was a significantly higher level of loneliness, positive affect had less influence on a patients' symptoms and behaviour, suggesting that a high level of loneliness could cause the effects of positive affect to be diminished.

It could be seen that during a lockdown, pain and stiffness level significantly decreased for IA patients which was a novel finding that current literature could not reflect. It was also the only study that utilised intensive longitudinal data that looked at how physical symptoms changed during a lockdown in an IA cohort. Loneliness levels increased and physical activity decreased during a lockdown as well, which was expected because of the restrictions that were in place. No significant differences between temporal associations were discovered between the two periods, and because of the smaller sample size involved in this study, some contradictory information was derived as well. However, significant associations that formed during lockdown could still be interpreted as important information for IA patients that had high loneliness levels. It could be seen that during a time of decreased physical activity and increased loneliness, more in-person social contact would result in a decrease in physical symptoms and positive affect did not possess much influence towards other variables.

9.2.2.4 Changes in associations after commencement of a new treatment

The APPro study recruited patients who were about to start on a new bDMARD treatment, and data were collected before and after the new treatment to investigate how symptoms and experiences changed. In addition, this study also included both physical activity and sleep as measurements. Sleep is an important quality of life variable for RA patients as it was shown that poor sleep worsens fatigue and pain score, and also increases depressive and anxiety symptoms (Irwin et al., 2012). This objective would thus reveal important associations between symptoms in RA with physical activity and sleep in patients who had high disease activity and were starting a new treatment, in order to provide clinicians with important clinical information about how new treatments affect these patients.

All physical symptoms, namely pain, fatigue, and stiffness significantly decreased after the exposure. The rate of change of pain was quadratic, while fatigue and stiffness had a linear rate of change. This meant that pain was the physical symptom that showed the fastest effect from a new treatment. This difference in rate of change in pain compared to fatigue and stiffness was not discovered before and could be a useful information to have. With pain being one of the main physical symptoms that patients suffer from, this larger immediate effect was beneficial to patients and could be used as a form of pain relief. However, placebo effects in studies of pain were widespread at about 40% (Holmes et al., 2016) which could explain why pain had such a large decrease immediately. This consideration meant that this finding should be interpreted with care, and that more research was needed to observe this rate of change in pain.

Positive affect also significantly decreased after exposure as a whole, with only enthusiasm having a non-significant decrease. Most of these also decreased at a quadratic rate of change. It was shown in a systematic review that a lack of positive affect would lead to poorer pain outcomes, and that positive affect could be a viable target for treatment of pain (Finan & Garland, 2015). When there is poorer positive affect, pain levels should rise, which was the opposite that was discovered in this study as it could be seen that even though there was a significant decrease in pain, positive affect significantly decreased as well. This meant that positive affect in RA patients starting a new treatment must have decreased for another reason, and that clinicians need to be aware of this, in particular because it was shown that having symptoms of depression at the start of a new treatment would lead to poorer treatment response (Matcham et al., 2018).

The last significant difference is physical activity recorded by the FitBit, both steps walked each day and minutes of intense activity. Even though there was a moderate correlation between physical activity measured using self-reported outcomes and FitBit, only the FitBit data showed a significant decrease after a new treatment. It was a linear rate of change for the decrease, meaning that it decreased steadily over the 16 days of tracking after exposure. Self-reported physical activity score collected does not measure the quantity of physical activity, but the highest level of physical activity achieved throughout the day, which explained why there was a different result from the FitBit data. A study that collected physical activity measurements at baseline and three months after DMARD treatment showed that physical activity increased in RA patients (Prioreschi et al., 2014) after treatment. However, the data used to compare with baseline was only collected three months after the treatment, while this study in Chapter 8 collected data immediately after for around 2 weeks which no other study had done before. It was shown that less arthritis pain should lead to increased physical activity (Knittle et al., 2011), which contradicted with the finding here where both pain and physical activity decreased. However, it was also shown that there was minimal impact on physical activity in those with chronic pain (van den Berg-Emons et al., 2007) which could explain why this finding is relevant as well. Furthermore, this decrease in physical activity could be due to the significant decrease in positive affect, as the association that was discovered in Chapter 6 where positive affect influences physical activity in the next time period could have played a part here. With the importance of physical activity in self-management for RA patients, finding out why physical activity levels dropped immediately after a new treatment would be useful to improve symptom outcomes.

There were no significant differences in temporal associations that were discovered before and after exposure to the new treatment. However, there were still observations that were made that could have clinically important implications. The significant associations that were discovered during the after-exposure analysis could still be applied to cases in which patients have just started a new treatment. It could be seen that before treatment, physical symptoms were only significantly associated with itself in a previous time point, while after treatment, both lag-1 positive affect and negative affect were significant with physical symptoms as well. This meant that after treatment when physical symptoms were significantly lower, physical symptoms were influenced by the previous

time points' psychological symptoms. This meant that clinicians need to be especially careful about the psychological state of patients after a new treatment, as physical symptoms are more vulnerable to fluctuations due to a change in psychological symptoms' severity.

Chapter 8 showed that there were significant differences immediately after a bDMARD treatment, where pain, fatigue, stiffness, positive affect and physical activity all significantly decreased. It was discovered that pain and positive affect had a quadratic rate of decrease, where there was a steep decrease immediately which tailed off at the end of the study. Physical activity decreased at a stable rate, and previous discovered associations hinted that this could have been caused by the decrease in positive affect. Temporal associations showed no significant difference, but the after-treatment analysis showed physical symptoms to be influenced by psychological symptoms from the previous time point.

9.2.3 Utility of Network Analysis in the Study of RA and Depression

It was shown in the scoping review in Chapter 3 that there was a lack of studies that in the field of musculoskeletal disorders that utilised longitudinal data which looked at multiple symptoms and variability in each. The network science approach, which was also used to explain the model of depression in Chapter 1, is a method that could consider numerous symptoms and its interactions with each other simultaneously. Furthermore, with the inclusion of both physical and psychological symptoms in the empirical studies, using network science could also help identify possible connections between the different types of symptoms and identify an influential node that had the largest impact on the symptom network plot through centrality values. No study in the field of RA had utilised network science before in the field of RA and depression and this thesis would be the first to introduce this tactic and to investigate how it could be used in different situations and what novel information it could provide.

9.2.3.1 Network Science in secondary cross-sectional data

Chapter 5 used two different cross-sectional datasets; the IMPARTS and TITRATE-US dataset, and two network plots were derived from TITRATE which varies in the number of symptoms included for psychological symptoms. It was discovered that all three symptom plots created had identical features which showed the reliability of using network science. Inflammatory markers, physical symptoms, and psychological symptoms are distinctly in separate clusters, with inflammatory markers in particular being separate from the symptoms of RA.. Fatigue was the symptom that could be seen in all three symptom plots to be very closely connected to both physical and psychological symptoms. Inflammatory markers were isolated in all three plots, with most of the connections into patient symptoms situated at the tender joints and swollen joints link. There were no direct links between inflammatory markers and psychological symptoms, suggesting that anti-inflammatory drugs prescribed by clinicians would only help with lowering inflammatory markers and certain physical symptoms, and not lead to a fast and direct effect on psychological symptoms. Some of these findings also coincide with what current literature showed, as tender joints are highly associated with swollen joints, and fatigue, especially measured by the FACIT scale included multiple psychological aspects in the questionnaire, were expected to be the physical symptom that had the most connection with psychological symptoms.

Having established the symptom network plot of RA patients in a cross-sectional dataset, further analysis was carried out to reveal additional information. Centrality values were calculated to evaluate the influences of each symptom, which could then show which symptom had a bigger impact on the entire symptom network. It could be seen that in both symptom plots from TITRATE-US, dysphoria has the highest degree centrality which meant that it had the most direct connections out of every symptom and that an activation of this symptom could spread to a lot of different symptoms. For closeness centrality, dysphoria had the highest value in the expanded TITRATE-US plot with 16 psychological symptoms, while pain had the highest closeness centrality in the simplified version. The expanded TITRATE-US had 16 out of 25 symptoms (64%) to be psychological symptoms which could skew the results. Furthermore, the stability analysis carried out also showed the simplified TITRATE-US network plot had greater accuracy to be compared than the expanded network plot. A high closeness centrality score meant that information could be spread quickly when

this node was activated, and thus this meant that treating pain would lead to a fast effect on other symptoms.

An inflammatory marker, total PD was the symptom with the highest betweenness score, suggesting that it was involved in a lot of pathways between other symptom, and thus the removal of it would destabilise the network. However, inflammatory markers all have low degree centrality scores, and thus a low degree centrality and high betweenness score meant that inflammation did not have much direct connections with symptoms but was involved with a lot of indirect associations. These centrality values showed that psychological symptoms played a big role in the entire symptom network of RA patients, which was also further reinforced by the highest expected influence value, which takes into account if the link between nodes are positive or negative. More focus should be on psychological symptoms because of its widespread connections with other symptoms, but pain was still an important symptom because of its fast-acting effect on overall disease activity.

The calculation of bridge strength centrality also showed that inflammatory markers have low bridge strength, meaning that they do not have much influence on the other aspects of RA. Fatigue and dysphoria respectively have the highest bridge strength for physical and psychological symptoms. This meant that fatigue is the physical symptom that when activated, has the most influence on the development of the psychological symptoms. Coupled with the fact that fatigue had the most connections with psychological symptoms, it could be interpreted that fatigue is the bridge between physical and psychological aspects in RA.

9.2.3.2 Comparison of network plots in individual patients

Having established the basic network structure of network science and tested its feasibility and reliability, the next step was to use network analysis to get more novel information. Chapter 6 created individual network plots for each participant using the longitudinal data that was collected. One participant exhibited a stable symptom behaviour with low severity, one with stable symptoms but high severity, one with symptoms that fluctuated throughout the 10 days, and the last participant had a flare in symptoms but was otherwise stable. It could be seen that in the participant with a flare, every symptom besides anxiousness and

loneliness are very closely connected, suggesting that physical and psychological symptoms were highly linked during a flare. This meant that a flare in the physical symptoms would also result in a flare in depressive symptoms, showing how devastating the effects of a flare could be in patients.

Comparing between fluctuant symptoms to stable, it could be seen that fatigue in both participants with stable symptoms were closely connected to other physical symptoms. In the fluctuant symptom plot, pain and joint stiffness was connected alone and fatigue was instead linked with positive affect symptoms negatively. This meant that when patients had high symptom variability, fatigue was activated by low positive affect instead of other physical symptoms, which was the case in a low symptom variability profile. No other study had investigated how symptom variability could cause an effect on fatigue and its interactions. Stability analysis carried out on the accuracy of edge-weight for the four participants' network plot showed that there was a large 95% confidence interval for all four plots, suggesting that care should be taken when comparing between graphs. The fluctuant network plot and stable low severity network plot in particular also had larger differences between bootstrap means and sample means, which meant that there could be more edges that should exist in the network plot that was disregarded. These meant that the findings derived from comparisons could be inaccurate. With no other studies displaying the connection between fatigue and fluctuant symptoms, this finding could be interpreted as an exploratory hypothesis that benefit from more research affirming its validity.

9.2.3.3 Comparison of network plot during lockdown and a period of no restrictions

The lockdown implemented because of the COVID-19 pandemic allowed data to be collected that could show how a lockdown affected IA patients' symptom and symptom interactions. It was also noted previously that physical symptoms and physical activity significantly decreased, while loneliness level significantly increased during the lockdown. This meant that the network plots could also be interpreted with those as context. The network plots contained physical and psychological symptoms, but also physical activity and social contact to evaluate how these variables play a part in the symptom network.

One of the biggest differences between the two network plots were that during a period of no restrictions, fatigue had the strongest connection to pain while during a

lockdown, fatigue was more linked to stiffness instead. This meant that during lockdown, where there was a significant decrease of physical activity and physical symptoms, fatigue had a higher connection to stiffness instead of pain. With the network plot being undirected, the direction of the connection between fatigue and stiffness is unclear. However, no studies had investigated the change in connection for fatigue during a lockdown, or the connection between fatigue and stiffness during lockdown. With multiple symptoms significantly changing due to the lockdown, the cause for the change for the connection of fatigue is unclear, and could benefit from future research. The symptom plot during lockdown also showed a strong connection between loneliness and anxiousness that was absent otherwise. It was shown that during the lockdown, the higher the worry for loneliness, the higher the anxiousness that the participant had (Isaac et al., 2021). This coincided with the finding of this study, where in the symptom plot with significantly increased loneliness, there was a connection between anxiousness and loneliness. The stability analysis that was carried out on the two network plots showed that there were a tight 95% confidence interval around the sample and bootstrap means, suggesting that the edge-weight were quite accurate. There were also minimal differences between the sample and bootstrap means for both graphs. This meant that comparison between the edge-weights for each graph should be considered seriously, and thus the findings were made from the comparison should be further researched to fully explore the possible associations.

9.2.3.4 Comparison of network plot before and after a new treatment

It was established previously that after a new treatment, there were significantly lower physical symptoms, which meant that findings made in the symptom plot after treatment could be made in that context. With the objective to investigate what clinical implications there are from a new treatment, the nodes included were purely patient symptoms in order to see how the interactions change.

The main difference that could be interpreted between symptom plots were the change in fatigue. Before treatment, fatigue was part of the physical symptom cluster and had a strong connection with stiffness. After treatment, fatigue lost all connection with physical symptom and instead were connected to both positive affect and negative affect. With fatigue having both physical and psychological aspects, this suggested that after

treatment where physical symptoms significantly decreased, fatigue were more influenced by the psychological aspect instead. As fatigue was one of the main symptoms that RA patients suffer from, being aware of what have an influence on it would be useful for clinicians who want to address it. To evaluate which symptom was the most influential in the network plots, centrality values were calculated. It could be seen that for both symptom plots, psychological symptoms especially content and irritable are highly influential, being top of degree centrality, closeness centrality, and betweenness centrality for both graphs. This showed the amount of influence that psychological symptoms have in a RA patient, and the importance of focusing on it to decrease disease activity as a whole.

Looking at centrality values, there were some differences before and after treatment, namely that the most influential physical symptom taking into account every centrality was stiffness before treatment, and pain after treatment. This meant that in if the clinician was treating physical symptoms to improve disease activity, it would be more important to address pain rather than stiffness after a new bDMARD. Stability analysis was also carried out on both plots. For before treatment, edge-accuracy graph showed some differences between bootstrap means and sample means which suggested some possible inaccuracy at identifying a link. The centrality stability plot also showed a low CS-coefficient with only degree centrality being stable enough to produce a significant result. For post-treatment, edge-accuracy graph showed a very tight 95% confidence interval and no differences between bootleg means and sample means, suggesting that the edges shown on the plots are accurate and could be interpreted. The CS-coefficient for centrality stability also showed that both degree and closeness centrality are above 0.5, suggesting that they are stable enough to be compared between each symptom. The sensitivity analysis showed that the post-treatment network plot was much more accurate, and the centrality values derived were stable as well. Pre-treatment network plot was still accurate and stable, however the results derived from it should be taken with caution. However, any findings that were derived from observing the post-treatment network plot would still be valid, specifically the disconnection of fatigue from other physical symptoms and the influence of psychological symptoms to the whole network.

9.3 Strength & Limitations

This study utilised intensive longitudinal data in order to investigate temporal associations and intra-individual symptom variability in the field of RA. This was an under-researched area of study, and with the fluctuant nature of RA symptoms, an area that is in need of more studies. It also utilised a new analytical method, the network approach to evaluate how multiple symptoms interact with each other in the comorbidity of depression and RA. However, in the planning of the thesis, there were some limitations as well. These strength and limitation would be shown in the following subsections.

9.3.1 Strength and Limitations of Longitudinal Study Design

The longitudinal datasets collected in Chapters 6, 7, and 8 meant that there were no recall bias from participants because the self-reported data were collected six times a day. The EMA methodology also meant that there were no ecological bias, and the lack of these two biases meant that the data collected would be more accurate. Furthermore, these data allowed for temporal associations to be made, which gave more cause-and-effect information than any cross-sectional associations could. This is because if there was a significant correlation between two variables and there was only one significant temporal association discovered, then the direction of the correlation could be deciphered. A prominent example from this thesis would be the discovery of the temporal association between lag-1 positive affect and physical activity which showed that physical activity could be influenced by the previous time point's positive affect. Intensive longitudinal data also meant that the trend of the symptoms could be investigated as well, showing a diurnal pattern of each symptom such as seen in Chapter 6. These findings that were derived from the longitudinal data thus allow for higher accuracy when observing changes of the symptoms that cross-sectional data could not. In all, the longitudinal study design collected enough data to eliminate recall and ecological bias. The quantity of data collected also meant that potential flares that changes symptom severity would not play a big role in changing symptom interactions.

There were some limitations with the study design in this thesis that could be improved. The first one was that the analysis of mixed effects dynamic modelling used the

whole symptom construct as the variable, for example negative affect instead of anxious. This meant that findings such as that of negative affect being significantly positively associated with next time period's physical symptom could not be specified, which would require more research to pinpoint the exact symptom that are in this association. Because of the number of symptoms included, it was difficult to include every symptom in the dynamic modelling which caused this problem. The next limitation was the required sample size. As shown in Chapter 7, the sample size decreased to 19 from the original sample in Chapter 6, and this resulted in one of the main findings of Chapter 6 to be found insignificant and reversed. A large sample size in longitudinal studies is harder to find because of the additional patient burden, and thus is an important limitation that needs to be considered. Furthermore, the period of the study also needs to be carefully considered. The duration of the study is a concern because it needs to be long enough to collect enough information, but not too long as to increase participant burden. In Chapter 6, it could be seen that the duration should be longer to accommodate for the possibility of a flare that could last for more than a week (Bykerk et al., 2014) and in Chapter 8, the duration could have been longer for both before and after treatment. The timing of the longitudinal data collection could also be a cause of concern, because as Chapter 6 showed, stretching out the period of collection into two different seasons could mean that seasonal variations influences the symptom severity as well.

The longitudinal study design could be improved tremendously based on the suggestions that were made from the studies carried out in this thesis. Even with the limitations, analysis of the longitudinal data revealed new interactions and clinical implications in the field of RA and showed promise in exploring the cause-and-effect of different symptoms.

9.3.2 Strength and Limitations of Network Approach

The network approach was used in every empirical chapter to investigate its suitability for use in the field of longitudinal data in RA, and also to reveal useful information about symptom interactions and influences. As it was displayed in every chapter, the network

approach could take into account all the symptoms and interactions into one clear and concise network plot. This meant that the network perspective could considers the strength of all interactions between symptoms when analysing the influence of a particular symptom. Most analysis methods such as the dynamic models utilised before could not include multiple symptoms without causing the results to be overcomplicated and overwhelming to pick out the important findings. The symptom network plot created allows for a very clear picture that could allow for quick hypothesis to be made. Furthermore, network science could also reveal the most influential and central symptoms by calculating centrality. The most central symptom could also be interpreted as the symptom that has a stronger causal influence on the whole symptom network compared to other symptoms (Borsboom & Cramer, 2013). This meant that if this symptom was activated, the probability of other symptoms being influenced and developing is the highest. The identification of this node would provide very useful clinical information because targeting these central symptoms as soon as possible would have a good chance of stopping the rest of the symptoms from developing. Chapter 6 also established the possibility of investigating individual differences using network analysis, showing how different situations affect the symptom plot differently. With each individual network determined by the individuals' own links between symptoms, it could also help in identifying individuals with links that could be activated into a disorder.

The network approach that was utilised in this thesis had some limitations as well unfortunately. Every empirical chapter utilised the data as a cross-sectional data, comparing between two separate time periods which assumes that each of the rows of data were independent. However, the data collected were time-series data, and were dependent on each other because data from the same participant correlate higher among the participant and that measurements at one time point could play a role in the next time point. This meant that additional information could have been derived from this data set if the temporal effects were taken into account, showing both between-person and within-person network plots. The lack of panel data analysis was because network science was never used before in the field of RA and depression, and thus there were insufficient time to carry out all possible analysis. The network analysis that was carried out in this thesis showed its feasibility in this field, and also provided novel information by comparing between individual differences and between time periods. The other limitation is the limited accuracy

and stability of some of the network plots and centrality values that were created in the empirical chapters. This meant that the findings that were derived from network analysis could not all be taken with significance, and more tests were needed to ensure its accuracy. There were no studies yet that showed the ideal number of observations and participants to allow for accurate edge-weight and centrality values, and thus this limitation affected the findings slightly. Furthermore, with network science being a relatively new theory and the application of network approach in psychological studies still in its infancy, the mechanics that were involved in carrying out network science were not all optimised. This could be seen in how edge selection was just an estimation which meant that unselected edges could not be guaranteed to be statistically zero, and the estimation methods that were used, specifically the regularised estimations are not perfectly reliable even though they were the preferred method (Borsboom et al., 2021). Centrality as a measure of causality was also a matter of discussion because of the potential inaccuracies (Dablander & Hinne, 2019), however it could still be used to interpret influence of symptoms.

It could be seen that network science was perfectly suitable for use in observing symptom interactions in the field of RA and depression and allowed for more information to be revealed that other analytical methods could not. However, because network science is still a relatively new methodology, a lot of aspects could still be optimised to allow for more accurate results. There were also more aspects of network science that could be utilised in the data collected here, but because of time constraints must be delegated to future research.

9.4 Clinical Implications

From the perspectives of a clinician, there are some important clinical implications that could be derived from the findings here. All the empirical chapters showed the importance of tracking psychological symptoms and depression in RA patients and how influential they are in the lives of RA patients. The longitudinal data collected affirmed the fluctuant nature of RA symptoms, and the success of Chapter 8's high intensity data collection with the FitBit also provided a template for how clinicians could track participant symptom variability. Furthermore, the effects of a change in treatment were also investigated for clinicians to

know how a new treatment affect their patients and what symptoms should be tracked more carefully during this time.

Psychological symptoms play an important role in the symptom network plot that was drawn in Chapter 5. Low mood in particular was the symptom node that had the highest degree centrality value, meaning that it was the symptom that had the most connections in the RA network. When mixed effects dynamic modelling was carried out on physical symptoms, positive affect, negative affect, and physical activity in Chapter 6, two novel findings were made regarding affect in IA patients. Increased positive affect was seen to be associated with increased physical activity in the next time period, and increased negative affect was seen to be associated with increased physical symptoms in the next time period. This was especially useful for clinicians to note because this meant an increase in depressive symptoms would not only lead to more physical symptoms, but also less physical activity which is one of the best self-management techniques. The importance of positive affect on physical activity could also be seen in Chapter 8 where there was a significant decrease in both physical activity and positive affect after the new treatment, when physical activity was supposed to increase because of the decrease in pain levels (Knittle et al., 2011). All these showed that clinicians need to be acutely aware of the psychological health of patients, because of the possibility of the influence it plays on not just physical symptoms, but also physical activity.

Chapter 6 also affirmed the diurnal variation of symptoms where physical activity significantly decreased and positive affect increased throughout the day. This meant that appointments with patients early in the morning could result in catastrophising of symptoms, and later appointments resulted in the underestimation of the severity. This fluctuant nature of symptoms thus discourages the measurement of patient symptoms only during a clinic visit because it only measures that point in time. The importance of tracking fluctuations of symptoms is emphasized by the finding from the network plot comparisons in Chapter 6, where it was shown that the symptom network plot between a fluctuant and stable patient is different. This change in symptom variability changed the connectivity of fatigue to the psychological aspects instead of other physical symptoms. With the stability of the edge-weight lacking, this hypothesis needs future research to ensure its accuracy but still shows that the effects of a fluctuant symptom pattern should be investigated. It was also established in the scoping review in Chapter 3 that no studies in the field of

musculoskeletal disorders actually investigated how symptom variability affect symptoms, and thus the knowledge in this particular area is lacking.

The successful recruitment and completion rate of the longitudinal study with FitBit in Chapter 8 established a framework that could be utilised for clinicians to be able to identify how patient symptoms vary throughout the day, with 6 measurements a day still providing a completion rate of 88.75%. This idea was implemented in some clinics already, with patients and clinicians tracking how symptoms vary via daily input using the My Arthritis App (Ampersand, 2019). An improvement on this idea by using FitBit which provides easily trackable data that are associated with self-reported data, and the inclusion of multiple inputs per day will provide an even more accurate look at fluctuations. These tracking of data will allow clinicians to be able to know how their patients' symptom trends are outside of clinics, and can also understand what potential effects a high fluctuant symptom behaviour will have on patients.

Last but not least, APPro study looked at how a new bDMARD treatment affect patients. These patients are generally with high disease activity for them to be prescribed with a bDMARD, and it was shown that right after treatment, physical symptoms and positive affect significantly decreased, alongside physical activity. It was also observed that the rate of decrease for pain and positive affect were larger than fatigue and stiffness, suggesting that these symptoms are more affected by the new treatment immediately. Pain and positive affect are negatively associated as stated above, however both symptoms decreased after a new treatment, suggesting that another factor is driving the decrease in positive affect. This is very important for clinicians because it was stated previously that depressive symptoms right after treatment will lead to poorer treatment response and the decrease in positive affect will predict higher depressive symptoms (Raes et al., 2012). Furthermore, temporal associations discovered that after treatment, positive and negative affect are both significantly associated with physical symptoms which strengthened the importance of psychological symptoms in a patient. The centrality values from network plots also showed psychological symptoms to be the most influential, both before and after treatment. It was also discovered that physical activity decreased immediately after, and with exercise being one of the main self-management tools, this discovery means that clinicians will need to remind patients of combining the new treatment with exercise. Fatigue was discovered by the network plot to have significantly different connections after

treatment, with fatigue losing the connection to stiffness and developing new connections with both affect instead.

It can be seen that there are a lot of potential clinical implications from the findings of this thesis, and some have immediate clinical implications such as the affirmation of the importance of psychological health in patients and the feasibility of tracking patient outcomes multiple times a day that can improve current clinical tracking. However it is also important to note that some of them are dependent on temporal associations discovered that may need to be reaffirmed in future studies. There are also some findings that are important for researchers, but are not specific enough yet to have clinical implications, such as the influence of positive affect on physical activity which requires more research on the type of positive affect that can increase physical activity in the next time periods. This means that specific future research on novel associations discovered in this thesis needs to be carried out, and the full analysis of APPro study after the completion of 30 participants is also needed in order to have a complete and accurate insight into the longitudinal associations of symptoms. The individual network plots shown in Chapter 5 displayed a potential clinical use for network modelling because it is able to show how different patients have different interacting symptoms, and thus will be able to provide clinicians with information needed to allow for personalised care. This means that more work needs to be done in order to streamline the process of creating the individualised network plots, and also an appropriate and standardised method is needed to analyse the plots.

This thesis showed the feasibility of tracking patient data remotely and over time, suggesting that clinicians should do the same in order to track how symptom variability affects patients and providing the framework to ensure a high completion rate. It also showed how important psychological symptoms are in RA patients, with it affecting physical symptoms and physical activities in the next time period, and also being the most influential nodes in a network model after a new treatment. Furthermore, fatigue also provided to be an important symptom to be on the look out for, as the connections for fatigue changes in different situations such as a new treatment or in a patient with fluctuant symptoms. This means that the cause of fatigue can vary, and as one of the main symptoms that patients suffer from, will need more attention on to reduce the effect. Fatigue is also calculated to be the bridge symptom between the physical and psychological symptoms in RA.

9.5 Future Research

This thesis has managed to achieve all three aims that was laid out in Chapter 2 by fulfilling each of the objectives. It was discovered that longitudinal data collection with a wearable device is very feasible, and should be encouraged in order to collect high quality data suitable for advanced analysis. It was also discovered that network science is a viable methodology to look at symptom interactions, and can provide novel hypothesis that needs to be fully researched on. The importance of psychological symptoms in RA patients was also shown, and clinical implications from the effect of a new treatment also provided a lot of new information for clinicians. However, because of time constraints and some of the elements of the thesis being used for the first time here, there are some future research that needs to be carried out.

The scoping review in Chapter 3 was carried out early during this PhD which spanned over four years. This means that an updated search on the same criterions will be helpful to show what updated current literature has in the field of intensive longitudinal data analysis in musculoskeletal disorders. This will help in deciding the route future research should take as well. It is discovered in a osteoarthritis sample that collected data 4 times a day for 7 days that depression predicts current pain and affect levels, and also change in pain and affect over the next 3-8 hours (Parmelee et al., 2022). Furthermore, the association between pain and negative affect is also more significant in OA patients that are diagnosed with depression. This is an important finding because it coincides with the EMA results that were derived from this thesis regarding the importance of psychological factors in physical symptoms in RA. Another study compared a fibromyalgia population with a general population by measuring EMA data 5 times a day for 7 days and discovered that there is a stronger inverse association between positive and negative affect during times of greater pain and fatigue levels in those with fibromyalgia (Kim et al., 2022). There is also another study carried out on fibromyalgia patients that utilised EMA methodology of 5 measurements for 7 days that looked at pain levels and cognitive dysfunction, and discovered that fibromyalgia patients report higher cognitive dysfunction when faced with an increase in pain compared to the general public (Whibley et al., 2022). There was also a study published that included one measurement a day of physical and psychological symptoms in RA patients over a period of three months in order to capture patient-reported

flares (Gandrup et al., 2022). These are a few examples from the updated search for 2022, and displayed the growing popularity of using EMA measurements to collect intensive longitudinal data and the recognition that analysis of longitudinal patterns are important. Some of these studies also included more than 3 symptoms, which was one of the major weaknesses of previous studies as brought up in Chapter 3. A quick search for network analysis in the field of RA yielded nothing, however a systematic review did use network meta-analysis which uses similar concepts of direct and indirect links between more than three interventions to look at the efficacy and safety of different DMARDs (Wang et al., 2021). Even though no network analysis had been utilised yet in this field, the change in focus towards temporal associations and multiple symptoms means that this the direction of this thesis is correct, and will be able to provide novel information and also lay down a template for future studies in this area.

Some of the associations discovered require further research to decipher if there are any causal meanings behind it. The significant associations between lag-1 negative affect and physical symptoms, and lag-1 positive affect and physical activity are novel findings, but the specific affect and physical symptoms need to be specified in order to provide more clinical implications. It is unclear which negative affect influences which physical symptom of the next time period, and thus future research will need to carry out similar temporal associations on each of the symptoms in order to discover this association.

It is also possible that some of the symptoms chosen are ineffectual, or that some important symptoms are missing from analysis. Qualitative interviews are carried out on the sample in Chapter 8, but because of time constraints could not be shown in this thesis. However, the interviews will be able to provide patient insight on the questions that were asked, and what new symptoms should be considered that are important to them. Furthermore, as mentioned in Chapter 7, some variables such as social contact and physical activity should be redesigned so as to allow for more accurate scoring of those variables.

Future research should also take into account the sample size and study duration of the studies. It was discovered that sample size for Chapter 7 which was reduced to 19 could be too little, as it changed the findings from the original sample size that was originally in Chapter 6. This also is applicable to network analysis, as since it is such a new technique, there are no guidelines to follow yet. A new study should be carried out to investigate how

much data is required in order to maintain an accurate edge-wise network plot with stable centrality scores.

9.6 Final Conclusions

RA is a chronic disabling condition with a high comorbidity with depression that affects all aspects of a patient's life. The fluctuant nature of RA means that tracking symptoms over time is required to have a full picture of symptom interactions and variations. This thesis has showed the feasibility of recruiting RA patients in carrying out intensive longitudinal assessments. The APPro study could be used as a framework for future research or clinicians when utilising remote measurement on symptoms over a period of time. Network science was shown to be a feasible analytical tool and showed potential for future developments in understanding comorbidity between RA and depression. Psychological symptoms are important to be tracked by clinicians because they are shown to have a significant association with physical activity, and with physical symptoms in the next time period. Furthermore, psychological symptoms are also very influential in symptom network plots, which meant that they play a big part in the overall disease outcome that patients feel. This means that in addition to addressing inflammation and pain in treatment, clinicians need to be careful of any potential spikes in psychological symptoms which could lead to worse clinical outcome. In conclusion, this thesis has managed to provide a template as to how remote measurement in RA should be carried out and introduced new methodologies in analysing large datasets. Furthermore, the importance of tracking and treating psychological symptoms has also been emphasised in order to improve overall outcomes for patients.

Bibliography

Abela, J. R., & D'Alessandro, D. U. (2002). Beck's cognitive theory of depression: a test of the diathesis-stress and causal mediation components. *Br J Clin Psychol*, *41*(Pt 2), 111-128. https://doi.org/10.1348/014466502163912

Acaster, S., Dickerhoof, R., DeBusk, K., Bernard, K., Strauss, W., & Allen, L. F. (2015). Qualitative and quantitative validation of the FACIT-fatigue scale in iron deficiency anemia. *Health Qual Life Outcomes*, *13*, 60. https://doi.org/10.1186/s12955-015-0257-x

Adams-Prassl, A., Boneva, T., Golin, M., & Rauh, C. (2020). *The Impact of the Coronavirus Lockdown on Mental Health: Evidence from the US*.

Adan, A., & Sanchez-Turet, M. (2001). Gender differences in diurnal variations of subjective activation and mood. *Chronobiol Int*, *18*(3), 491-502. https://doi.org/10.1081/cbi-100103971

Aho, K., & Heliovaara, M. (2004). Risk factors for rheumatoid arthritis. *Ann Med*, *36*(4), 242-251. https://doi.org/10.1080/07853890410026025

Aho, K., Koskenvuo, M., Tuominen, J., & Kaprio, J. (1986). Occurrence of rheumatoid arthritis in a nationwide series of twins. *J Rheumatol*, *13*(5), 899-902.

Akhondi, H., & Varacallo, M. (2021). Rheumatoid Arthritis And Ankylosing Spondylitis. In *StatPearls*.

Akkoc, N., & Khan, M. A. (2020). Is Axial Spondyloarthritis More Common Than Rheumatoid Arthritis? *Curr Rheumatol Rep*, *22*(9), 54. https://doi.org/10.1007/s11926-020-00934-3

Al-shair, K., Kolsum, U., Dockry, R., Morris, J., Singh, D., & Vestbo, J. (2011). Biomarkers of systemic inflammation and depression and fatigue in moderate clinically stable COPD. *Respir Res*, *12*, 3. https://doi.org/10.1186/1465-9921-12-3

Alamanos, Y., & Drosos, A. A. (2005). Epidemiology of adult rheumatoid arthritis. *Autoimmun Rev*, *4*(3), 130-136. https://doi.org/10.1016/j.autrev.2004.09.002

Alamanos, Y., Voulgari, P. V., & Drosos, A. A. (2006). Incidence and prevalence of rheumatoid arthritis, based on the 1987 American College of Rheumatology criteria: a systematic review. *Semin Arthritis Rheum*, *36*(3), 182-188. https://doi.org/10.1016/j.semarthrit.2006.08.006

Aletaha, D., Neogi, T., Silman, A. J., Funovits, J., Felson, D. T., Bingham, C. O., 3rd, . . . Hawker, G. (2010). 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum*, *62*(9), 2569-2581. https://doi.org/10.1002/art.27584

Alexandratos, K., Barnett, F., & Thomas, Y. (2012). The Impact of Exercise on the Mental Health and Quality of Life of People with Severe Mental Illness: A Critical Review. *British Journal of Occupational Therapy*, *75*(2), 48-60. https://doi.org/10.4276/030802212X13286281650956

Ali, S., Rhodes, L., Moreea, O., McMillan, D., Gilbody, S., Leach, C., . . . Delgadillo, J. (2017). How durable is the effect of low intensity CBT for depression and anxiety? Remission and relapse in a longitudinal cohort study. *Behav Res Ther*, *94*, 1-8. https://doi.org/10.1016/j.brat.2017.04.006

Almeida, C., Choy, E. H., Hewlett, S., Kirwan, J. R., Cramp, F., Chalder, T., . . . Christensen, R. (2016). Biologic interventions for fatigue in rheumatoid arthritis. *Cochrane Database Syst Rev*(6), CD008334. https://doi.org/10.1002/14651858.CD008334.pub2

Aloush, V., Gurfinkel, A., Shachar, N., Ablin, J. N., & Elkana, O. (2021). Physical and mental impact of COVID-19 outbreak on fibromyalgia patients. *Clin Exp Rheumatol*, *39 Suppl 130*(3), 108-114.

Althoff, T., Sosic, R., Hicks, J. L., King, A. C., Delp, S. L., & Leskovec, J. (2017). Large-scale physical activity data reveal worldwide activity inequality. *Nature*, *547*(7663), 336-339. https://doi.org/10.1038/nature23018

Ambrona, T., & Lopez-Perez, B. (2014). A Longitudinal Analysis of the Relationship between Positive and Negative Affect and Health. *Psychology*, *5*, 859-863. https://doi.org/10.4236/psych.2014.58097

Amini, L., Kalhor, M., Haghighi, A., Seyedfatemi, N., & Hosseini, F. (2018). Effect of oral contraceptive pills on rheumatoid arthritis disease activity in women: A randomized clinical trial. *Med J Islam Repub Iran*, *32*, 61. https://doi.org/10.14196/mjiri.32.61

Ampersand. (2019). *NRAS and Ampersand Health Partner to Launch Innovative App to Help People with Rheumatoid Arthritis*. Retrieved 10 Oct 2019 from https://ampersandhealth.co.uk/clinicians/research/nras-ampersand-health-launch-innovative-rheumatoid-arthritis-app/

Anderson, R. J., Freedland, K. E., Clouse, R. E., & Lustman, P. J. (2001). The prevalence of comorbid depression in adults with diabetes: a meta-analysis. *Diabetes Care*, *24*(6), 1069-1078. https://doi.org/10.2337/diacare.24.6.1069

Andone, I., Blaszkiewicz, K., Eibes, M., Trendafilov, B., Montag, C., & Markowetz, A. (2016). *How age and gender affect smartphone usage* UbiComp '16: The 2016 ACM International Joint Conference on Pervasive and Ubiquitous Computing, Germany.

Andrade, L., Caraveo-Anduaga, J. J., Berglund, P., Bijl, R. V., De Graaf, R., Vollebergh, W., . . . Wittchen, H. U. (2003). The epidemiology of major depressive episodes: results from the International Consortium of Psychiatric Epidemiology (ICPE) Surveys. *Int J Methods Psychiatr Res*, *12*(1), 3-21. https://doi.org/10.1002/mpr.138

Ang, D. C., Choi, H., Kroenke, K., & Wolfe, F. (2005). Comorbid depression is an independent risk factor for mortality in patients with rheumatoid arthritis. *J Rheumatol*, *32*(6), 1013-1019.

Angst, J., Gamma, A., Gastpar, M., Lepine, J. P., Mendlewicz, J., Tylee, A., & Depression Research in European Society, S. (2002). Gender differences in depression. Epidemiological findings from the European DEPRES I and II studies. *Eur Arch Psychiatry Clin Neurosci*, *252*(5), 201-209. https://doi.org/10.1007/s00406-002-0381-6

Aragones, E., Pinol, J. L., & Labad, A. (2007). Depression and physical comorbidity in primary care. *J Psychosom Res*, *63*(2), 107-111. https://doi.org/10.1016/j.jpsychores.2007.05.008

Arnett, F. C., Edworthy, S. M., Bloch, D. A., McShane, D. J., Fries, J. F., Cooper, N. S., . . . et al. (1988). The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum*, *31*(3), 315-324. https://doi.org/10.1002/art.1780310302

Association, A. P. (2013). *Diagnostic and statistical manual of mental disorders (5th ed.)*. American Psychiatric Association.

Bacci, E. D., DeLozier, A. M., Lin, C. Y., Gaich, C. L., Rooney, T., Hoffman, R., & Wyrwich, K. W. (2017). Psychometric properties of morning joint stiffness duration and severity measures in patients with moderately to severely active rheumatoid arthritis. *Health Qual Life Outcomes*, *15*(1), 239. https://doi.org/10.1186/s12955-017-0813-7

Baerwald, C., Manger, B., & Hueber, A. (2019). [Depression as comorbidity of rheumatoid arthritis]. *Z Rheumatol*, *78*(3), 243-248. https://doi.org/10.1007/s00393-018-0568-5 (Depression als Komorbiditat bei rheumatoider Arthritis.)

Baillet, A., Gossec, L., Carmona, L., Wit, M., van Eijk-Hustings, Y., Bertheussen, H., . . . Dougados, M. (2016). Points to consider for reporting, screening for and preventing selected comorbidities in chronic inflammatory rheumatic diseases in daily practice: a EULAR initiative. *Ann Rheum Dis*, *75*(6), 965-973. https://doi.org/10.1136/annrheumdis-2016-209233

Barr, D. J. (2008). Analyzing "visual world" eyetracking data using multilevel logistic regression. *Journal of Memory and Language*, *59*(4), 457-474.

Barra, L., Scinocca, M., Saunders, S., Bhayana, R., Rohekar, S., Racape, M., . . . Bell, D. A. (2013). Anti-citrullinated protein antibodies in unaffected first-degree relatives of rheumatoid arthritis patients. *Arthritis Rheum*, *65*(6), 1439-1447. https://doi.org/10.1002/art.37911

Bartlett, S. J., Orbai, A. M., Duncan, T., DeLeon, E., Ruffing, V., Clegg-Smith, K., & Bingham, C. O., 3rd. (2015). Reliability and Validity of Selected PROMIS Measures in People with Rheumatoid Arthritis. *PLoS One*, *10*(9), e0138543. https://doi.org/10.1371/journal.pone.0138543

Baughman, F. (2006). There is no such thing as a psychiatric disorder/disease/chemical imbalance. *PLoS Med*, *3*(7), e318. https://doi.org/10.1371/journal.pmed.0030318

Baumeister, A. A., Hawkins, M. F., & Uzelac, S. M. (2003). The myth of reserpine-induced depression: role in the historical development of the monoamine hypothesis. *J Hist Neurosci*, *12*(2), 207-220. https://doi.org/10.1076/jhin.12.2.207.15535

Beach, S. R., & Whisman, M. A. (2012). Affective disorders. *J Marital Fam Ther*, *38*(1), 201-219. https://doi.org/10.1111/j.1752-0606.2011.00243.x

Beard, C., Millner, A. J., Forgeard, M. J., Fried, E. I., Hsu, K. J., Treadway, M. T., . . . Bjorgvinsson, T. (2016). Network analysis of depression and anxiety symptom relationships in a psychiatric sample. *Psychol Med*, *46*(16), 3359-3369. https://doi.org/10.1017/S0033291716002300

Bechman, K., Yates, M., Norton, S., Cope, A. P., & Galloway, J. B. (2020). Placebo Response in Rheumatoid Arthritis Clinical Trials. *J Rheumatol*, *47*(1), 28-34. https://doi.org/10.3899/jrheum.190008

Beck, A. T., & Bredemeier, K. (2016). Integrating Clinical, Cognitive, Biological, and Evolutionary Perspectives. *Clinical Psychological Science*, *4*(4), 596-619.

Beck, J. S. (1964). *Cognitive Therapy: Basics and Beyond*. Guildford Press.

Belleau, E. L., Treadway, M. T., & Pizzagalli, D. A. (2019). The Impact of Stress and Major Depressive Disorder on Hippocampal and Medial Prefrontal Cortex Morphology. *Biol Psychiatry*, *85*(6), 443-453. https://doi.org/10.1016/j.biopsych.2018.09.031

Beltman, M. W., Voshaar, R. C., & Speckens, A. E. (2010). Cognitive-behavioural therapy for depression in people with a somatic disease: meta-analysis of randomised controlled trials. *Br J Psychiatry*, *197*(1), 11-19. https://doi.org/10.1192/bjp.bp.109.064675

Bijur, P. E., Latimer, C. T., & Gallagher, E. J. (2003). Validation of a verbally administered numerical rating scale of acute pain for use in the emergency department. *Acad Emerg Med*, *10*(4), 390-392. https://doi.org/10.1111/j.1553-2712.2003.tb01355.x

Bijur, P. E., Silver, W., & Gallagher, E. J. (2001). Reliability of the visual analog scale for measurement of acute pain. *Acad Emerg Med*, *8*(12), 1153-1157. https://doi.org/10.1111/j.1553-2712.2001.tb01132.x

Bilberg, A., Bremell, T., Bjersing, J., & Mannerkorpi, K. (2018). High prevalence of widespread pain in women with early rheumatoid arthritis. *Scand J Rheumatol*, *47*(6), 447-454. https://doi.org/10.1080/03009742.2018.1447683

Bildt, C., Alfredsson, L., Punnett, L., Theobald, H., Torgen, M., & Wikman, A. (2001). Effects of drop out in a longitudinal study of musculoskeletal disorders. *Occup Environ Med*, *58*(3), 194-199. https://doi.org/10.1136/oem.58.3.194

Billingham, S. A., Whitehead, A. L., & Julious, S. A. (2013). An audit of sample sizes for pilot and feasibility trials being undertaken in the United Kingdom registered in the United Kingdom Clinical Research Network database. *BMC Med Res Methodol*, *13*, 104. https://doi.org/10.1186/1471-2288-13-104

Bird, M. L., Callisaya, M. L., Cannell, J., Gibbons, T., Smith, S. T., & Ahuja, K. D. (2016). Accuracy, Validity, and Reliability of an Electronic Visual Analog Scale for Pain on a Touch Screen Tablet in Healthy Older Adults: A Clinical Trial. *Interact J Med Res*, *5*(1), e3. https://doi.org/10.2196/ijmr.4910

Boehm, J. K., Winning, A., Segerstrom, S., & Kubzansky, L. D. (2015). Variability Modifies Life Satisfaction's Association With Mortality Risk in Older Adults. *Psychol Sci*, *26*(7), 1063-1070. https://doi.org/10.1177/0956797615581491

Bogdan, R., Agrawal, A., Gaffrey, M. S., Tillman, R., & Luby, J. L. (2014). Serotonin transporter-linked polymorphic region (5-HTTLPR) genotype and stressful life events interact to predict preschool-onset depression: a replication and developmental extension. *J Child Psychol Psychiatry*, *55*(5), 448-457. https://doi.org/10.1111/jcpp.12142

Bogren, M., Bradvik, L., Holmstrand, C., Nobbelin, L., & Mattisson, C. (2018). Gender differences in subtypes of depression by first incidence and age of onset: a follow-up of the Lundby population. *Eur Arch Psychiatry Clin Neurosci*, *268*(2), 179-189. https://doi.org/10.1007/s00406-017-0778-x

Bolger, N., & Zuckerman, A. (1995). A framework for studying personality in the stress process. *J Pers Soc Psychol*, *69*(5), 890-902. https://doi.org/10.1037//0022-3514.69.5.890

Booth, J., Moseley, G. L., Schiltenwolf, M., Cashin, A., Davies, M., & Hubscher, M. (2017). Exercise for chronic musculoskeletal pain: A biopsychosocial approach. *Musculoskeletal Care*, *15*(4), 413-421. https://doi.org/10.1002/msc.1191

Borsboom, D. (2008a). Latent Variable Theory. *Measurement: Interdisciplinary Research and Perspectives*, *6*(1-2), 25-53. https://doi.org/https://doi.org/10.1080/15366360802035497

Borsboom, D. (2008b). Psychometric perspectives on diagnostic systems. *J Clin Psychol*, *64*(9), 1089-1108. https://doi.org/10.1002/jclp.20503

Borsboom, D. (2017). A network theory of mental disorders. *World Psychiatry*, *16*(1), 5-13. https://doi.org/10.1002/wps.20375

Borsboom, D., & Cramer, A. O. (2013). Network analysis: an integrative approach to the structure of psychopathology. *Annu Rev Clin Psychol*, *9*, 91-121. https://doi.org/10.1146/annurev-clinpsy-050212-185608

Borsboom, D., Deserno, M., Rhemtulla, M., Epskamp, S., Fried, E. I., McNally, R. J., . . . Waldorp, L. J. (2021). Network analysis of multivariate data in psychological science. *Nature Reviews Methods Primers*, *1*.

Boschloo, L., Schoevers, R. A., van Borkulo, C. D., Borsboom, D., & Oldehinkel, A. J. (2016). The network structure of psychopathology in a community sample of

preadolescents. *J Abnorm Psychol*, *125*(4), 599-606. https://doi.org/10.1037/abn0000150

Boury, M., Treadwell, T., & Kumar, V. K. (2001). Integrating psychodrama and cognitive therapy--an exploratory study. *International Journal of Action Methods: Psychodrama, Skill Training, and Role Playing*, *54*, 13-37.

Boyd, T. A., Eastman, P. S., Huynh, D. H., Qureshi, F., Sasso, E. H., Bolce, R., . . . Kavanaugh, A. (2020). Correlation of serum protein biomarkers with disease activity in psoriatic arthritis. *Expert Rev Clin Immunol*, *16*(3), 335-341. https://doi.org/10.1080/1744666X.2020.1729129

Bradburn, N. M., Rips, L. J., & Shevell, S. K. (1987). Answering autobiographical questions: the impact of memory and inference on surveys. *Science*, *236*(4798), 157-161. https://doi.org/10.1126/science.3563494

Brady, S. M., Fenton, S. A. M., Metsios, G. S., Bosworth, A., Duda, J. L., Kitas, G. D., & Veldhuijzen van Zanten, J. (2021). Different types of physical activity are positively associated with indicators of mental health and psychological wellbeing in rheumatoid arthritis during COVID-19. *Rheumatol Int*, *41*(2), 335-344. https://doi.org/10.1007/s00296-020-04751-w

Brand, R., Timme, S., & Nosrat, S. (2020). When Pandemic Hits: Exercise Frequency and Subjective Well-Being During COVID-19 Pandemic. *Front Psychol*, *11*, 570567. https://doi.org/10.3389/fpsyg.2020.570567

Brannon, E. E., Cushing, C. C., Crick, C. J., & Mitchell, T. B. (2016). The promise of wearable sensors and ecological momentary assessment measures for dynamical systems modeling in adolescents: a feasibility and acceptability study. *Transl Behav Med*, *6*(4), 558-565. https://doi.org/10.1007/s13142-016-0442-4

Braun, J., & Sieper, J. (2007). Ankylosing spondylitis. *Lancet*, *369*(9570), 1379-1390. https://doi.org/10.1016/S0140-6736(07)60635-7

Bringmann, L. F., Pe, M. L., Vissers, N., Ceulemans, E., Borsboom, D., Vanpaemel, W., & Kuppens, P. (2016). Assessing temporal emotion dynamics using networks. *Assessment*, *23*(4), 425-435. https://doi.org/10.1177/1073191116645909

Bromberg, M. H., Connelly, M., Anthony, K. K., Gil, K. M., & Schanberg, L. E. (2014). Self-reported pain and disease symptoms persist in juvenile idiopathic arthritis despite treatment advances: an electronic diary study. *Arthritis Rheumatol*, *66*(2), 462-469. https://doi.org/10.1002/art.38223

Bromberg, M. H., Connelly, M., Anthony, K. K., Gil, K. M., & Schanberg, L. E. (2016). Prospective Mediation Models of Sleep, Pain, and Daily Function in Children With Arthritis Using Ecological Momentary Assessment. *Clin J Pain*, *32*(6), 471-477. https://doi.org/10.1097/AJP.0000000000000298

Bromberg, M. H., Gil, K. M., & Schanberg, L. E. (2012). Daily sleep quality and mood as predictors of pain in children with juvenile polyarticular arthritis [Empirical Study; Quantitative Study]. *Health Psychology*, *31*(2), 202-209. https://doi.org/http://dx.doi.org/10.1037/a0025075

Bromet, E., Andrade, L. H., Hwang, I., Sampson, N. A., Alonso, J., de Girolamo, G., . . . Kessler, R. C. (2011). Cross-national epidemiology of DSM-IV major depressive episode. *BMC Med*, *9*, 90. https://doi.org/10.1186/1741-7015-9-90

Brooks, S. K., Webster, R. K., Smith, L. E., Woodland, L., Wessely, S., Greenberg, N., & Rubin, G. J. (2020). The psychological impact of quarantine and how to reduce it: rapid

review of the evidence. *Lancet*, *395*(10227), 912-920. https://doi.org/10.1016/S0140-6736(20)30460-8
Brown, L. F., & Kroenke, K. (2009). Cancer-related fatigue and its associations with depression and anxiety: a systematic review. *Psychosomatics*, *50*(5), 440-447. https://doi.org/10.1176/appi.psy.50.5.440
Brown, S. C., Glass, J. M., & Park, D. C. (2002). The relationship of pain and depression to cognitive function in rheumatoid arthritis patients. *Pain*, *96*(3), 279-284. https://doi.org/10.1016/s0304-3959(01)00457-2
Brown, V. (2021). An Introduction to Linear Mixed-Effects Modeling in R. *Advances in Methods and Practices in Psychological Science*. https://doi.org/https://doi.org/10.1177/2515245920960351
Bruce, B., & Fries, J. F. (2003). The Stanford Health Assessment Questionnaire: a review of its history, issues, progress, and documentation. *J Rheumatol*, *30*(1), 167-178.
Bruce, T. O. (2008). Comorbid depression in rheumatoid arthritis: pathophysiology and clinical implications. *Curr Psychiatry Rep*, *10*(3), 258-264. https://doi.org/10.1007/s11920-008-0042-1
Bruehl, S., Liu, X., Burns, J. W., Chont, M., & Jamison, R. N. (2012). Associations between daily chronic pain intensity, daily anger expression, and trait anger expressiveness: An ecological momentary assessment study. *Pain*, *153*(12), 2352-2358. https://doi.org/http://dx.doi.org/10.1016/j.pain.2012.08.001
Brunson, J. C., Agresta, T. P., & Laubenbacher, R. C. (2020). Sensitivity of comorbidity network analysis. *JAMIA Open*, *3*(1), 94-103. https://doi.org/10.1093/jamiaopen/ooz067
Brunson, J. C., & Laubenbacher, R. C. (2018). Applications of network analysis to routinely collected health care data: a systematic review. *J Am Med Inform Assoc*, *25*(2), 210-221. https://doi.org/10.1093/jamia/ocx052
Bu, F., Steptoe, A., & Fancourt, D. (2020a). Loneliness during a strict lockdown: Trajectories and predictors during the COVID-19 pandemic in 38,217 United Kingdom adults. *Soc Sci Med*, *265*, 113521. https://doi.org/10.1016/j.socscimed.2020.113521
Bu, F., Steptoe, A., & Fancourt, D. (2020b). Who is lonely in lockdown? Cross-cohort analyses of predictors of loneliness before and during the COVID-19 pandemic. *Public Health*, *186*, 31-34. https://doi.org/10.1016/j.puhe.2020.06.036
Bulloch, A. G., Williams, J. V., Lavorato, D. H., & Patten, S. B. (2009). The relationship between major depression and marital disruption is bidirectional. *Depress Anxiety*, *26*(12), 1172-1177. https://doi.org/10.1002/da.20618
Bulloch, A. G. M., Williams, J. V. A., Lavorato, D. H., & Patten, S. B. (2017). The depression and marital status relationship is modified by both age and gender. *J Affect Disord*, *223*, 65-68. https://doi.org/10.1016/j.jad.2017.06.007
Bullock, J., Rizvi, S. A. A., Saleh, A. M., Ahmed, S. S., Do, D. P., Ansari, R. A., & Ahmed, J. (2018). Rheumatoid Arthritis: A Brief Overview of the Treatment. *Med Princ Pract*, *27*(6), 501-507. https://doi.org/10.1159/000493390
Burckhardt, C. S., & Anderson, K. L. (2003). The Quality of Life Scale (QOLS): reliability, validity, and utilization. *Health Qual Life Outcomes*, *1*, 60. https://doi.org/10.1186/1477-7525-1-60
Burke, W. J., Gergel, I., & Bose, A. (2002). Fixed-dose trial of the single isomer SSRI escitalopram in depressed outpatients. *J Clin Psychiatry*, *63*(4), 331-336. https://doi.org/10.4088/jcp.v63n0410

Burns, J. W., Gerhart, J. I., Bruehl, S., Peterson, K. M., Smith, D. A., Porter, L. S., . . . Keefe, F. J. (2015). Anger arousal and behavioral anger regulation in everyday life among patients with chronic low back pain: Relationships to patient pain and function. *Health Psychology*, *34*(5), 547-555. https://doi.org/http://dx.doi.org/10.1037/hea0000091

Buttgereit, F., Mehta, D., Kirwan, J., Szechinski, J., Boers, M., Alten, R. E., . . . Saag, K. G. (2013). Low-dose prednisone chronotherapy for rheumatoid arthritis: a randomised clinical trial (CAPRA-2). *Ann Rheum Dis*, *72*(2), 204-210. https://doi.org/10.1136/annrheumdis-2011-201067

Bykerk, V. P., Shadick, N., Frits, M., Bingham, C. O., 3rd, Jeffery, I., Iannaccone, C., . . . Solomon, D. H. (2014). Flares in rheumatoid arthritis: frequency and management. A report from the BRASS registry. *J Rheumatol*, *41*(2), 227-234. https://doi.org/10.3899/jrheum.121521

Cadena, J., Vinaccia, S., Perez, A., Rico, M. I., Hinojosa, R., & Anaya, J. M. (2003). The impact of disease activity on the quality of life, mental health status, and family dysfunction in colombian patients with rheumatoid arthritis. *J Clin Rheumatol*, *9*(3), 142-150. https://doi.org/10.1097/01.RHU.0000073434.59752.f3

Callhoff, J., Weiss, A., Zink, A., & Listing, J. (2013). Impact of biologic therapy on functional status in patients with rheumatoid arthritis--a meta-analysis. *Rheumatology (Oxford)*, *52*(12), 2127-2135. https://doi.org/10.1093/rheumatology/ket266

Cameron, I. M., Crawford, J. R., Lawton, K., & Reid, I. C. (2008). Psychometric comparison of PHQ-9 and HADS for measuring depression severity in primary care. *Br J Gen Pract*, *58*(546), 32-36. https://doi.org/10.3399/bjgp08X263794

Capobianco, E., & Lio, P. (2015). Comorbidity networks: beyond disease correlations. *Journal of Complex Networks*, *3*, 319-332.

Capuron, L., & Dantzer, R. (2003). Cytokines and depression: the need for a new paradigm. *Brain Behav Immun*, *17 Suppl 1*, S119-124.

Carette, S., Surtees, P. G., Wainwright, N. W., Khaw, K. T., Symmons, D. P., & Silman, A. J. (2000). The role of life events and childhood experiences in the development of rheumatoid arthritis. *J Rheumatol*, *27*(9), 2123-2130.

Carney, R. M., & Freedland, K. E. (2017). Depression and coronary heart disease. *Nat Rev Cardiol*, *14*(3), 145-155. https://doi.org/10.1038/nrcardio.2016.181

Carosella, A. M., Lackner, J. M., & Feuerstein, M. (1994). Factors associated with early discharge from a multidisciplinary work rehabilitation program for chronic low back pain. *Pain*, *57*(1), 69-76. https://doi.org/10.1016/0304-3959(94)90109-0

Carpenter, L., Norton, S., Nikiphorou, E., Kiely, P., Walsh, D. A., Dixey, J., & Young, A. (2018). Validation of methods for converting the original Disease Activity Score (DAS) to the DAS28. *Rheumatol Int*, *38*(12), 2297-2305. https://doi.org/10.1007/s00296-018-4184-0

Caruana, E. J., Roman, M., Hernandez-Sanchez, J., & Solli, P. (2015). Longitudinal studies. *J Thorac Dis*, *7*(11), E537-540. https://doi.org/10.3978/j.issn.2072-1439.2015.10.63

Caspi, A., Sugden, K., Moffitt, T. E., Taylor, A., Craig, I. W., Harrington, H., . . . Poulton, R. (2003). Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science*, *301*(5631), 386-389. https://doi.org/10.1126/science.1083968

Castro, D., Ferreira, F., de Castro, I., Rodrigues, A. R., Correia, M., Ribeiro, J., & Ferreira, T. B. (2019). The Differential Role of Central and Bridge Symptoms in Deactivating

Psychopathological Networks. *Front Psychol*, *10*, 2448. https://doi.org/10.3389/fpsyg.2019.02448
Cavalli-Sforza, L. L. (1974). The genetics of human populations. *Sci Am*, *231*(3), 80-89. https://doi.org/10.1038/scientificamerican0974-80
Cella, D., Wilson, H., Shalhoub, H., Revicki, D. A., Cappelleri, J. C., Bushmakin, A. G., . . . Hsu, M. A. (2019). Content validity and psychometric evaluation of Functional Assessment of Chronic Illness Therapy-Fatigue in patients with psoriatic arthritis. *J Patient Rep Outcomes*, *3*(1), 30. https://doi.org/10.1186/s41687-019-0115-4
Cella, D., Yount, S., Sorensen, M., Chartash, E., Sengupta, N., & Grober, J. (2005). Validation of the Functional Assessment of Chronic Illness Therapy Fatigue Scale relative to other instrumentation in patients with rheumatoid arthritis. *J Rheumatol*, *32*(5), 811-819.
Chandola, T., Kumari, M., Booker, C. L., & Benzeval, M. (2020). The mental health impact of COVID-19 and lockdown-related stressors among adults in the UK. *Psychol Med*, 1-10. https://doi.org/10.1017/S0033291720005048
Chandrashekara, S., & Sachin, S. (2012). Measures in rheumatoid arthritis: are we measuring too many parameters. *Int J Rheum Dis*, *15*(3), 239-248. https://doi.org/10.1111/j.1756-185X.2012.01754.x
Charles, S. T., & Almeida, D. M. (2006). Daily reports of symptoms and negative affect: Not all symptoms are the same. *Psychology and Health*, *21*(1), 1-17. https://doi.org/10.1080/14768320500129239
Chen, J., & Chen, Z. (2008). Extended Bayesian information criteria for model selection with large model spaces. *Biometrika*, *95*(3), 759-771.
Chew, L. C., Xin, X., Yang, H., & Thumboo, J. (2019). An evaluation of the Virtual Monitoring Clinic, a novel nurse-led service for monitoring patients with stable rheumatoid arthritis. *Int J Rheum Dis*, *22*(4), 619-625. https://doi.org/10.1111/1756-185X.13436
Clark, L. A., & Watson, D. (1991). Tripartite model of anxiety and depression: psychometric evidence and taxonomic implications. *J Abnorm Psychol*, *100*(3), 316-336.
Clarke, L., Jessop, D., Hunt, L., Straub, R., & Perry, M. (2011). Alleviation of morning joint stiffness by low-dose prednisone in rheumatoid arthritis is associated with circadian changes in IL-6 and cortisol. *International Journal of Clinical Rheumatology*, *6*(2), 241-249. https://doi.org/DOI:10.2217/ijr.11.12
Cobb, S., Merchant, W. R., & Warren, J. E. (1955). An epidemiologic look at the problem of classification in the field of arthritis. *J Chronic Dis*, *2*(1), 50-54. https://doi.org/10.1016/0021-9681(55)90107-7
Coenen, M., Cieza, A., Stamm, T. A., Amann, E., Kollerits, B., & Stucki, G. (2006). Validation of the International Classification of Functioning, Disability and Health (ICF) Core Set for rheumatoid arthritis from the patient perspective using focus groups. *Arthritis Res Ther*, *8*(4), R84. https://doi.org/10.1186/ar1956
Cohen, J. (2013). *Statistical Power Analysis for the Behavioural Sciences*. Routledge.
Cojocaru, M., Cojocaru, I. M., Silosi, I., Vrabie, C. D., & Tanasescu, R. (2010). Extra-articular Manifestations in Rheumatoid Arthritis. *Maedica (Bucur)*, *5*(4), 286-291.
Colangelo, K., Haig, S., Bonner, A., Zelenietz, C., & Pope, J. (2011). Self-reported flaring varies during the menstrual cycle in systemic lupus erythematosus compared with rheumatoid arthritis and fibromyalgia. *Rheumatology (Oxford)*, *50*(4), 703-708. https://doi.org/10.1093/rheumatology/keq360

Collins, N. J., Crossley, K. M., Darnell, R., & Vicenzino, B. (2010). Predictors of short and long term outcome in patellofemoral pain syndrome: a prospective longitudinal study. *BMC Musculoskelet Disord*, *11*, 11. https://doi.org/10.1186/1471-2474-11-11

Combe, B. (2007). Early rheumatoid arthritis: strategies for prevention and management. *Best Pract Res Clin Rheumatol*, *21*(1), 27-42. https://doi.org/10.1016/j.berh.2006.08.011

Consonni, M., Telesca, A., Grazzi, L., Cazzato, D., & Lauria, G. (2021). Life with chronic pain during COVID-19 lockdown: the case of patients with small fibre neuropathy and chronic migraine. *Neurol Sci*, *42*(2), 389-397. https://doi.org/10.1007/s10072-020-04890-9

Constandt, B., Thibaut, E., De Bosscher, V., Scheerder, J., Ricour, M., & Willem, A. (2020). Exercising in Times of Lockdown: An Analysis of the Impact of COVID-19 on Levels and Patterns of Exercise among Adults in Belgium. *Int J Environ Res Public Health*, *17*(11). https://doi.org/10.3390/ijerph17114144

Contreras, A., Nieto, I., Valiente, C., Espinosa, R., & Vazquez, C. (2019). The Study of Psychopathology from the Network Analysis Perspective: A Systematic Review. *Psychother Psychosom*, *88*(2), 71-83. https://doi.org/10.1159/000497425

Cook, C., Cox, H., Fu, X., Zhang, Y., Stone, J. H., Choi, H. K., & Wallace, Z. S. (2021). Perceived Risk and Associated Shielding Behaviors in Patients With Rheumatoid Arthritis During the Coronavirus 2019 Pandemic. *ACR Open Rheumatol*, *3*(12), 834-841. https://doi.org/10.1002/acr2.11340

Corfield, E. C., Martin, N. G., & Nyholt, D. R. (2016). Co-occurrence and symptomatology of fatigue and depression. *Compr Psychiatry*, *71*, 1-10. https://doi.org/10.1016/j.comppsych.2016.08.004

Courvoisier, D. S., Eid, M., & Lischetzke, T. (2012). Compliance to a cell phone-based ecological momentary assessment study: the effect of time and personality characteristics. *Psychol Assess*, *24*(3), 713-720. https://doi.org/10.1037/a0026733

Covic, T., Cumming, S. R., Pallant, J. F., Manolios, N., Emery, P., Conaghan, P. G., & Tennant, A. (2012). Depression and anxiety in patients with rheumatoid arthritis: prevalence rates based on a comparison of the Depression, Anxiety and Stress Scale (DASS) and the hospital, Anxiety and Depression Scale (HADS). *BMC Psychiatry*, *12*, 6. https://doi.org/10.1186/1471-244X-12-6

Cox, L. A., Jr. (2018). Modernizing the Bradford Hill criteria for assessing causal relationships in observational data. *Crit Rev Toxicol*, *48*(8), 682-712. https://doi.org/10.1080/10408444.2018.1518404

Cramer, A. O., Waldorp, L. J., van der Maas, H. L., & Borsboom, D. (2010). Comorbidity: a network perspective. *Behav Brain Sci*, *33*(2-3), 137-150; discussion 150-193. https://doi.org/10.1017/S0140525X09991567

Criswell, L. A., Merlino, L. A., Cerhan, J. R., Mikuls, T. R., Mudano, A. S., Burma, M., . . . Saag, K. G. (2002). Cigarette smoking and the risk of rheumatoid arthritis among postmenopausal women: results from the Iowa Women's Health Study. *Am J Med*, *112*(6), 465-471. https://doi.org/10.1016/s0002-9343(02)01051-3

Crofford, L. J. (2013). Use of NSAIDs in treating patients with arthritis. *Arthritis Res Ther*, *15 Suppl 3*, S2. https://doi.org/10.1186/ar4174

Crosby, L. J. (1991). Factors which contribute to fatigue associated with rheumatoid arthritis. *J Adv Nurs*, *16*(8), 974-981. https://doi.org/10.1111/j.1365-2648.1991.tb01803.x

Cruise, C. E., Broderick, J., Porter, L., Kaell, A., & Stone, A. A. (1996). Reactive effects of diary self-assessment in chronic pain patients. *Pain*, *67*(2-3), 253-258. https://doi.org/http://dx.doi.org/10.1016/0304-3959%2896%2903125-9

Culpepper, L. (2008). Primary care management of patients with co-occurring disorders. *CNS Spectr*, *13*(4 Suppl 6), 13-15.

Cutolo, M., Seriolo, B., Craviotto, C., Pizzorni, C., & Sulli, A. (2003). Circadian rhythms in RA. *Ann Rheum Dis*, *62*(7), 593-596. https://doi.org/10.1136/ard.62.7.593

Dablander, F., & Hinne, M. (2019). Node centrality measures are a poor substitute for causal inference. *Sci Rep*, *9*(1), 6846. https://doi.org/10.1038/s41598-019-43033-9

Dalal, D. S., Zhang, T., & Shireman, T. I. (2020). Medicare expenditures for conventional and biologic disease modifying agents commonly used for treatment of rheumatoid arthritis. *Semin Arthritis Rheum*, *50*(5), 822-826. https://doi.org/10.1016/j.semarthrit.2020.08.002

Danoff-Burg, S., & Revenson, T. A. (2005). Benefit-finding among patients with rheumatoid arthritis: positive effects on interpersonal relationships. *J Behav Med*, *28*(1), 91-103. https://doi.org/10.1007/s10865-005-2720-3

Danon, L., Ford, A. P., House, T., Jewell, C. P., Keeling, M. J., Roberts, G. O., . . . Vernon, M. C. (2011). Networks and the epidemiology of infectious disease. *Interdiscip Perspect Infect Dis*, *2011*, 284909. https://doi.org/10.1155/2011/284909

Dantzer, R., O'Connor, J. C., Freund, G. G., Johnson, R. W., & Kelley, K. W. (2008). From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat Rev Neurosci*, *9*(1), 46-56. https://doi.org/10.1038/nrn2297

De Cock, D., Doumen, M., Vervloesem, C., Van Breda, A., Bertrand, D., Pazmino, S., . . . Verschueren, P. (2022). Psychological stress in rheumatoid arthritis: a systematic scoping review. *Semin Arthritis Rheum*, *55*, 152014. https://doi.org/10.1016/j.semarthrit.2022.152014

de Williams, A. C., Davies, H. T. O., & Chadury, Y. (2000). Simple pain rating scales hide complex idiosyncratic meanings. *Pain*, *85*(3), 457-463. https://doi.org/10.1016/S0304-3959(99)00299-7

Demoruelle, M. K., Deane, K. D., & Holers, V. M. (2014). When and where does inflammation begin in rheumatoid arthritis? *Curr Opin Rheumatol*, *26*(1), 64-71. https://doi.org/10.1097/BOR.0000000000000017

Devlin, N. J., & Krabbe, P. F. (2013). The development of new research methods for the valuation of EQ-5D-5L. *Eur J Health Econ*, *14 Suppl 1*, S1-3. https://doi.org/10.1007/s10198-013-0502-3

Diaz, K. M., Krupka, D. J., Chang, M. J., Peacock, J., Ma, Y., Goldsmith, J., . . . Davidson, K. W. (2015). Fitbit(R): An accurate and reliable device for wireless physical activity tracking. *Int J Cardiol*, *185*, 138-140. https://doi.org/10.1016/j.ijcard.2015.03.038

Dickens, C., McGowan, L., Clark-Carter, D., & Creed, F. (2002). Depression in rheumatoid arthritis: a systematic review of the literature with meta-analysis. *Psychosom Med*, *64*(1), 52-60.

Diffin, J. G., Lunt, M., Marshall, T., Chipping, J. R., Symmons, D. P., & Verstappen, S. M. (2014). Has the severity of rheumatoid arthritis at presentation diminished over time? *J Rheumatol*, *41*(8), 1590-1599. https://doi.org/10.3899/jrheum.131136

Disner, S. G., Beevers, C. G., Haigh, E. A., & Beck, A. T. (2011). Neural mechanisms of the cognitive model of depression. *Nat Rev Neurosci*, *12*(8), 467-477. https://doi.org/10.1038/nrn3027

Doan, Q. V., Chiou, C. F., & Dubois, R. W. (2006). Review of eight pharmacoeconomic studies of the value of biologic DMARDs (adalimumab, etanercept, and infliximab) in the management of rheumatoid arthritis. *J Manag Care Pharm*, *12*(7), 555-569. https://doi.org/10.18553/jmcp.2006.12.7.555

Doerr, J. M., Fischer, S., Nater, U. M., & Strahler, J. (2017). Influence of stress systems and physical activity on different dimensions of fatigue in female fibromyalgia patients. *Journal of Psychosomatic Research*, *93*, 55-61. https://doi.org/http://dx.doi.org/10.1016/j.jpsychores.2016.12.005

Donvito, T. (2018). *The 4 Stages of Rheumatoid Arthritis Progression*. https://creakyjoints.org/about-arthritis/rheumatoid-arthritis/ra-overview/rheumatoid-arthritis-stages-progression/

Dougados, M., Aletaha, D., & van Riel, P. (2007). Disease activity measures for rheumatoid arthritis. *Clin Exp Rheumatol*, *25*(5 Suppl 46), S22-29.

Dougados, M., & Baeten, D. (2011). Spondyloarthritis. *Lancet*, *377*(9783), 2127-2137. https://doi.org/10.1016/S0140-6736(11)60071-8

Dougados, M., Soubrier, M., Antunez, A., Balint, P., Balsa, A., Buch, M. H., . . . Kay, J. (2014). Prevalence of comorbidities in rheumatoid arthritis and evaluation of their monitoring: results of an international, cross-sectional study (COMORA). *Ann Rheum Dis*, *73*(1), 62-68. https://doi.org/10.1136/annrheumdis-2013-204223

Drageset, J. (2004). The importance of activities of daily living and social contact for loneliness: a survey among residents in nursing homes. *Scand J Caring Sci*, *18*(1), 65-71. https://doi.org/10.1111/j.0283-9318.2003.00251.x

Drewes, A. M., Svendsen, L., Taagholt, S. J., Bjerregard, K., Nielsen, K. D., & Hansen, B. (1998). Sleep in rheumatoid arthritis: a comparison with healthy subjects and studies of sleep/wake interactions. *Br J Rheumatol*, *37*(1), 71-81. https://doi.org/10.1093/rheumatology/37.1.71

Dudeney, J., Law, E. F., Meyyappan, A., Palermo, T. M., & Rabbitts, J. A. (2019). Evaluating the psychometric properties of the Widespread Pain Index and the Symptom Severity scale in youth with painful conditions. *Can J Pain*, *3*(1), 137-147. https://doi.org/10.1080/24740527.2019.1620097

Duman, C. H. (2010). Models of depression. *Vitam Horm*, *82*, 1-21. https://doi.org/10.1016/S0083-6729(10)82001-1

Dures, E. K., Hewlett, S. E., Cramp, F. A., Greenwood, R., Nicklin, J. K., Urban, M., & Kirwan, J. R. (2013). Reliability and sensitivity to change of the Bristol Rheumatoid Arthritis Fatigue scales. *Rheumatology (Oxford)*, *52*(10), 1832-1839. https://doi.org/10.1093/rheumatology/ket218

Eaton, W. W., Shao, H., Nestadt, G., Lee, H. B., Bienvenu, O. J., & Zandi, P. (2008). Population-based study of first onset and chronicity in major depressive disorder. *Arch Gen Psychiatry*, *65*(5), 513-520. https://doi.org/10.1001/archpsyc.65.5.513

Ebesutani, C., Fierstein, M., Viana, A., Trent, L., Young, J., & Sprung, M. (2015). THE ROLE OF LONELINESS IN THE RELATIONSHIP BETWEEN ANXIETY AND DEPRESSION IN CLINICAL AND SCHOOL-BASED YOUTH. *Psychology in the Schools*, *52*(3), 223-234. https://doi.org/https://doi.org/10.1002/pits.21818

Edwards, R. R., Cahalan, C., Mensing, G., Smith, M., & Haythornthwaite, J. A. (2011). Pain, catastrophizing, and depression in the rheumatic diseases. *Nat Rev Rheumatol*, *7*(4), 216-224. https://doi.org/10.1038/nrrheum.2011.2

Ekman, P. (1992). Are there basic emotions? *Psychol Rev*, *99*(3), 550-553. https://doi.org/10.1037/0033-295x.99.3.550
El-Miedany, Y. M., & El-Rasheed, A. H. (2002). Is anxiety a more common disorder than depression in rheumatoid arthritis? *Joint Bone Spine*, *69*(3), 300-306. https://doi.org/10.1016/s1297-319x(02)00368-8
El-Tallawy, S. N., Nalamasu, R., Pergolizzi, J. V., & Gharibo, C. (2020). Pain Management During the COVID-19 Pandemic. *Pain Ther*, *9*(2), 453-466. https://doi.org/10.1007/s40122-020-00190-4
Eldridge, S. M., Lancaster, G. A., Campbell, M. J., Thabane, L., Hopewell, S., Coleman, C. L., & Bond, C. M. (2016). Defining Feasibility and Pilot Studies in Preparation for Randomised Controlled Trials: Development of a Conceptual Framework. *PLoS One*, *11*(3), e0150205. https://doi.org/10.1371/journal.pone.0150205
Emery, P., Pope, J. E., Kruger, K., Lippe, R., DeMasi, R., Lula, S., & Kola, B. (2018). Efficacy of Monotherapy with Biologics and JAK Inhibitors for the Treatment of Rheumatoid Arthritis: A Systematic Review. *Adv Ther*, *35*(10), 1535-1563. https://doi.org/10.1007/s12325-018-0757-2
Emmungil, H., Ilgen, U., Turan, S., & Kilic, O. (2021). Assessment of loneliness in patients with inflammatory arthritis. *Int J Rheum Dis*, *24*(2), 223-230. https://doi.org/10.1111/1756-185X.14041
Enders, C. K. (2022). *Applied Missing Data Analysis* (2nd Edition ed.). Guilford Publications.
Endstrasser, F., Braito, M., Linser, M., Spicher, A., Wagner, M., & Brunner, A. (2020). The negative impact of the COVID-19 lockdown on pain and physical function in patients with end-stage hip or knee osteoarthritis. *Knee Surg Sports Traumatol Arthrosc*, *28*(8), 2435-2443. https://doi.org/10.1007/s00167-020-06104-3
Englbrecht, M., Gossec, L., DeLongis, A., Scholte-Voshaar, M., Sokka, T., Kvien, T. K., & Schett, G. (2012). The impact of coping strategies on mental and physical well-being in patients with rheumatoid arthritis. *Semin Arthritis Rheum*, *41*(4), 545-555. https://doi.org/10.1016/j.semarthrit.2011.07.009
Epskamp, S. (2020). Psychometric network models from time-series and panel data. *Psychometrika*, *85*(1), 206-231. https://doi.org/10.1007/s11336-020-09697-3
Epskamp, S., Borsboom, D., & Fried, E. I. (2018). Estimating psychological networks and their accuracy: A tutorial paper. *Behav Res Methods*, *50*(1), 195-212. https://doi.org/10.3758/s13428-017-0862-1
Epskamp, S., Cramer, A. O., Waldorp, L. J., Schmittmann, V. D., & Borsboom, D. (2012). qgraph: Network Visualizations of Relationships in Psychometric Data. *Journal of Statistical Software*, *48*(4). https://doi.org/10.18637/jss.v048.i04
Epskamp, S., & Fried, E. I. (2018). A tutorial on regularized partial correlation networks. *Psychol Methods*, *23*(4), 617-634. https://doi.org/10.1037/met0000167
Epskamp, S., Kruis, J., & Marsman, M. (2017). Estimating psychopathological networks: Be careful what you wish for. *PLoS One*, *12*(6), e0179891. https://doi.org/10.1371/journal.pone.0179891
Epskamp, S., Rhemtulla, M., & Borsboom, D. (2017). Generalized Network Psychometrics: Combining Network and Latent Variable Models. *Psychometrika*, *82*(4), 904-927. https://doi.org/10.1007/s11336-017-9557-x
Evers, A. W., Verhoeven, E. W., van Middendorp, H., Sweep, F. C., Kraaimaat, F. W., Donders, A. R., . . . van Riel, P. L. (2014). Does stress affect the joints? Daily stressors, stress vulnerability, immune and HPA axis activity, and short-term disease and

symptom fluctuations in rheumatoid arthritis. *Ann Rheum Dis*, *73*(9), 1683-1688. https://doi.org/10.1136/annrheumdis-2012-203143

Eyre, H. A., Air, T., Proctor, S., Rositano, S., & Baune, B. T. (2015). A critical review of the efficacy of non-steroidal anti-inflammatory drugs in depression. *Prog Neuropsychopharmacol Biol Psychiatry*, *57*, 11-16. https://doi.org/10.1016/j.pnpbp.2014.10.003

Fahrmeir, L., Kneib, T., Lang, S., & Marx, B. (2007). *Regression* (1 ed.). Springer. https://doi.org/https://doi.org/10.1007/978-3-642-34333-9

Falconer, J., Murphy, A. N., Young, S. P., Clark, A. R., Tiziani, S., Guma, M., & Buckley, C. D. (2018). Review: Synovial Cell Metabolism and Chronic Inflammation in Rheumatoid Arthritis. *Arthritis Rheumatol*, *70*(7), 984-999. https://doi.org/10.1002/art.40504

Fan, J., Feng, Y., & Wu, Y. (2009). Network Exploration Via the Adaptive Lasso and Scad Penalties. *Ann Appl Stat*, *3*(2), 521-541. https://doi.org/10.1214/08-AOAS215SUPP

Fava, G. A., Carrozzino, D., Lindberg, L., & Tomba, E. (2018). The Clinimetric Approach to Psychological Assessment: A Tribute to Per Bech, MD (1942-2018). *Psychother Psychosom*, *87*(6), 321-326. https://doi.org/10.1159/000493746

Feehan, L., Clayton, C., Carruthers, E., & Li, L. (2014). Feasibility of Using Fitbit Flex to Motivate People with Rheumatoid Arthritis to BE Physically Active. *Annals of the Rheumatic Diseases*, *73*, 1204-1205.

Feehan, L. M., Geldman, J., Sayre, E. C., Park, C., Ezzat, A. M., Yoo, J. Y., . . . Li, L. C. (2018). Accuracy of Fitbit Devices: Systematic Review and Narrative Syntheses of Quantitative Data. *JMIR Mhealth Uhealth*, *6*(8), e10527. https://doi.org/10.2196/10527

Feeney, S. L. (2004). The relationship between pain and negative affect in older adults: anxiety as a predictor of pain. *J Anxiety Disord*, *18*(6), 733-744. https://doi.org/10.1016/j.janxdis.2001.04.001

Feldtkeller, E., Khan, M. A., van der Heijde, D., van der Linden, S., & Braun, J. (2003). Age at disease onset and diagnosis delay in HLA-B27 negative vs. positive patients with ankylosing spondylitis. *Rheumatol Int*, *23*(2), 61-66. https://doi.org/10.1007/s00296-002-0237-4

Felson, D. T., Anderson, J. J., Boers, M., Bombardier, C., Chernoff, M., Fried, B., . . . et al. (1993). The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. The Committee on Outcome Measures in Rheumatoid Arthritis Clinical Trials. *Arthritis Rheum*, *36*(6), 729-740. https://doi.org/10.1002/art.1780360601

Fenn, K., & Bryrne, M. (2013). The key principles of cognitive behavioural therapy. *InnovAiT*, *6*, 579-585. https://doi.org/https://doi.org/10.1177/1755738012471029

Ferrari, R. (2015). Effect of a pain diary use on recovery from acute low back (lumbar) sprain. *Rheumatol Int*, *35*(1), 55-59. https://doi.org/10.1007/s00296-014-3082-3

Ferreira-Valente, M. A., Pais-Ribeiro, J. L., & Jensen, M. P. (2011). Validity of four pain intensity rating scales. *Pain*, *152*(10), 2399-2404. https://doi.org/10.1016/j.pain.2011.07.005

Finan, P. H., & Garland, E. L. (2015). The role of positive affect in pain and its treatment. *Clin J Pain*, *31*(2), 177-187. https://doi.org/10.1097/AJP.0000000000000092

Finan, P. H., Okun, M. A., Kruszewski, D., Davis, M. C., Zautra, A. J., & Tennen, H. (2010). Interplay of concurrent positive and negative interpersonal events in the prediction

of daily negative affect and fatigue for rheumatoid arthritis patients. *Health Psychol*, *29*(4), 429-437. https://doi.org/10.1037/a0020230
Firestein, G. S. (2003). Evolving concepts of rheumatoid arthritis. *Nature*, *423*(6937), 356-361. https://doi.org/10.1038/nature01661
Fischer, S., Doerr, J. M., Strahler, J., Mewes, R., Thieme, K., & Nater, U. M. (2016). Stress exacerbates pain in the everyday lives of women with fibromyalgia syndrome--The role of cortisol and alpha-amylase [Research Support, Non-U.S. Gov't]. *Psychoneuroendocrinology*, *63*, 68-77. https://doi.org/https://dx.doi.org/10.1016/j.psyneuen.2015.09.018
Fleischmann, R., Schiff, M., van der Heijde, D., Ramos-Remus, C., Spindler, A., Stanislav, M., . . . Takeuchi, T. (2017). Baricitinib, Methotrexate, or Combination in Patients With Rheumatoid Arthritis and No or Limited Prior Disease-Modifying Antirheumatic Drug Treatment. *Arthritis Rheumatol*, *69*(3), 506-517. https://doi.org/10.1002/art.39953
Flint, J., & Kendler, K. S. (2014). The Genetics of Major Depression. *Neuron*, *81*(5), 1214. https://doi.org/10.1016/j.neuron.2014.02.033
Flurey, C. A., Morris, M., Richards, P., Hughes, R., & Hewlett, S. (2014). It's like a juggling act: rheumatoid arthritis patient perspectives on daily life and flare while on current treatment regimes. *Rheumatology (Oxford)*, *53*(4), 696-703. https://doi.org/10.1093/rheumatology/ket416
Flynn, D., van Schaik, P., & van Wersch, A. (2004). A comparison of multi-item likert and visual analogue scales for the assessment of transactionally defined coping. *European Journal of Psychological Assessment*, *20*, 49-58. https://doi.org/10.1027/1015-5759.20.1.49
Foygel Barber, R., & Drton, M. (2015). High-dimensional Ising model selection with bayesian information criteria. *Electronic Journal of Statistics*, *9*(1), 567-607.
Fransen, J., Uebelhart, D., Stucki, G., Langenegger, T., Seitz, M., & Michel, B. A. (2002). The ICIDH-2 as a framework for the assessment of functioning and disability in rheumatoid arthritis. *Ann Rheum Dis*, *61*(3), 225-231. https://doi.org/10.1136/ard.61.3.225
Fredrickson, B. L. (2001). The role of positive emotions in positive psychology. The broaden-and-build theory of positive emotions. *Am Psychol*, *56*(3), 218-226. https://doi.org/10.1037//0003-066x.56.3.218
Fried, E. I. (2017). The 52 symptoms of major depression: Lack of content overlap among seven common depression scales. *J Affect Disord*, *208*, 191-197. https://doi.org/10.1016/j.jad.2016.10.019
Fried, E. I., & Cramer, A. O. J. (2017). Moving Forward: Challenges and Directions for Psychopathological Network Theory and Methodology. *Perspect Psychol Sci*, *12*(6), 999-1020. https://doi.org/10.1177/1745691617705892
Fried, E. I., Epskamp, S., Nesse, R. M., Tuerlinckx, F., & Borsboom, D. (2016). What are 'good' depression symptoms? Comparing the centrality of DSM and non-DSM symptoms of depression in a network analysis. *J Affect Disord*, *189*, 314-320. https://doi.org/10.1016/j.jad.2015.09.005
Fried, E. I., & Nesse, R. M. (2015). Depression sum-scores don't add up: why analyzing specific depression symptoms is essential. *BMC Med*, *13*, 72. https://doi.org/10.1186/s12916-015-0325-4
Friedewald, V. E., Ganz, P., Kremer, J. M., Mease, P. J., O'Dell, J. R., Pearson, T. A., . . . Roberts, W. C. (2010). AJC editor's consensus: rheumatoid arthritis and

atherosclerotic cardiovascular disease. *Am J Cardiol*, *106*(3), 442-447. https://doi.org/10.1016/j.amjcard.2010.04.005
Friedman, J., Hastie, T., & Tibshirani, R. (2008). Sparse inverse covariance estimation with the graphical lasso. *Biostatistics*, *9*(3), 432-441. https://doi.org/10.1093/biostatistics/kxm045
Friedman, N. (2004). Inferring cellular networks using probabilistic graphical models. *Science*, *303*(5659), 799-805. https://doi.org/10.1126/science.1094068
Friedrich, M. J. (2017). Depression Is the Leading Cause of Disability Around the World. *JAMA*, *317*(15), 1517. https://doi.org/10.1001/jama.2017.3826
Fries, J. F., Spitz, P., Kraines, R. G., & Holman, H. R. (1980). Measurement of patient outcome in arthritis. *Arthritis Rheum*, *23*(2), 137-145. https://doi.org/10.1002/art.1780230202
Gabriel, S. E., Crowson, C. S., & O'Fallon, W. M. (1999). The epidemiology of rheumatoid arthritis in Rochester, Minnesota, 1955-1985. *Arthritis Rheum*, *42*(3), 415-420. https://doi.org/10.1002/1529-0131(199904)42:3<415::AID-ANR4>3.0.CO;2-Z
Gabriel, S. E., & Michaud, K. (2009). Epidemiological studies in incidence, prevalence, mortality, and comorbidity of the rheumatic diseases. *Arthritis Res Ther*, *11*(3), 229. https://doi.org/10.1186/ar2669
Galvez-Sanchez, C. M., de la Coba, P., Duschek, S., & Reyes Del Paso, G. A. (2020). Reliability, Factor Structure and Predictive Validity of the Widespread Pain Index and Symptom Severity Scales of the 2010 American College of Rheumatology Criteria of Fibromyalgia. *J Clin Med*, *9*(8). https://doi.org/10.3390/jcm9082460
Gandrup, J., Selby, D. A., van der Veer, S. N., McBeth, J., & Dixon, W. G. (2022). Using patient-reported data from a smartphone app to capture and characterize real-time patient-reported flares in rheumatoid arthritis. *Rheumatol Adv Pract*, *6*(1), rkac021. https://doi.org/10.1093/rap/rkac021
Garcia, D., Archer, T., Moradi, S., & Andersson-Arntenm A. (2012). Exercise Frequency, High Activation Positive Affect, and Psychological Well-Being: Beyond Age, Gender, and Occupation. *Psychology*, *3*(4), 328-336. https://doi.org/http://dx.doi.org/10.4236/psych.2012.34047
Garcia-Palacios, A., Herrero, R., Belmonte, M. A., Castilla, D., Guixeres, J., Molinari, G., . . . Botella, C. (2014). Ecological momentary assessment for chronic pain in fibromyalgia using a smartphone: A randomized crossover study. *European Journal of Pain (United Kingdom)*, *18*(6), 862-872. https://doi.org/http://dx.doi.org/10.1002/j.1532-2149.2013.00425.x
Gatchel, R. J., Peng, Y. B., Peters, M. L., Fuchs, P. N., & Turk, D. C. (2007). The biopsychosocial approach to chronic pain: scientific advances and future directions. *Psychol Bull*, *133*(4), 581-624. https://doi.org/10.1037/0033-2909.133.4.581
Gavish, R., Levinsky, Y., Dizitzer, Y., Bilavsky, E., Livni, G., Pirogovsky, A., . . . Krause, I. (2021). The COVID-19 pandemic dramatically reduced admissions of children with and without chronic conditions to general paediatric wards. *Acta Paediatr*, *110*(7), 2212-2217. https://doi.org/10.1111/apa.15792
Gaylord-Harden, N. K., Elmore, C. A., Campbell, C. L., & Wethington, A. (2011). An examination of the tripartite model of depressive and anxiety symptoms in African American youth: stressors and coping strategies as common and specific correlates. *J Clin Child Adolesc Psychol*, *40*(3), 360-374. https://doi.org/10.1080/15374416.2011.563467

Gebhardt, C., Kirchberger, I., Stucki, G., & Cieza, A. (2010). Validation of the comprehensive ICF Core Set for rheumatoid arthritis: the perspective of physicians. *J Rehabil Med*, *42*(8), 780-788. https://doi.org/10.2340/16501977-0599

Geenen, R., & Dures, E. (2019). A biopsychosocial network model of fatigue in rheumatoid arthritis: a systematic review. *Rheumatology (Oxford)*, *58*(Suppl 5), v10-v21. https://doi.org/10.1093/rheumatology/kez403

Geweke, J. (1982). Measurement of Conditional Linear Dependence and Feedback Between Time Series. *Journal of the American Statistical Association*, *79*(388). https://doi.org/10.2307/2288723

Gibofsky, A., & Yazici, Y. (2010). Treatment of rheumatoid arthritis: strategies for achieving optimal outcomes. *Ann Rheum Dis*, *69*(6), 941-942. https://doi.org/10.1136/ard.2010.131730

Goekoop, R., & Goekoop, J. G. (2014). A network view on psychiatric disorders: network clusters of symptoms as elementary syndromes of psychopathology. *PLoS One*, *9*(11), e112734. https://doi.org/10.1371/journal.pone.0112734

Goes, A. C. J., Reis, L. A. B., Silva, M. B. G., Kahlow, B. S., & Skare, T. L. (2017). Rheumatoid arthritis and sleep quality. *Rev Bras Reumatol Engl Ed*, *57*(4), 294-298. https://doi.org/10.1016/j.rbre.2016.07.011

Goldberg, D. (2006). The aetiology of depression. *Psychol Med*, *36*(10), 1341-1347. https://doi.org/10.1017/S0033291706007665

Goldenberg, D. L. (2010). The interface of pain and mood disturbances in the rheumatic diseases. *Semin Arthritis Rheum*, *40*(1), 15-31. https://doi.org/10.1016/j.semarthrit.2008.11.005

Gossec, L., McGonagle, D., Korotaeva, T., Lubrano, E., de Miguel, E., Ostergaard, M., & Behrens, F. (2018). Minimal Disease Activity as a Treatment Target in Psoriatic Arthritis: A Review of the Literature. *J Rheumatol*, *45*(1), 6-13. https://doi.org/10.3899/jrheum.170449

Gossec, L., Salejan, F., Nataf, H., Nguyen, M., Gaud-Listrat, V., Hudry, C., . . . Network, R. R. (2013). Challenges of cardiovascular risk assessment in the routine rheumatology outpatient setting: an observational study of 110 rheumatoid arthritis patients. *Arthritis Care Res (Hoboken)*, *65*(5), 712-717. https://doi.org/10.1002/acr.21935

GOV.UK. (2020a). *Prime Minister announces new national restrictions*. Gov.uk. https://www.gov.uk/government/news/prime-minister-announces-new-national-restrictions

GOV.UK. (2020b). *Prime Minister's statement on coronavirus (COVID-19): 23 March 2020*. GOV.UK. https://www.gov.uk/government/speeches/pm-address-to-the-nation-on-coronavirus-23-march-2020

Graham-Engeland, J. E., Zawadzki, M. J., Slavish, D. C., & Smyth, J. M. (2016). Depressive Symptoms and Momentary Mood Predict Momentary Pain Among Rheumatoid Arthritis Patients. *Annals of behavioral medicine : a publication of the Society of Behavioral Medicine*, *50*(1), 12-23. https://doi.org/http://dx.doi.org/10.1007/s12160-015-9723-2

Granat, A., Gadassi, R., Gilboa-Schechtman, E., & Feldman, R. (2017). Maternal depression and anxiety, social synchrony, and infant regulation of negative and positive emotions. *Emotion*, *17*(1), 11-27. https://doi.org/10.1037/emo0000204

Gu, S., Wang, F., Patel, N. P., Bourgeois, J. A., & Huang, J. H. (2019). A Model for Basic Emotions Using Observations of Behavior in Drosophila. *Front Psychol*, *10*, 781. https://doi.org/10.3389/fpsyg.2019.00781

Gullick, N. J., & Scott, D. L. (2011). Co-morbidities in established rheumatoid arthritis. *Best Pract Res Clin Rheumatol*, *25*(4), 469-483. https://doi.org/10.1016/j.berh.2011.10.009

Guo, Q., Wang, Y., Xu, D., Nossent, J., Pavlos, N. J., & Xu, J. (2018). Rheumatoid arthritis: pathological mechanisms and modern pharmacologic therapies. *Bone Res*, *6*, 15. https://doi.org/10.1038/s41413-018-0016-9

Gwinnutt, J. M., Verstappen, S. M., & Humphreys, J. H. (2020). The impact of lifestyle behaviours, physical activity and smoking on morbidity and mortality in patients with rheumatoid arthritis. *Best Pract Res Clin Rheumatol*, *34*(2), 101562. https://doi.org/10.1016/j.berh.2020.101562

Hacker, E. D., & Ferrans, C. E. (2007). Ecological Momentary Assessment of Fatigue in Patients Receiving Intensive Cancer Therapy [Empirical Study; Longitudinal Study; Prospective Study; Quantitative Study]. *Journal of Pain and Symptom Management*, *33*(3), 267-275. https://doi.org/http://dx.doi.org/10.1016/j.jpainsymman.2006.08.007

Haddad, M., & Tylee, A. (2011). The chronic disease management model for depression in primary care. *Clinical Neuropsychiatry*, *8*(4), 252-259.

Haghayegh, S., Khoshnevis, S., Smolensky, M. H., Diller, K. R., & Castriotta, R. J. (2019). Accuracy of Wristband Fitbit Models in Assessing Sleep: Systematic Review and Meta-Analysis. *J Med Internet Res*, *21*(11), e16273. https://doi.org/10.2196/16273

Hamaker, E. L., Asparouhov, T., Brose, A., Schmiedek, F., & Muthen, B. (2018). At the Frontiers of Modeling Intensive Longitudinal Data: Dynamic Structural Equation Models for the Affective Measurements from the COGITO Study. *Multivariate Behav Res*, *53*(6), 820-841. https://doi.org/10.1080/00273171.2018.1446819

Hamaker, E. L., Kuiper, R. M., & Grasman, R. P. (2015). A critique of the cross-lagged panel model. *Psychol Methods*, *20*(1), 102-116. https://doi.org/10.1037/a0038889

Hamilton, N. A., Affleck, G., Tennen, H., Karlson, C., Luxton, D., Preacher, K. J., & Templin, J. L. (2008). Fibromyalgia: The Role of Sleep in Affect and in Negative Event Reactivity and Recovery. *Health Psychology*, *27*(4), 490-497. https://doi.org/http://dx.doi.org/10.1037/0278-6133.27.4.490

Hamilton, N. A., Catley, D., & Karlson, C. (2007). Sleep and the affective response to stress and pain. *Health Psychology*, *26*(3), 288-295. https://doi.org/http://dx.doi.org/10.1037/0278-6133.26.3.288

Hammer, R. E., Maika, S. D., Richardson, J. A., Tang, J. P., & Taurog, J. D. (1990). Spontaneous inflammatory disease in transgenic rats expressing HLA-B27 and human beta 2m: an animal model of HLA-B27-associated human disorders. *Cell*, *63*(5), 1099-1112. https://doi.org/10.1016/0092-8674(90)90512-d

Harkness, J. A., Richter, M. B., Panayi, G. S., Van de Pette, K., Unger, A., Pownall, R., & Geddawi, M. (1982). Circadian variation in disease activity in rheumatoid arthritis. *Br Med J (Clin Res Ed)*, *284*(6315), 551-554. https://doi.org/10.1136/bmj.284.6315.551

Harvey, G. P., Fitzsimmons, T. R., Dhamarpatni, A. A., Marchant, C., Haynes, D. R., & Bartold, P. M. (2013). Expression of peptidylarginine deiminase-2 and -4, citrullinated proteins and anti-citrullinated protein antibodies in human gingiva. *J Periodontal Res*, *48*(2), 252-261. https://doi.org/10.1111/jre.12002

Hasseli, R., Muller-Ladner, U., Schmeiser, T., Lorenz, H. M., Krause, A., Schulze-Koops, H., . . . Hoyer, B. F. (2021). *Disease activity and pain levels are not influenced by the current COVID19 pandemic in patients with rheumatic diseases in germany-data from the german COVID-19 patient survey.* European Congress of Rheumatology, EULAR 2021, Virtual.

Hastie, T., Tibshirani, R., & Wainwright, N. W. (2015). *Statistical learning with sparsity: the lasso and generalizations*. CRC Press.

Hastie, T., Tibshirani, R. J., & Friedman, J. (2001). *The Elements of Statistical Learning*. Springer New York Inc.

Haucke, M., Liu, S., & Heinzel, S. (2021). The Persistence of the Impact of COVID-19-Related Distress, Mood Inertia, and Loneliness on Mental Health During a Postlockdown Period in Germany: An Ecological Momentary Assessment Study. *JMIR Ment Health*, *8*(8), e29419. https://doi.org/10.2196/29419

Haug, H. J., & Fahndrich, E. (1990). Diurnal variations of mood in depressed patients in relation to severity of depression. *J Affect Disord*, *19*(1), 37-41. https://doi.org/10.1016/0165-0327(90)90007-u

Hawker, G. A., Mian, S., Kendzerska, T., & French, M. (2011). Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). *Arthritis Care Res (Hoboken)*, *63 Suppl 11*, S240-252. https://doi.org/10.1002/acr.20543

Hayes, A. M., & Andrews, L. A. (2020). A complex systems approach to the study of change in psychotherapy. *BMC Med*, *18*(1), 197. https://doi.org/10.1186/s12916-020-01662-2

Heiberg, T., & Kvien, T. K. (2002). Preferences for improved health examined in 1,024 patients with rheumatoid arthritis: pain has highest priority. *Arthritis Rheum*, *47*(4), 391-397. https://doi.org/10.1002/art.10515

Heliovaara, M., Aho, K., Knekt, P., Impivaara, O., Reunanen, A., & Aromaa, A. (2000). Coffee consumption, rheumatoid factor, and the risk of rheumatoid arthritis. *Ann Rheum Dis*, *59*(8), 631-635. https://doi.org/10.1136/ard.59.8.631

Henshaw, S. (2018, 2nd July 2019). *Mobile Phone Usage Statistics in the UK: How Many Smartphone Users Are There*. Tigermobiles. Retrieved 13th September from https://www.tigermobiles.com/blog/mobile-phone-usage-statistics/

Hevey, D. (2018). Network analysis: a brief overview and tutorial. *Health Psychol Behav Med*, *6*(1), 301-328. https://doi.org/10.1080/21642850.2018.1521283

Hewlett, S., Chalder, T., Choy, E., Cramp, F., Davis, B., Dures, E., . . . Kirwan, J. (2011). Fatigue in rheumatoid arthritis: time for a conceptual model. *Rheumatology (Oxford)*, *50*(6), 1004-1006. https://doi.org/10.1093/rheumatology/keq282

Hewlett, S., Sanderson, T., May, J., Alten, R., Bingham, C. O., 3rd, Cross, M., . . . Bartlett, S. J. (2012). 'I'm hurting, I want to kill myself': rheumatoid arthritis flare is more than a high joint count--an international patient perspective on flare where medical help is sought. *Rheumatology (Oxford)*, *51*(1), 69-76. https://doi.org/10.1093/rheumatology/keq455

Hieronymus, F., Emilsson, J. F., Nilsson, S., & Eriksson, E. (2016). Consistent superiority of selective serotonin reuptake inhibitors over placebo in reducing depressed mood in

patients with major depression. *Mol Psychiatry*, *21*(4), 523-530. https://doi.org/10.1038/mp.2015.53

Hill, J. C., Kang, S., Benedetto, E., Myers, H., Blackburn, S., Smith, S., . . . Price, A. (2016). Development and initial cohort validation of the Arthritis Research UK Musculoskeletal Health Questionnaire (MSK-HQ) for use across musculoskeletal care pathways. *BMJ Open*, *6*(8), e012331. https://doi.org/10.1136/bmjopen-2016-012331

Hillhouse, T. M., & Porter, J. H. (2015). A brief history of the development of antidepressant drugs: from monoamines to glutamate. *Exp Clin Psychopharmacol*, *23*(1), 1-21. https://doi.org/10.1037/a0038550

Hiroto, D. S. (1974). Locus of control and learned helplessness. *Journal of Experimental Psychology*, *102*, 187-183.

Hitchon, C. A., Zhang, L., Peschken, C. A., Lix, L. M., Graff, L. A., Fisk, J. D., . . . Marrie, R. A. (2020). Validity and Reliability of Screening Measures for Depression and Anxiety Disorders in Rheumatoid Arthritis. *Arthritis Care Res (Hoboken)*, *72*(8), 1130-1139. https://doi.org/10.1002/acr.24011

Hjermstad, M. J., Fayers, P. M., Haugen, D. F., Caraceni, A., Hanks, G. W., Loge, J. H., . . . European Palliative Care Research, C. (2011). Studies comparing Numerical Rating Scales, Verbal Rating Scales, and Visual Analogue Scales for assessment of pain intensity in adults: a systematic literature review. *J Pain Symptom Manage*, *41*(6), 1073-1093. https://doi.org/10.1016/j.jpainsymman.2010.08.016

Hoffart, A., & Johnson, S. U. (2020). Latent trait, latent-trait state, and a network approach to mental problems and their mechanisms of change. *Clinical Psychology: Science and Practice*, *8*, 595-613. https://doi.org/https://doi.org/10.1177/2167702620901744

Hofmann, S. G., Asnaani, A., Vonk, I. J., Sawyer, A. T., & Fang, A. (2012). The Efficacy of Cognitive Behavioral Therapy: A Review of Meta-analyses. *Cognit Ther Res*, *36*(5), 427-440. https://doi.org/10.1007/s10608-012-9476-1

Hofmann, S. G., Curtiss, J. E., & Hayes, S. C. (2020). Beyond linear mediation: Toward a dynamic network approach to study treatment processes. *Clin Psychol Rev*, *76*, 101824. https://doi.org/10.1016/j.cpr.2020.101824

Holmes, R. D., Tiwari, A. K., & Kennedy, J. L. (2016). Mechanisms of the placebo effect in pain and psychiatric disorders. *Pharmacogenomics J*, *16*(6), 491-500. https://doi.org/10.1038/tpj.2016.15

Howard, A. (2015). Leveraging time-varying covariates to test within- and between-person effects and interactions in the multilevel linear model. *Emerging Adulthood*, *3*(6), 400-412.

Hoyt, L. T., Craske, M. G., Mineka, S., & Adam, E. K. (2015). Positive and negative affect and arousal: cross-sectional and longitudinal associations with adolescent cortisol diurnal rhythms. *Psychosom Med*, *77*(4), 392-401. https://doi.org/10.1097/PSY.0000000000000178

Hummel, M., Cummons, T., Lu, P., Mark, L., Harrison, J. E., Kennedy, J. D., & Whiteside, G. T. (2010). Pain is a salient "stressor" that is mediated by corticotropin-releasing factor-1 receptors. *Neuropharmacology*, *59*(3), 160-166. https://doi.org/10.1016/j.neuropharm.2010.05.001

Humphreys, J., Hyrich, K., & Symmons, D. (2016). What is the impact of biologic therapies on common co-morbidities in patients with rheumatoid arthritis? *Arthritis Res Ther*, *18*(1), 282. https://doi.org/10.1186/s13075-016-1176-x

Ioannidis, J. P. (2016). Exposure-wide epidemiology: revisiting Bradford Hill. *Stat Med*, *35*(11), 1749-1762. https://doi.org/10.1002/sim.6825

Irwin, M. R., Olmstead, R., Carrillo, C., Sadeghi, N., Fitzgerald, J. D., Ranganath, V. K., & Nicassio, P. M. (2012). Sleep loss exacerbates fatigue, depression, and pain in rheumatoid arthritis. *Sleep*, *35*(4), 537-543. https://doi.org/10.5665/sleep.1742

Isaac, V., Cheng, T., Townsin, L., Assareh, H., Li, A., & McLachlan, C. S. (2021). Associations of the Initial COVID-19 Lockdown on Self-Reported Happiness and Worry about Developing Loneliness: A Cross-Sectional Analysis of Rural, Regional, and Urban Australian Communities. *Int J Environ Res Public Health*, *18*(18). https://doi.org/10.3390/ijerph18189501

Isik, A., Koca, S. S., Ozturk, A., & Mermi, O. (2007). Anxiety and depression in patients with rheumatoid arthritis. *Clin Rheumatol*, *26*(6), 872-878. https://doi.org/10.1007/s10067-006-0407-y

Jacquemin, C., Servy, H., Molto, A., Sellam, J., Foltz, V., Gandjbakhch, F., . . . Gossec, L. (2018). Physical Activity Assessment Using an Activity Tracker in Patients with Rheumatoid Arthritis and Axial Spondyloarthritis: Prospective Observational Study. *JMIR Mhealth Uhealth*, *6*(1), e1. https://doi.org/10.2196/mhealth.7948

Jakobsson, U., & Hallberg, I. R. (2002). Pain and quality of life among older people with rheumatoid arthritis and/or osteoarthritis: a literature review. *J Clin Nurs*, *11*(4), 430-443. https://doi.org/10.1046/j.1365-2702.2002.00624.x

Jakubovski, E., Varigonda, A. L., Freemantle, N., Taylor, M. J., & Bloch, M. H. (2016). Systematic Review and Meta-Analysis: Dose-Response Relationship of Selective Serotonin Reuptake Inhibitors in Major Depressive Disorder. *Am J Psychiatry*, *173*(2), 174-183. https://doi.org/10.1176/appi.ajp.2015.15030331

Jamison, R. N., Raymond, S. A., Levine, J. G., Slawsby, E. A., Nedeljkovic, S. S., & Katz, N. P. (2001). Electronic diaries for monitoring chronic pain: 1-Year validation study. *Pain*, *91*(3), 277-285. https://doi.org/http://dx.doi.org/10.1016/S0304-3959%2800%2900450-4

Jang, S. N., Kawachi, I., Chang, J., Boo, K., Shin, H. G., Lee, H., & Cho, S. I. (2009). Marital status, gender, and depression: analysis of the baseline survey of the Korean Longitudinal Study of Ageing (KLoSA). *Soc Sci Med*, *69*(11), 1608-1615. https://doi.org/10.1016/j.socscimed.2009.09.007

Jim, H. S., Small, B., Faul, L. A., Franzen, J., Apte, S., & Jacobsen, P. B. (2011). Fatigue, depression, sleep, and activity during chemotherapy: daily and intraday variation and relationships among symptom changes. *Ann Behav Med*, *42*(3), 321-333. https://doi.org/10.1007/s12160-011-9294-9

Johnson, A. C., & Greenwood-Van Meerveld, B. (2014). Stress-induced pain: a target for the development of novel therapeutics. *J Pharmacol Exp Ther*, *351*(2), 327-335. https://doi.org/10.1124/jpet.114.218065

Johnson, M. D., Galambos, N. L., Finn, C., Neyer, F. J., & Horne, R. M. (2017). Pathways between self-esteem and depression in couples. *Dev Psychol*, *53*(4), 787-799. https://doi.org/10.1037/dev0000276

Johnstone, G., Treharne, G. J., Fletcher, B. D., Lamar, R. S. M., White, D., Harrison, A., & Stebbings, S. (2021). Mental health and quality of life for people with rheumatoid arthritis or ankylosing spondylitis in Aotearoa New Zealand following the COVID-19 national lockdown. *Rheumatol Int*, *41*(10), 1763-1772. https://doi.org/10.1007/s00296-021-04952-x

Jones, A., Remmerswaal, D., Verveer, I., Robinson, E., Franken, I. H. A., Wen, C. K. F., & Field, M. (2019). Compliance with ecological momentary assessment protocols in substance users: a meta-analysis. *Addiction*, *114*(4), 609-619. https://doi.org/10.1111/add.14503

Jones, A. K., Huneke, N. T., Lloyd, D. M., Brown, C. A., & Watson, A. (2012). Role of functional brain imaging in understanding rheumatic pain. *Curr Rheumatol Rep*, *14*(6), 557-567. https://doi.org/10.1007/s11926-012-0287-x

Jones, P. J., Ma, R., & McNally, R. J. (2021). Bridge Centrality: A Network Approach to Understanding Comorbidity. *Multivariate Behav Res*, *56*(2), 353-367. https://doi.org/10.1080/00273171.2019.1614898

Jones, P. J., Mair, P., & McNally, R. J. (2018). Visualizing Psychological Networks: A Tutorial in R. *Front Psychol*, *9*, 1742. https://doi.org/10.3389/fpsyg.2018.01742

Joyce, A. T., Smith, P., Khandker, R., Melin, J. M., & Singh, A. (2009). Hidden cost of rheumatoid arthritis (RA): estimating cost of comorbid cardiovascular disease and depression among patients with RA. *J Rheumatol*, *36*(4), 743-752. https://doi.org/10.3899/jrheum.080670

Julian, L. J. (2011). Measures of anxiety: State-Trait Anxiety Inventory (STAI), Beck Anxiety Inventory (BAI), and Hospital Anxiety and Depression Scale-Anxiety (HADS-A). *Arthritis Care Res (Hoboken)*, *63 Suppl 11*, S467-472. https://doi.org/10.1002/acr.20561

Kahneman, D., Krueger, A. B., Schkade, D. A., Schwarz, N., & Stone, A. A. (2004). A survey method for characterizing daily life experience: the day reconstruction method. *Science*, *306*(5702), 1776-1780. https://doi.org/10.1126/science.1103572

Kamaleri, Y., Natvig, B., Ihlebaek, C. M., & Bruusgaard, D. (2008). Localized or widespread musculoskeletal pain: does it matter? *Pain*, *138*(1), 41-46. https://doi.org/10.1016/j.pain.2007.11.002

Kameda, H., Ueki, Y., Saito, K., Nagaoka, S., Hidaka, T., Atsumi, T., . . . Japan Biological Agent Study Integrated, C. (2010). Etanercept (ETN) with methotrexate (MTX) is better than ETN monotherapy in patients with active rheumatoid arthritis despite MTX therapy: a randomized trial. *Mod Rheumatol*, *20*(6), 531-538. https://doi.org/10.1007/s10165-010-0324-4

Kanik, K. S., & Wilder, R. L. (2000). Hormonal alterations in rheumatoid arthritis, including the effects of pregnancy. *Rheum Dis Clin North Am*, *26*(4), 805-823. https://doi.org/10.1016/s0889-857x(05)70170-8

Kaparounaki, C. K., Patsali, M. E., Mousa, D. V., Papadopoulou, E. V. K., Papadopoulou, K. K. K., & Fountoulakis, K. N. (2020). University students' mental health amidst the COVID-19 quarantine in Greece. *Psychiatry Res*, *290*, 113111. https://doi.org/10.1016/j.psychres.2020.113111

Karger, A. (2014). [Gender differences in depression]. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz*, *57*(9), 1092-1098. https://doi.org/10.1007/s00103-014-2019-z (Geschlechtsspezifische Aspekte bei depressiven Erkrankungen.)

Karlson, E. W., Mandl, L. A., Aweh, G. N., & Grodstein, F. (2003). Coffee consumption and risk of rheumatoid arthritis. *Arthritis Rheum*, *48*(11), 3055-3060. https://doi.org/10.1002/art.11306

Keefe, F. J., Affleck, G., Lefebvre, J., Underwood, L., Caldwell, D. S., Drew, J., . . . Pargament, K. (2001). Living with rheumatoid arthritis: The role of daily spirituality and daily

religious and spiritual coping. *Journal of Pain*, *2*(2), 101-110. https://doi.org/http://dx.doi.org/10.1054/jpai.2001.19296
Keller, M. C., Neale, M. C., & Kendler, K. S. (2007). Association of different adverse life events with distinct patterns of depressive symptoms. *Am J Psychiatry*, *164*(10), 1521-1529; quiz 1622. https://doi.org/10.1176/appi.ajp.2007.06091564
Kemp, J. J., Lickel, J. J., & Deacon, B. J. (2014). Effects of a chemical imbalance causal explanation on individuals' perceptions of their depressive symptoms. *Behav Res Ther*, *56*, 47-52. https://doi.org/10.1016/j.brat.2014.02.009
Kendler, K. S., Aggen, S. H., & Neale, M. C. (2013). Evidence for multiple genetic factors underlying DSM-IV criteria for major depression. *JAMA Psychiatry*, *70*(6), 599-607. https://doi.org/10.1001/jamapsychiatry.2013.751
Kendler, K. S., & Gardner, C. O. (2001). Monozygotic twins discordant for major depression: a preliminary exploration of the role of environmental experiences in the aetiology and course of illness. *Psychol Med*, *31*(3), 411-423. https://doi.org/10.1017/s0033291701003622
Kennedy, D. M., Stratford, P. W., Wessel, J., Gollish, J. D., & Penney, D. (2005). Assessing stability and change of four performance measures: a longitudinal study evaluating outcome following total hip and knee arthroplasty. *BMC Musculoskelet Disord*, *6*, 3. https://doi.org/10.1186/1471-2474-6-3
Kessler, R., Partridge, M. R., Miravitlles, M., Cazzola, M., Vogelmeier, C., Leynaud, D., & Ostinelli, J. (2011). Symptom variability in patients with severe COPD: a pan-European cross-sectional study. *Eur Respir J*, *37*(2), 264-272. https://doi.org/10.1183/09031936.00051110
Kessler, R. C., Amminger, G. P., Aguilar-Gaxiola, S., Alonso, J., Lee, S., & Ustun, T. B. (2007). Age of onset of mental disorders: a review of recent literature. *Curr Opin Psychiatry*, *20*(4), 359-364. https://doi.org/10.1097/YCO.0b013e32816ebc8c
Kessler, R. C., & Bromet, E. J. (2013). The epidemiology of depression across cultures. *Annu Rev Public Health*, *34*, 119-138. https://doi.org/10.1146/annurev-publhealth-031912-114409
Khan, N. A., Spencer, H. J., Abda, E., Aggarwal, A., Alten, R., Ancuta, C., . . . Sokka, T. (2012). Determinants of discordance in patients' and physicians' rating of rheumatoid arthritis disease activity. *Arthritis Care Res (Hoboken)*, *64*(2), 206-214. https://doi.org/10.1002/acr.20685
Khot, R., Dube, A., Rathod, B., Joshi, P., & Kumbhalkar, S. (2021). Impact of lockdown period on chronic diseases. *Indian Journal of Medical Specialities*, *12*(3), 155-160.
Khurana, R., & Berney, S. M. (2005). Clinical aspects of rheumatoid arthritis. *Pathophysiology*, *12*(3), 153-165. https://doi.org/10.1016/j.pathophys.2005.07.009
Killgore, W. D. S., Cloonan, S. A., Taylor, E. C., Miller, M. A., & Dailey, N. S. (2020). Three months of loneliness during the COVID-19 lockdown. *Psychiatry Res*, *293*, 113392. https://doi.org/10.1016/j.psychres.2020.113392
Kim, M. A., Suh, M. K., Park, J., Kim, J. H., Kim, T. H., Kim, E. K., . . . Lee, J. H. (2019). Impact of symptom variability on clinical outcomes in COPD: analysis of a longitudinal cohort. *Int J Chron Obstruct Pulmon Dis*, *14*, 2135-2144. https://doi.org/10.2147/COPD.S203715
Kim, S., Dowgwillo, E., & Kratz, A. (2022). Examining the Dynamic Relationship between Positive and Negative Emotions as a Function of Pain, Fatigue, and Stress in

Individuals with and without Fibromyalgia. *Journal of Pain*, *23*(5), 56-57. https://doi.org/https://doi.org/10.1016/j.jpain.2022.03.213

Kirwan, J. R., Minnock, P., Adebajo, A., Bresnihan, B., Choy, E., de Wit, M., . . . Hewlett, S. (2007). Patient perspective: fatigue as a recommended patient centered outcome measure in rheumatoid arthritis. *J Rheumatol*, *34*(5), 1174-1177.

Klimek, L., Bergmann, K. C., Biedermann, T., Bousquet, J., Hellings, P., Jung, K., . . . Pfaar, O. (2017). Visual analogue scales (VAS): Measuring instruments for the documentation of symptoms and therapy monitoring in cases of allergic rhinitis in everyday health care: Position Paper of the German Society of Allergology (AeDA) and the German Society of Allergy and Clinical Immunology (DGAKI), ENT Section, in collaboration with the working group on Clinical Immunology, Allergology and Environmental Medicine of the German Society of Otorhinolaryngology, Head and Neck Surgery (DGHNOKHC). *Allergo J Int*, *26*(1), 16-24. https://doi.org/10.1007/s40629-016-0006-7

Knittle, K. P., De Gucht, V., Hurkmans, E. J., Vlieland, T. P., Peeters, A. J., Ronday, H. K., & Maes, S. (2011). Effect of self-efficacy and physical activity goal achievement on arthritis pain and quality of life in patients with rheumatoid arthritis. *Arthritis Care Res (Hoboken)*, *63*(11), 1613-1619. https://doi.org/10.1002/acr.20587

Kohler, O., Benros, M. E., Nordentoft, M., Farkouh, M. E., Iyengar, R. L., Mors, O., & Krogh, J. (2014). Effect of anti-inflammatory treatment on depression, depressive symptoms, and adverse effects: a systematic review and meta-analysis of randomized clinical trials. *JAMA Psychiatry*, *71*(12), 1381-1391. https://doi.org/10.1001/jamapsychiatry.2014.1611

Kong, S. Y., Stabler, T. V., Criscione, L. G., Elliott, A. L., Jordan, J. M., & Kraus, V. B. (2006). Diurnal variation of serum and urine biomarkers in patients with radiographic knee osteoarthritis. *Arthritis Rheum*, *54*(8), 2496-2504. https://doi.org/10.1002/art.21977

Kramer, N., Schafer, J., & Boulesteix, A. L. (2009). Regularized estimation of large-scale gene association networks using graphical Gaussian models. *BMC Bioinformatics*, *10*, 384. https://doi.org/10.1186/1471-2105-10-384

Kratz, A. L., Murphy, S. L., & Braley, T. J. (2017). Ecological Momentary Assessment of Pain, Fatigue, Depressive, and Cognitive Symptoms Reveals Significant Daily Variability in Multiple Sclerosis. *Arch Phys Med Rehabil*, *98*(11), 2142-2150. https://doi.org/10.1016/j.apmr.2017.07.002

Kroenke, K., Spitzer, R. L., & Williams, J. B. (2001). The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*, *16*(9), 606-613. https://doi.org/10.1046/j.1525-1497.2001.016009606.x

Kroenke, K., Spitzer, R. L., & Williams, J. B. (2003). The Patient Health Questionnaire-2: validity of a two-item depression screener. *Med Care*, *41*(11), 1284-1292. https://doi.org/10.1097/01.MLR.0000093487.78664.3C

Kroenke, K., Spitzer, R. L., Williams, J. B., Monahan, P. O., & Lowe, B. (2007). Anxiety disorders in primary care: prevalence, impairment, comorbidity, and detection. *Ann Intern Med*, *146*(5), 317-325. https://doi.org/10.7326/0003-4819-146-5-200703060-00004

Kroenke, K., Wu, J., Bair, M. J., Krebs, E. E., Damush, T. M., & Tu, W. (2011). Reciprocal relationship between pain and depression: a 12-month longitudinal analysis in primary care. *J Pain*, *12*(9), 964-973. https://doi.org/10.1016/j.jpain.2011.03.003

Kurko, J., Besenyei, T., Laki, J., Glant, T. T., Mikecz, K., & Szekanecz, Z. (2013). Genetics of rheumatoid arthritis - a comprehensive review. *Clin Rev Allergy Immunol*, *45*(2), 170-179. https://doi.org/10.1007/s12016-012-8346-7

Kvien, T. K. (2004). Epidemiology and burden of illness of rheumatoid arthritis. *Pharmacoeconomics*, *22*(2 Suppl 1), 1-12. https://doi.org/10.2165/00019053-200422001-00002

Ladyman, J., Lambert, J., & Wiesner, K. (2013). What is a Complex System? *European Journal for Philosophy of Science*, *3*, 33-67. https://doi.org/10.1007/s13194-012-0056-8

Lakens, D., Adolfi, F. G., Albers, C. J., Anvari, F., & Zwaan, R. A. (2018). Justify your alpha. *nature human behaviour*, *2*, 168-171.

Lauritzen, S. L. (1997). *Graphical Models* (Vol. Vol. 17). Clarendon Press.

Lawrence, J. S. (1970). Heberden Oration, 1969. Rheumatoid arthritis--nature or nurture? *Ann Rheum Dis*, *29*(4), 357-379. https://doi.org/10.1136/ard.29.4.357

Lawyer, G. (2015). Understanding the influence of all nodes in a network. *Sci Rep*, *5*, 8665. https://doi.org/10.1038/srep08665

Lee, C. H., & Giuliani, F. (2019). The Role of Inflammation in Depression and Fatigue. *Front Immunol*, *10*, 1696. https://doi.org/10.3389/fimmu.2019.01696

Lee, I. M., Shiroma, E. J., Lobelo, F., Puska, P., Blair, S. N., Katzmarzyk, P. T., & Lancet Physical Activity Series Working, G. (2012). Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. *Lancet*, *380*(9838), 219-229. https://doi.org/10.1016/S0140-6736(12)61031-9

Lee, J. L., Sinnathurai, P., Buchbinder, R., Hill, C., Lassere, M., & March, L. (2018). Biologics and cardiovascular events in inflammatory arthritis: a prospective national cohort study. *Arthritis Res Ther*, *20*(1), 171. https://doi.org/10.1186/s13075-018-1669-x

Lee Pe, M., Kircanski, K., Thompson, R. J., Bringmann, L. F., Tuerlinckx, F., Mestdagh, M., . . . Gotlib, I. H. (2015). Emotion-Network Density in Major Depressive Disorder. *Clin Psychol Sci*, *3*(2), 292-300. https://doi.org/10.1177/2167702614540645

Lee, S., Jeong, J., Kwak, Y., & Park, S. K. (2010). Depression research: where are we now? *Mol Brain*, *3*, 8. https://doi.org/10.1186/1756-6606-3-8

Lee, S. H., Cotte, J., & Noseworthy, T. J. (2009). The role of network centrality in the flow of consumer influence. *Journal of Consumer Psychology*.

Lee, Y. C. (2013). Effect and treatment of chronic pain in inflammatory arthritis. *Curr Rheumatol Rep*, *15*(1), 300. https://doi.org/10.1007/s11926-012-0300-4

Lee, Y. C., Lu, B., Edwards, R. R., Wasan, A. D., Nassikas, N. J., Clauw, D. J., . . . Karlson, E. W. (2013). The role of sleep problems in central pain processing in rheumatoid arthritis. *Arthritis Rheum*, *65*(1), 59-68. https://doi.org/10.1002/art.37733

Lekamwasam, R., & Lekamwasam, S. (2020). Effects of COVID-19 Pandemic on Health and Wellbeing of Older People: A Comprehensive Review. *Ann Geriatr Med Res*, *24*(3), 166-172. https://doi.org/10.4235/agmr.20.0027

Leo, J., & Lacasse, J. R. (2007). The Media and the Chemical Imbalance Theory of Depression. *Society*, *45*, 35-45.

Leventhal, E. A., Hansell, S., Diefenbach, M., Leventhal, H., & Glass, D. C. (1996). Negative affect and self-report of physical symptoms: two longitudinal studies of older adults. *Health Psychol*, *15*(3), 193-199. https://doi.org/10.1037//0278-6133.15.3.193

Levinson, C. A., Zerwas, S., Calebs, B., Forbush, K., Kordy, H., Watson, H., . . . Bulik, C. M. (2017). The core symptoms of bulimia nervosa, anxiety, and depression: A network analysis. *J Abnorm Psychol*, *126*(3), 340-354. https://doi.org/10.1037/abn0000254

Levy-Weil, F. E., Jousse-Joulin, S., Tiffreau, V., Perez, R., Morisseau, V., Bombezin-Domino, A., & Flipo, R. M. (2021). Physical activity and quality of life of patients with rheumatoid arthritis at the time of COVID-19 lockdown: an online patient survey. *Joint Bone Spine*, *88*(5), 105212. https://doi.org/10.1016/j.jbspin.2021.105212

Li, N., Chan, E., & Peterson, S. (2019). The economic burden of depression among adults with rheumatoid arthritis in the United States. *J Med Econ*, *22*(4), 372-378. https://doi.org/10.1080/13696998.2019.1572015

Li, Z., Hu, J., Bao, C., Li, X., Li, X., Xu, J., . . . Zerbini, C. A. F. (2020). Baricitinib in patients with rheumatoid arthritis with inadequate response to methotrexate: results from a phase 3 study. *Clin Exp Rheumatol*, *38*(4), 732-741.

Liberati, A., Altman, D. G., Tetzlaff, J., Mulrow, C., Gotzsche, P. C., Ioannidis, J. P., . . . Moher, D. (2009). The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol*, *62*(10), e1-34. https://doi.org/10.1016/j.jclinepi.2009.06.006

Lin, E. H., Katon, W., Von Korff, M., Tang, L., Williams, J. W., Jr., Kroenke, K., . . . Investigators, I. (2003). Effect of improving depression care on pain and functional outcomes among older adults with arthritis: a randomized controlled trial. *JAMA*, *290*(18), 2428-2429. https://doi.org/10.1001/jama.290.18.2428

Lin, M. C., Guo, H. R., Lu, M. C., Livneh, H., Lai, N. S., & Tsai, T. Y. (2015). Increased risk of depression in patients with rheumatoid arthritis: a seven-year population-based cohort study. *Clinics (Sao Paulo)*, *70*(2), 91-96. https://doi.org/10.6061/clinics/2015(02)04

Linde, L., Sorensen, J., Ostergaard, M., Horslev-Petersen, K., & Hetland, M. L. (2008). Health-related quality of life: validity, reliability, and responsiveness of SF-36, 15D, EQ-5D [corrected] RAQoL, and HAQ in patients with rheumatoid arthritis. *J Rheumatol*, *35*(8), 1528-1537.

Linnemann, A., Kappert, M. B., Fischer, S., Doerr, J. M., Strahler, J., & Nater, U. M. (2015). The effects of music listening on pain and stress in the daily life of patients with fibromyalgia syndrome. *Frontiers in Human Neuroscience*, *9*(JULY), 1-10. https://doi.org/http://dx.doi.org/10.3389/fnhum.2015.00434

Linos, A., Kaklamani, V. G., Kaklamani, E., Koumantaki, Y., Giziaki, E., Papazoglou, S., & Mantzoros, C. S. (1999). Dietary factors in relation to rheumatoid arthritis: a role for olive oil and cooked vegetables? *Am J Clin Nutr*, *70*(6), 1077-1082. https://doi.org/10.1093/ajcn/70.6.1077

Lion, K. C., Mangione-Smith, R., & Britto, M. T. (2014). Individualized plans of care to improve outcomes among children and adults with chronic illness: a systematic review. *Care Manag J*, *15*(1), 11-25. https://doi.org/10.1891/1521-0987.15.1.11

Lopez-Campos, J. L., Calero, C., & Quintana-Gallego, E. (2013). Symptom variability in COPD: a narrative review. *Int J Chron Obstruct Pulmon Dis*, *8*, 231-238. https://doi.org/10.2147/COPD.S42866

Lowe, B., Decker, O., Muller, S., Brahler, E., Schellberg, D., Herzog, W., & Herzberg, P. Y. (2008). Validation and standardization of the Generalized Anxiety Disorder Screener

(GAD-7) in the general population. *Med Care*, *46*(3), 266-274. https://doi.org/10.1097/MLR.0b013e318160d093

Lowe, B., Willand, L., Eich, W., Zipfel, S., Ho, A. D., Herzog, W., & Fiehn, C. (2004). Psychiatric comorbidity and work disability in patients with inflammatory rheumatic diseases. *Psychosom Med*, *66*(3), 395-402.

Lwin, M. N., Serhal, L., Holroyd, C., & Edwards, C. J. (2020). Rheumatoid Arthritis: The Impact of Mental Health on Disease: A Narrative Review. *Rheumatol Ther*, *7*(3), 457-471. https://doi.org/10.1007/s40744-020-00217-4

Lynn, A., Sharp, C., van der veer, S., Machin, M., Humphreys, J., Mellor, P., . . . Dixon, W. (2020). Providing 'the bigger picture': benefits and feasibility of integrating remote monitoring from smartphones into the electronic health record: Findings from the Remote Monitoring of Rheumatoid Arthritis (REMORA) study. *Rheumatology*, *59*(2), Pages 367–378.

Lyon, M. E., Jacobs, S., Briggs, L., Cheng, Y. I., & Wang, J. (2014). A longitudinal, randomized, controlled trial of advance care planning for teens with cancer: anxiety, depression, quality of life, advance directives, spirituality. *J Adolesc Health*, *54*(6), 710-717. https://doi.org/10.1016/j.jadohealth.2013.10.206

Madhoo, M., & Levine, S. Z. (2016). Network analysis of the Quick Inventory of Depressive Symptomatology: Reanalysis of the STAR*D clinical trial. *Eur Neuropsychopharmacol*, *26*(11), 1768-1774. https://doi.org/10.1016/j.euroneuro.2016.09.368

Mahil, S. K., Yates, M., Langan, S. M., Yiu, Z. Z. N., Tsakok, T., Dand, N., . . . PsoProtect, C.-U. K. s. g. (2021). Risk-mitigating behaviours in people with inflammatory skin and joint disease during the COVID-19 pandemic differ by treatment type: a cross-sectional patient survey. *Br J Dermatol*, *185*(1), 80-90. https://doi.org/10.1111/bjd.19755

Majithia, V., & Geraci, S. A. (2007). Rheumatoid arthritis: diagnosis and management. *Am J Med*, *120*(11), 936-939. https://doi.org/10.1016/j.amjmed.2007.04.005

Majka, D. S., Deane, K. D., Parrish, L. A., Lazar, A. A., Baron, A. E., Walker, C. W., . . . Holers, V. M. (2008). Duration of preclinical rheumatoid arthritis-related autoantibody positivity increases in subjects with older age at time of disease diagnosis. *Ann Rheum Dis*, *67*(6), 801-807. https://doi.org/10.1136/ard.2007.076679

Makinen, H., Kautiainen, H., Hannonen, P., & Sokka, T. (2005). Is DAS28 an appropriate tool to assess remission in rheumatoid arthritis? *Ann Rheum Dis*, *64*(10), 1410-1413. https://doi.org/10.1136/ard.2005.037333

Maradit-Kremers, H., Crowson, C. S., Nicola, P. J., Ballman, K. V., Roger, V. L., Jacobsen, S. J., & Gabriel, S. E. (2005). Increased unrecognized coronary heart disease and sudden deaths in rheumatoid arthritis: a population-based cohort study. *Arthritis Rheum*, *52*(2), 402-411. https://doi.org/10.1002/art.20853

Margaretten, M., Julian, L., Katz, P., & Yelin, E. (2011). Depression in patients with rheumatoid arthritis: description, causes and mechanisms. *Int J Clin Rheumtol*, *6*(6), 617-623. https://doi.org/10.2217/IJR.11.6

Marrie, R. A., Hitchon, C. A., Walld, R., Patten, S. B., Bolton, J. M., Sareen, J., . . . Managing the Effects of Psychiatric Comorbidity in Chronic Immunoinflammatory, D. (2018). Increased Burden of Psychiatric Disorders in Rheumatoid Arthritis. *Arthritis Care Res (Hoboken)*, *70*(7), 970-978. https://doi.org/10.1002/acr.23539

Martin, A., Rief, W., Klaiberg, A., & Braehler, E. (2006). Validity of the Brief Patient Health Questionnaire Mood Scale (PHQ-9) in the general population. *Gen Hosp Psychiatry*, *28*(1), 71-77. https://doi.org/10.1016/j.genhosppsych.2005.07.003

Martinez-de-Quel, O., Suarez-Iglesias, D., Lopez-Flores, M., & Perez, C. A. (2021). Physical activity, dietary habits and sleep quality before and during COVID-19 lockdown: A longitudinal study. *Appetite*, *158*, 105019. https://doi.org/10.1016/j.appet.2020.105019

Maska, L., Anderson, J., & Michaud, K. (2011). Measures of functional status and quality of life in rheumatoid arthritis: Health Assessment Questionnaire Disability Index (HAQ), Modified Health Assessment Questionnaire (MHAQ), Multidimensional Health Assessment Questionnaire (MDHAQ), Health Assessment Questionnaire II (HAQ-II), Improved Health Assessment Questionnaire (Improved HAQ), and Rheumatoid Arthritis Quality of Life (RAQoL). *Arthritis Care Res (Hoboken)*, *63 Suppl 11*, S4-13. https://doi.org/10.1002/acr.20620

Matcham, F., Ali, S., Irving, K., Hotopf, M., & Chalder, T. (2016). Are depression and anxiety associated with disease activity in rheumatoid arthritis? A prospective study. *BMC Musculoskelet Disord*, *17*, 155. https://doi.org/10.1186/s12891-016-1011-1

Matcham, F., Barattieri di San Pietro, C., Bulgari, V., de Girolamo, G., Dobson, R., Eriksson, H., . . . consortium, R.-C. (2019). Remote assessment of disease and relapse in major depressive disorder (RADAR-MDD): a multi-centre prospective cohort study protocol. *BMC Psychiatry*, *19*(1), 72. https://doi.org/10.1186/s12888-019-2049-z

Matcham, F., Davies, R., Hotopf, M., Hyrich, K. L., Norton, S., Steer, S., & Galloway, J. (2018). The relationship between depression and biologic treatment response in rheumatoid arthritis: An analysis of the British Society for Rheumatology Biologics Register. *Rheumatology (Oxford)*, *57*(5), 835-843. https://doi.org/10.1093/rheumatology/kex528

Matcham, F., Rayner, L., Steer, S., & Hotopf, M. (2013). The prevalence of depression in rheumatoid arthritis: a systematic review and meta-analysis. *Rheumatology (Oxford)*, *52*(12), 2136-2148. https://doi.org/10.1093/rheumatology/ket169

Matcham, F., Scott, I. C., Rayner, L., Hotopf, M., Kingsley, G. H., Norton, S., . . . Steer, S. (2014). The impact of rheumatoid arthritis on quality-of-life assessed using the SF-36: a systematic review and meta-analysis. *Semin Arthritis Rheum*, *44*(2), 123-130. https://doi.org/10.1016/j.semarthrit.2014.05.001

Matei, C., Moise, A., & Suteanu, S. (1992). [An association between ankylosing spondylitis and rheumatoid polyarthritis; comments on 3 cases]. *Med Interna*, *44*(2-4), 61-65. (Asocierea intre spondilita anchilozanta si poliartrita reumatoida; consideratii pe marginea a 3 cazuri.)

May, M., Junghaenel, D. U., Ono, M., Stone, A. A., & Schneider, S. (2018). Ecological Momentary Assessment Methodology in Chronic Pain Research: A Systematic Review. *J Pain*, *19*(7), 699-716. https://doi.org/10.1016/j.jpain.2018.01.006

McColl, E. (2004). Best practice in symptom assessment: a review. *Gut*, *53 Suppl 4*, iv49-54. https://doi.org/10.1136/gut.2003.034355

McGrath, R. E. (2005). Conceptual complexity and construct validity. *J Pers Assess*, *85*(2), 112-124. https://doi.org/10.1207/s15327752jpa8502_02

McNally, R. J. (2016). Can network analysis transform psychopathology? *Behav Res Ther*, *86*, 95-104. https://doi.org/10.1016/j.brat.2016.06.006

Mehta, R. K., & Parasuraman, R. (2014). Effects of mental fatigue on the development of physical fatigue: a neuroergonomic approach. *Hum Factors*, *56*(4), 645-656. https://doi.org/10.1177/0018720813507279

Mella, L. F., Bertolo, M. B., & Dalgalarrondo, P. (2010). Depressive symptoms in rheumatoid arthritis. *Braz J Psychiatry*, *32*(3), 257-263. https://doi.org/10.1590/s1516-44462010005000021

Mesnier, J., Cottin, Y., Coste, P., Ferrari, E., Schiele, F., Lemesle, G., . . . Danchin, N. (2020). Hospital admissions for acute myocardial infarction before and after lockdown according to regional prevalence of COVID-19 and patient profile in France: a registry study. *Lancet Public Health*, *5*(10), e536-e542. https://doi.org/10.1016/S2468-2667(20)30188-2

Messier, S. P., Loeser, R. F., Miller, G. D., Morgan, T. M., Rejeski, W. J., Sevick, M. A., . . . Williamson, J. D. (2004). Exercise and dietary weight loss in overweight and obese older adults with knee osteoarthritis: the Arthritis, Diet, and Activity Promotion Trial. *Arthritis Rheum*, *50*(5), 1501-1510. https://doi.org/10.1002/art.20256

Metsios, G. S., & Kitas, G. D. (2018). Physical activity, exercise and rheumatoid arthritis: Effectiveness, mechanisms and implementation. *Best Pract Res Clin Rheumatol*, *32*(5), 669-682. https://doi.org/10.1016/j.berh.2019.03.013

Metsios, G. S., Stavropoulos-Kalinoglou, A., & Kitas, G. D. (2015). The role of exercise in the management of rheumatoid arthritis. *Expert Rev Clin Immunol*, *11*(10), 1121-1130. https://doi.org/10.1586/1744666X.2015.1067606

Michelsen, B., Kristianslund, E. K., Sexton, J., Hammer, H. B., Fagerli, K. M., Lie, E., . . . Kvien, T. K. (2017). Do depression and anxiety reduce the likelihood of remission in rheumatoid arthritis and psoriatic arthritis? Data from the prospective multicentre NOR-DMARD study. *Ann Rheum Dis*, *76*(11), 1906-1910. https://doi.org/10.1136/annrheumdis-2017-211284

Midway, S. (2019). *Bayesian Hierarchical Models in Ecology*

Mikuls, T. R., Cerhan, J. R., Criswell, L. A., Merlino, L., Mudano, A. S., Burma, M., . . . Saag, K. G. (2002). Coffee, tea, and caffeine consumption and risk of rheumatoid arthritis: results from the Iowa Women's Health Study. *Arthritis Rheum*, *46*(1), 83-91. https://doi.org/10.1002/1529-0131(200201)46:1<83::AID-ART10042>3.0.CO;2-D

Mikuls, T. R., Fay, B. T., Michaud, K., Sayles, H., Thiele, G. M., Caplan, L., . . . Reimold, A. (2011). Associations of disease activity and treatments with mortality in men with rheumatoid arthritis: results from the VARA registry. *Rheumatology (Oxford)*, *50*(1), 101-109. https://doi.org/10.1093/rheumatology/keq232

Mikuls, T. R., Johnson, S. R., Fraenkel, L., Arasaratnam, R. J., Baden, L. R., Bermas, B. L., . . . Saag, K. G. (2021). American College of Rheumatology Guidance for the Management of Rheumatic Disease in Adult Patients During the COVID-19 Pandemic: Version 3. *Arthritis Rheumatol*, *73*(2), e1-e12. https://doi.org/10.1002/art.41596

Mikuls, T. R., Thiele, G. M., Deane, K. D., Payne, J. B., O'Dell, J. R., Yu, F., . . . Norris, J. M. (2012). Porphyromonas gingivalis and disease-related autoantibodies in individuals at increased risk of rheumatoid arthritis. *Arthritis Rheum*, *64*(11), 3522-3530. https://doi.org/10.1002/art.34595

Miller, A. H., Haroon, E., & Felger, J. C. (2017). Therapeutic Implications of Brain-Immune Interactions: Treatment in Translation. *Neuropsychopharmacology*, *42*(1), 334-359. https://doi.org/10.1038/npp.2016.167

Miller, A. H., Maletic, V., & Raison, C. L. (2009). Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. *Biol Psychiatry*, *65*(9), 732-741. https://doi.org/10.1016/j.biopsych.2008.11.029

Mineka, S., Watson, D., & Clark, L. A. (1998). Comorbidity of anxiety and unipolar mood disorders. *Annu Rev Psychol*, *49*, 377-412. https://doi.org/10.1146/annurev.psych.49.1.377

Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., & Group, P. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*, *6*(7), e1000097. https://doi.org/10.1371/journal.pmed.1000097

Mok, C. C. (2018). Morning Stiffness in Elderly Patients with Rheumatoid Arthritis: What is Known About the Effect of Biological and Targeted Agents? *Drugs Aging*, *35*(6), 477-483. https://doi.org/10.1007/s40266-018-0548-0

Moraliyage, H., De Silva, D., Ranasinghe, W., Adikari, A., Alahakoon, D., Prasad, R., . . . Bolton, D. (2021). Cancer in Lockdown: Impact of the COVID-19 Pandemic on Patients with Cancer. *Oncologist*, *26*(2), e342-e344. https://doi.org/10.1002/onco.13604

Moreau, J. L., Jenck, F., Martin, J. R., Mortas, P., & Haefely, W. E. (1992). Antidepressant treatment prevents chronic unpredictable mild stress-induced anhedonia as assessed by ventral tegmentum self-stimulation behavior in rats. *Eur Neuropsychopharmacol*, *2*(1), 43-49. https://doi.org/10.1016/0924-977x(92)90035-7

Moser, D. K., Frazier, S. K., Worrall-Carter, L., Biddle, M. J., Chung, M. L., Lee, K. S., & Lennie, T. A. (2011). Symptom variability, not severity, predicts rehospitalization and mortality in patients with heart failure. *Eur J Cardiovasc Nurs*, *10*(2), 124-129. https://doi.org/10.1016/j.ejcnurse.2010.05.006

Moussavi, S., Chatterji, S., Verdes, E., Tandon, A., Patel, V., & Ustun, B. (2007). Depression, chronic diseases, and decrements in health: results from the World Health Surveys. *Lancet*, *370*(9590), 851-858. https://doi.org/10.1016/S0140-6736(07)61415-9

Munn, Z., Peters, M. D. J., Stern, C., Tufanaru, C., McArthur, A., & Aromataris, E. (2018). Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. *BMC Med Res Methodol*, *18*(1), 143. https://doi.org/10.1186/s12874-018-0611-x

Muschetto, T., & Siegel, J. T. (2019). Attribution theory and support for individuals with depression: The impact of controllability, stability, and interpersonal relationship. *Stigma and Health*, *4*(2), 126-135. https://doi.org/https://doi.org/10.1037/sah0000131

Muthen, B., Asparouhov, T., Hunter, A. M., & Leuchter, A. F. (2011). Growth modeling with nonignorable dropout: alternative analyses of the STAR*D antidepressant trial. *Psychol Methods*, *16*(1), 17-33. https://doi.org/10.1037/a0022634

Myasoedova, E., Chandran, A., Ilhan, B., Major, B. T., Michet, C. J., Matteson, E. L., & Crowson, C. S. (2016). The role of rheumatoid arthritis (RA) flare and cumulative burden of RA severity in the risk of cardiovascular disease. *Ann Rheum Dis*, *75*(3), 560-565. https://doi.org/10.1136/annrheumdis-2014-206411

Myin-Germeys, I., Oorschot, M., Collip, D., Lataster, J., Delespaul, P., & van Os, J. (2009). Experience sampling research in psychopathology: opening the black box of daily life. *Psychol Med*, *39*(9), 1533-1547. https://doi.org/10.1017/S0033291708004947

Najim, R., Mahmood, M., & Albayati, A. (2021). Seasonal Fluctuations of Inflammatory Cytokines in Rheumatoid Arthritis Iraqi Patients. *Journal of Research in Medical and Dental Science*, *9*(8), 335-338.

Natvig, J. B., & Tonder, O. (1998). The discovery of the rheumatoid factor. I. Erik Waaler. 1940. *Clin Exp Rheumatol*, *16*(3), 340-344.

Nelson, B., McGorry, P. D., Wichers, M., Wigman, J. T. W., & Hartmann, J. A. (2017). Moving From Static to Dynamic Models of the Onset of Mental Disorder: A Review. *JAMA Psychiatry*, *74*(5), 528-534. https://doi.org/10.1001/jamapsychiatry.2017.0001

Nemeroff, C. B. (1998). The neurobiology of depression. *Sci Am*, *278*(6), 42-49. https://doi.org/10.1038/scientificamerican0698-42

Neogi, T. (2013). The epidemiology and impact of pain in osteoarthritis. *Osteoarthritis Cartilage*, *21*(9), 1145-1153. https://doi.org/10.1016/j.joca.2013.03.018

Nerurkar, L., Siebert, S., McInnes, I. B., & Cavanagh, J. (2019). Rheumatoid arthritis and depression: an inflammatory perspective. *Lancet Psychiatry*, *6*(2), 164-173. https://doi.org/10.1016/S2215-0366(18)30255-4

NHS. (2019). *Symptoms of Rheumatoid Arthritis*. NHS. Retrieved June from

Nicassio, P. M., Ormseth, S. R., Custodio, M. K., Irwin, M. R., Olmstead, R., & Weisman, M. H. (2012). A multidimensional model of fatigue in patients with rheumatoid arthritis. *J Rheumatol*, *39*(9), 1807-1813. https://doi.org/10.3899/jrheum.111068

NICE. (2009). *Depression in adults with a chronic physical health problem: recognition and management* (Depression, Issue. NICE. https://www.nice.org.uk/guidance/cg91

NICE. (2018, 12 October 2020). *Rheumatoid arthritis in adults: management*. National Institute for Health and Care Excellence. https://www.nice.org.uk/guidance/ng100/resources/rheumatoid-arthritis-in-adults-management-pdf-66141531233989

Nicholson, L. M., Schwirian, P. M., Klein, E. G., Skybo, T., Murray-Johnson, L., Eneli, I., . . . Groner, J. A. (2011). Recruitment and retention strategies in longitudinal clinical studies with low-income populations. *Contemp Clin Trials*, *32*(3), 353-362. https://doi.org/10.1016/j.cct.2011.01.007

Nicklin, J., Cramp, F., Kirwan, J., Greenwood, R., Urban, M., & Hewlett, S. (2010). Measuring fatigue in rheumatoid arthritis: a cross-sectional study to evaluate the Bristol Rheumatoid Arthritis Fatigue Multi-Dimensional questionnaire, visual analog scales, and numerical rating scales. *Arthritis Care Res (Hoboken)*, *62*(11), 1559-1568. https://doi.org/10.1002/acr.20282

Niedzwiedz, C. L., Green, M. J., Benzeval, M., Campbell, D., Craig, P., Demou, E., . . . Katikireddi, S. V. (2021). Mental health and health behaviours before and during the initial phase of the COVID-19 lockdown: longitudinal analyses of the UK Household Longitudinal Study. *J Epidemiol Community Health*, *75*(3), 224-231. https://doi.org/10.1136/jech-2020-215060

Nielsen, S. F., Bojesen, S. E., Schnohr, P., & Nordestgaard, B. G. (2012). Elevated rheumatoid factor and long term risk of rheumatoid arthritis: a prospective cohort study. *BMJ*, *345*, e5244. https://doi.org/10.1136/bmj.e5244

Niki, H., Hirano, T., Okada, H., & Beppu, M. (2010). Combination joint-preserving surgery for forefoot deformity in patients with rheumatoid arthritis. *J Bone Joint Surg Br*, *92*(3), 380-386. https://doi.org/10.1302/0301-620X.92B3.23186

Nikiphorou, E., Norton, S., Carpenter, L., Dixey, J., Andrew Walsh, D., Kiely, P., . . . the Early Rheumatoid Arthritis Network, C. (2017). Secular Changes in Clinical Features at Presentation of Rheumatoid Arthritis: Increase in Comorbidity But Improved Inflammatory States. *Arthritis Care Res (Hoboken)*, *69*(1), 21-27. https://doi.org/10.1002/acr.23014

Noah, J. A., Spierer, D. K., Gu, J., & Bronner, S. (2013). Comparison of steps and energy expenditure assessment in adults of Fitbit Tracker and Ultra to the Actical and indirect calorimetry. *Journal of Medical Engineering & Technology*, *37*(7), 456-462.

Norton, K., Norton, L., & Sadgrove, D. (2010). Position statement on physical activity and exercise intensity terminology. *J Sci Med Sport*, *13*(5), 496-502. https://doi.org/10.1016/j.jsams.2009.09.008

Norton, P. J., Hayes, S. A., & Hope, D. A. (2004). Effects of a transdiagnostic group treatment for anxiety on secondary depression. *Depress Anxiety*, *20*(4), 198-202. https://doi.org/10.1002/da.20045

Norton, S., Koduri, G., Nikiphorou, E., Dixey, J., Williams, P., & Young, A. (2013). A study of baseline prevalence and cumulative incidence of comorbidity and extra-articular manifestations in RA and their impact on outcome. *Rheumatology (Oxford)*, *52*(1), 99-110. https://doi.org/10.1093/rheumatology/kes262

Noteboom, A., Beekman, A. T. F., Vogelzangs, N., & Penninx, B. (2016). Personality and social support as predictors of first and recurrent episodes of depression. *J Affect Disord*, *190*, 156-161. https://doi.org/10.1016/j.jad.2015.09.020

Nyman, E. S., Sulkava, S., Soronen, P., Miettunen, J., Loukola, A., Leppa, V., . . . Paunio, T. (2011). Interaction of early environment, gender and genes of monoamine neurotransmission in the aetiology of depression in a large population-based Finnish birth cohort. *BMJ Open*, *1*(1), e000087. https://doi.org/10.1136/bmjopen-2011-000087

Ogdie, A., Haynes, K., Troxel, A. B., Love, T. J., Hennessy, S., Choi, H., & Gelfand, J. M. (2014). Risk of mortality in patients with psoriatic arthritis, rheumatoid arthritis and psoriasis: a longitudinal cohort study. *Ann Rheum Dis*, *73*(1), 149-153. https://doi.org/10.1136/annrheumdis-2012-202424

Ohayon, M., Wickwire, E. M., Hirshkowitz, M., Albert, S. M., Avidan, A., Daly, F. J., . . . Vitiello, M. V. (2017). National Sleep Foundation's sleep quality recommendations: first report. *Sleep Health*, *3*(1), 6-19. https://doi.org/10.1016/j.sleh.2016.11.006

Okifuji, A., Bradshaw, D. H., Donaldson, G. W., & Turk, D. C. (2011). Sequential analyses of daily symptoms in women with fibromyalgia syndrome. *Journal of Pain*, *12*(1), 84-93. https://doi.org/http://dx.doi.org/10.1016/j.jpain.2010.05.003

Ono, M., Schneider, S., Junghaenel, D. U., & Stone, A. A. (2019). What Affects the Completion of Ecological Momentary Assessments in Chronic Pain Research? An Individual Patient Data Meta-Analysis. *J Med Internet Res*, *21*(2), e11398. https://doi.org/10.2196/11398

Ottenstein, C., & Lischetzke, T. (2020). Recall bias in emotional intensity ratings: investigating person-level and event-level predictors. *Motivation and Emotion*, *44*, 464-473.

Ozyemisci-Taskiran, O., Batur, E. B., Yuksel, S., Cengiz, M., & Karatas, G. K. (2019). Validity and reliability of fatigue severity scale in stroke. *Top Stroke Rehabil*, *26*(2), 122-127. https://doi.org/10.1080/10749357.2018.1550957

Palmer, K., Monaco, A., Kivipelto, M., Onder, G., Maggi, S., Michel, J. P., . . . Donde, S. (2020). The potential long-term impact of the COVID-19 outbreak on patients with non-communicable diseases in Europe: consequences for healthy ageing. *Aging Clin Exp Res*, *32*(7), 1189-1194. https://doi.org/10.1007/s40520-020-01601-4

Parmelee, P. A., Behrens, E. A., Costlow Hill, K., Cox, B. S., DeCaro, J. A., Keefe, F. J., & Smith, D. M. (2022). Momentary Associations of Osteoarthritis Pain and Affect: Depression

as Moderator. *J Gerontol B Psychol Sci Soc Sci*, *77*(7), 1240-1249. https://doi.org/10.1093/geronb/gbab221

Pattison, D. J., Symmons, D. P., Lunt, M., Welch, A., Luben, R., Bingham, S. A., . . . Silman, A. J. (2004). Dietary risk factors for the development of inflammatory polyarthritis: evidence for a role of high level of red meat consumption. *Arthritis Rheum*, *50*(12), 3804-3812. https://doi.org/10.1002/art.20731

Peacock, J., & Peacock, P. (2011). *Oxford Handbook of Medical Statistics*. Oxford University Press.

Peck, J. R., Smith, T. W., Ward, J. R., & Milano, R. (1989). Disability and depression in rheumatoid arthritis. A multi-trait, multi-method investigation. *Arthritis Rheum*, *32*(9), 1100-1106. https://doi.org/10.1002/anr.1780320908

Peeters, F., Berkhof, J., Delespaul, P., Rottenberg, J., & Nicolson, N. A. (2006). Diurnal mood variation in major depressive disorder. *Emotion*, *6*(3), 383-391. https://doi.org/10.1037/1528-3542.6.3.383

Perez-Chada, L. M., & Merola, J. F. (2020). Comorbidities associated with psoriatic arthritis: Review and update. *Clin Immunol*, *214*, 108397. https://doi.org/10.1016/j.clim.2020.108397

Perrot, S., Dieude, P., Perocheau, D., & Allanore, Y. (2013). Comparison of pain, pain burden, coping strategies, and attitudes between patients with systemic sclerosis and patients with rheumatoid arthritis: a cross-sectional study. *Pain Med*, *14*(11), 1776-1785. https://doi.org/10.1111/pme.12213

Picchianti Diamanti, A., Cattaruzza, M. S., Di Rosa, R., Del Porto, F., Salemi, S., Sorgi, M. L., . . . Lagana, B. (2020). Psychological Distress in Patients with Autoimmune Arthritis during the COVID-19 Induced Lockdown in Italy. *Microorganisms*, *8*(11). https://doi.org/10.3390/microorganisms8111818

Piedimonte, A., Benedetti, F., & Carlino, E. (2015). Placebo-induced decrease in fatigue: evidence for a central action on the preparatory phase of movement. *Eur J Neurosci*, *41*(4), 492-497. https://doi.org/10.1111/ejn.12806

Pietrowsky, R., & Lahl, O. (2008). Diurnal variation of physical and mental fatigue. *Sleep and Biological Rhythms*, *6*, 228-233.

Pincus, D. (2019). Clinical Psychology at the Crossroads: An Introduction to the Special Issue on Nonlinear Dynamical Systems. *Nonlinear Dynamics Psychol Life Sci*, *23*(1), 1-15.

Pisetsky, D. S., & Ward, M. M. (2012). Advances in the treatment of inflammatory arthritis. *Best Pract Res Clin Rheumatol*, *26*(2), 251-261. https://doi.org/10.1016/j.berh.2012.03.001

Plasqui, G. (2008). The role of physical activity in rheumatoid arthritis. *Physiol Behav*, *94*(2), 270-275. https://doi.org/10.1016/j.physbeh.2007.12.012

Plummer, F., Manea, L., Trepel, D., & McMillan, D. (2016). Screening for anxiety disorders with the GAD-7 and GAD-2: a systematic review and diagnostic metaanalysis. *Gen Hosp Psychiatry*, *39*, 24-31. https://doi.org/10.1016/j.genhosppsych.2015.11.005

Polese, J. C., Faria-Fortini, I., Basilio, M. L., Faria, G. S., & Teixeira-Salmela, L. F. (2017). Recruitment rate and retention of stroke subjects in cross-sectional studies. *Cien Saude Colet*, *22*(1), 255-260. https://doi.org/10.1590/1413-81232017221.14262015

Pollard, L. C., Choy, E. H., Gonzalez, J., Khoshaba, B., & Scott, D. L. (2006). Fatigue in rheumatoid arthritis reflects pain, not disease activity. *Rheumatology (Oxford)*, *45*(7), 885-889. https://doi.org/10.1093/rheumatology/kel021

Pressman, S. D., & Cohen, S. (2005). Does positive affect influence health? *Psychol Bull*, *131*(6), 925-971. https://doi.org/10.1037/0033-2909.131.6.925

Prevoo, M. L., Van 't Hof, M. A., Kuper, H. H., van Leeuwen, M. A., van de Putte, L. B., & van Riel, P. L. (1995). Modified Disease Activity Scores that Include Twenty-Eight-Joint Counts. *American College of Rheumatology*, *38*(1), 44-48.

Prioreschi, A., Hodkinson, B., Tikly, M., & McVeigh, J. A. (2014). Changes in physical activity measured by accelerometry following initiation of DMARD therapy in rheumatoid arthritis. *Rheumatology (Oxford)*, *53*(5), 923-926. https://doi.org/10.1093/rheumatology/ket457

Probst, B. (2015). *Critical Thinking in Clinical Assessment and Diagnosis*. Springer.

Raes, F., Smets, J., Nelis, S., & Schoofs, H. (2012). Dampening of positive affect prospectively predicts depressive symptoms in non-clinical samples. *Cogn Emot*, *26*(1), 75-82. https://doi.org/10.1080/02699931.2011.555474

Rat, A. C., Brignon, M., Beauvais, C., Beranger, M., Boujut, E., Cohen, J. D., . . . proxy, R. I. C. w. g. (2021). Patients and spouses coping with inflammatory arthritis: Impact of communication and spousal perceived social support and burden. *Joint Bone Spine*, *88*(3), 105125. https://doi.org/10.1016/j.jbspin.2020.105125

Rausch Osthoff, A.-K., Niedermann, K., Braun, J., Adams, J., Brodin, N., Dagfinrud, H., . . . Vliet Vlieland, T. P. M. (2018). 2018 EULAR recommendations for physical activity in people with inflammatory arthritis and osteoarthritis. *Annals of the Rheumatic Diseases*, *77*(9), 1251-1260. https://doi.org/10.1136/annrheumdis-2018-213585

Reichert, M., Giurgiu, M., Koch, E., Wieland, L. M., Lautenbach, S., Neubauer, A. B., . . . Liao, Y. (2020). Ambulatory Assessment for Physical Activity Research: State of the Science, Best Practices and Future Directions. *Psychol Sport Exerc*, *50*. https://doi.org/10.1016/j.psychsport.2020.101742

Rice, S. M., Oliffe, J. L., Kelly, M. T., Cormie, P., Chambers, S., Ogrodniczuk, J. S., & Kealy, D. (2018). Depression and Prostate Cancer: Examining Comorbidity and Male-Specific Symptoms. *Am J Mens Health*, *12*(6), 1864-1872. https://doi.org/10.1177/1557988318784395

Ripke, S., Wray, N. R., Lewis, C. M., Hamilton, S. P., Weissman, M. M., Breen, G., . . . Sullivan, P. F. (2013). A mega-analysis of genome-wide association studies for major depressive disorder. *Mol Psychiatry*, *18*(4), 497-511. https://doi.org/10.1038/mp.2012.21

Ritchlin, C. T., Colbert, R. A., & Gladman, D. D. (2017). Psoriatic Arthritis. *N Engl J Med*, *376*(21), 2095-2096. https://doi.org/10.1056/NEJMc1704342

Robbins, M. L., Mehl, M. R., Holleran, S. E., & Kasle, S. (2011). Naturalistically Observed Sighing and Depression in Rheumatoid Arthritis Patients: A Preliminary Study. *Health Psychology*, *30*(1), 129-133. https://doi.org/http://dx.doi.org/10.1037/a0021558

Robinaugh, D. J., Hoekstra, R. H. A., Toner, E. R., & Borsboom, D. (2020). The network approach to psychopathology: a review of the literature 2008-2018 and an agenda for future research. *Psychol Med*, *50*(3), 353-366. https://doi.org/10.1017/S0033291719003404

Robinaugh, D. J., Millner, A. J., & McNally, R. J. (2016). Identifying highly influential nodes in the complicated grief network. *J Abnorm Psychol*, *125*(6), 747-757. https://doi.org/10.1037/abn0000181

Robinson, M. D., & Clore, G. L. (2002). Belief and feeling: evidence for an accessibility model of emotional self-report. *Psychol Bull*, *128*(6), 934-960. https://doi.org/10.1037/0033-2909.128.6.934
Roddy, E., & Doherty, M. (2010). Epidemiology of gout. *Arthritis Res Ther*, *12*(6), 223. https://doi.org/10.1186/ar3199
Rodriguez-Raecke, R., Ihle, K., Ritter, C., Muhtz, C., Otte, C., & May, A. (2014). Neuronal differences between chronic low back pain and depression regarding long-term habituation to pain. *Eur J Pain*, *18*(5), 701-711. https://doi.org/10.1002/j.1532-2149.2013.00407.x
Rongen-van Dartel, S. A., Repping-Wuts, H., Donders, R., van Hoogmoed, D., Knoop, H., Bleijenberg, G., . . . Fransen, J. (2016). A multidimensional 'path analysis' model of factors explaining fatigue in rheumatoid arthritis. *Clin Exp Rheumatol*, *34*(2), 200-206.
Rosenberg, E. L. (1998). Levels of analysis and the organization of affect. *Review of General Psychology*, *2*(3), 247-270.
Rossi, R., Socci, V., Talevi, D., Mensi, S., Niolu, C., Pacitti, F., . . . Di Lorenzo, G. (2020). COVID-19 Pandemic and Lockdown Measures Impact on Mental Health Among the General Population in Italy. *Front Psychiatry*, *11*, 790. https://doi.org/10.3389/fpsyt.2020.00790
Roverato, A., & Castelo, R. (2017). The networked partial correlation and its application to the analysis of genetic interactions. *Journal of the Royal Statistical Society*, *66*, 647-665.
Ruderman, E. M. (2012). Overview of safety of non-biologic and biologic DMARDs. *Rheumatology (Oxford)*, *51 Suppl 6*, vi37-43. https://doi.org/10.1093/rheumatology/kes283
Rudwaleit, M., van der Heijde, D., Landewe, R., Akkoc, N., Brandt, J., Chou, C. T., . . . Sieper, J. (2011). The Assessment of SpondyloArthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. *Ann Rheum Dis*, *70*(1), 25-31. https://doi.org/10.1136/ard.2010.133645
Russell, J. A. (1980). A circumplex model of affect. *Journal of Personality and Social Psychology*, *39*(6), 1161-1178. https://doi.org/https://doi.org/10.1037/h0077714
Ryff, C. D., & Keyes, C. L. (1995). The structure of psychological well-being revisited. *J Pers Soc Psychol*, *69*(4), 719-727. https://doi.org/10.1037//0022-3514.69.4.719
Sacks, J. J., Luo, Y. H., & Helmick, C. G. (2010). Prevalence of specific types of arthritis and other rheumatic conditions in the ambulatory health care system in the United States, 2001-2005. *Arthritis Care Res (Hoboken)*, *62*(4), 460-464. https://doi.org/10.1002/acr.20041
Salk, R. H., Hyde, J. S., & Abramson, L. Y. (2017). Gender differences in depression in representative national samples: Meta-analyses of diagnoses and symptoms. *Psychol Bull*, *143*(8), 783-822. https://doi.org/10.1037/bul0000102
Sanderson, T., & Kirwan, J. (2009). Patient-reported outcomes for arthritis: time to focus on personal life impact measures? *Arthritis Rheum*, *61*(1), 1-3. https://doi.org/10.1002/art.24270
Sanderson, T., Morris, M., Calnan, M., Richards, P., & Hewlett, S. (2010). What outcomes from pharmacologic treatments are important to people with rheumatoid arthritis? Creating the basis of a patient core set. *Arthritis Care Res (Hoboken)*, *62*(5), 640-646. https://doi.org/10.1002/acr.20034

Santor, D. A., Gregus, M., & Welch, A. (2006). Eight Decades of Measurement in Depression. *Measurement: Interdisciplinary Research and Perspectives*, *4*(3), 135-155.
Schanberg, L. E., Anthony, K. K., Gil, K. M., & Maurin, E. C. (2003). Daily pain and symptoms in children with polyarticular arthritis. *Arthritis Rheum*, *48*(5), 1390-1397. https://doi.org/10.1002/art.10986
Schellekens, G. A., Visser, H., de Jong, B. A., van den Hoogen, F. H., Hazes, J. M., Breedveld, F. C., & van Venrooij, W. J. (2000). The diagnostic properties of rheumatoid arthritis antibodies recognizing a cyclic citrullinated peptide. *Arthritis Rheum*, *43*(1), 155-163. https://doi.org/10.1002/1529-0131(200001)43:1<155::AID-ANR20>3.0.CO;2-3
Scher, J. U., Nayak, R. R., Ubeda, C., Turnbaugh, P. J., & Abramson, S. B. (2020). Pharmacomicrobiomics in inflammatory arthritis: gut microbiome as modulator of therapeutic response. *Nat Rev Rheumatol*, *16*(5), 282-292. https://doi.org/10.1038/s41584-020-0395-3
Schneider, S., Junghaenel, D. U., Keefe, F. J., Schwartz, J. E., Stone, A. A., & Broderick, J. E. (2012). Individual differences in the day-to-day variability of pain, fatigue, and well-being in patients with rheumatic disease: associations with psychological variables. *Pain*, *153*(4), 813-822. https://doi.org/10.1016/j.pain.2012.01.001
Schneider, S., Junghaenel, D. U., Keefe, F. J., Schwartz, J. E., Stone, A. A., & Broderick, J. E. (2012). Individual differences in the day-to-day variability of pain, fatigue, and well-being in patients with rheumatic disease: Associations with psychological variables [Empirical Study; Quantitative Study]. *Pain*, *153*(4), 813-822. https://doi.org/http://dx.doi.org/10.1016/j.pain.2012.01.001
Scott, D., Wolfe, F., & Huizinga, T. W. (2010). Rheumatoid arthritis. *The Lancet*, *376*(9746), 1094-1108.
Scott, D. I. C., McCray, D. G., Lancaster, P. G., Foster, P. N. E., & Hill, D. J. C. (2020). Validation of the Musculoskeletal Health Questionnaire (MSK-HQ) in primary care patients with musculoskeletal pain. *Semin Arthritis Rheum*, *50*(5), 813-820. https://doi.org/10.1016/j.semarthrit.2020.06.022
Scott, D. L. (2012). Biologics-based therapy for the treatment of rheumatoid arthritis. *Clin Pharmacol Ther*, *91*(1), 30-43. https://doi.org/10.1038/clpt.2011.278
Scott, D. L., Galloway, J., Cope, A., Pratt, A., & Strand, V. (2020). *Oxford Textbook of Rheumatoid Arthritis*. Oxford University Press. https://doi.org/10.1093/med/9780198831433.001.0001
Scott, J. T. (1960). Morning stiffness in rheumatoid arthritis. *Ann Rheum Dis*, *19*, 361-368. https://doi.org/10.1136/ard.19.4.361
Scott, K. M., Bruffaerts, R., Tsang, A., Ormel, J., Alonso, J., Angermeyer, M. C., . . . Von Korff, M. (2007). Depression-anxiety relationships with chronic physical conditions: results from the World Mental Health Surveys. *J Affect Disord*, *103*(1-3), 113-120. https://doi.org/10.1016/j.jad.2007.01.015
Sediri, S., Zgueb, Y., Ouanes, S., Ouali, U., Bourgou, S., Jomli, R., & Nacef, F. (2020). Women's mental health: acute impact of COVID-19 pandemic on domestic violence. *Arch Womens Ment Health*, *23*(6), 749-756. https://doi.org/10.1007/s00737-020-01082-4
Seligman, M. E. (1972). Learned helplessness. *Annu Rev Med*, *23*, 407-412. https://doi.org/10.1146/annurev.me.23.020172.002203
Selya, A. S., Rose, J. S., Dierker, L. C., Hedeker, D., & Mermelstein, R. J. (2012). A Practical Guide to Calculating Cohen's f(2), a Measure of Local Effect Size, from PROC MIXED. *Front Psychol*, *3*, 111. https://doi.org/10.3389/fpsyg.2012.00111

Semerano, L., Gutierrez, M., Falgarone, G., Filippucci, E., Guillot, X., Boissier, M. C., & Grassi, W. (2011). Diurnal variation of power Doppler in metacarpophalangeal joints of patients with rheumatoid arthritis: a preliminary study. *Ann Rheum Dis*, *70*(9), 1699-1700. https://doi.org/10.1136/ard.2010.146761

Serafini, G., Pompili, M., Innamorati, M., Dwivedi, Y., Brahmachari, G., & Girardi, P. (2013). Pharmacological properties of glutamatergic drugs targeting NMDA receptors and their application in major depression. *Curr Pharm Des*, *19*(10), 1898-1922. https://doi.org/10.2174/13816128113199990293

Service, N. H. (2021, 28th August 2019). *Treatment Rheumatoid Arthritis*. NHS. Retrieved May from

Shafshak, T. S., & Elnemr, R. (2020). The Visual Analogue Scale Versus Numerical Rating Scale in Measuring Pain Severity and Predicting Disability in Low Back Pain. *J Clin Rheumatol*. https://doi.org/10.1097/RHU.0000000000001320

Shapiro, J. A., Koepsell, T. D., Voigt, L. F., Dugowson, C. E., Kestin, M., & Nelson, J. L. (1996). Diet and rheumatoid arthritis in women: a possible protective effect of fish consumption. *Epidemiology*, *7*(3), 256-263. https://doi.org/10.1097/00001648-199605000-00007

Shaw, Y., Bradley, M., Zhang, C., Dominique, A., Michaud, K., McDonald, D., & Simon, T. A. (2020). Development of Resilience Among Rheumatoid Arthritis Patients: A Qualitative Study. *Arthritis Care Res (Hoboken)*, *72*(9), 1257-1265. https://doi.org/10.1002/acr.24024

Sheehy, C., Murphy, E., & Barry, M. (2006). Depression in rheumatoid arthritis--underscoring the problem. *Rheumatology (Oxford)*, *45*(11), 1325-1327. https://doi.org/10.1093/rheumatology/kel231

Sheng, J., Liu, S., Wang, Y., Cui, R., & Zhang, X. (2017). The Link between Depression and Chronic Pain: Neural Mechanisms in the Brain. *Neural Plasticity*, *2017*. https://doi.org/10.1155/2017/9724371

Shiffman, S., Stone, A. A., & Hufford, M. R. (2008). Ecological momentary assessment [Literature Review]. *Annual Review of Clinical Psychology*, *4*, 1-32. https://doi.org/http://dx.doi.org/10.1146/annurev.clinpsy.3.022806.091415

Shiffman, S., Stone, A. A., & Hufford, M. R. (2008). Ecological momentary assessment. *Annu Rev Clin Psychol*, *4*, 1-32. https://doi.org/10.1146/annurev.clinpsy.3.022806.091415

Shor, B., Bafumi, J., Keele, L., & Park, D. (2007). A Bayesian multilevel modeling approach to time-series cross-sectional data. *Political Analysis*, *15*(2), 165-181.

Shuman, V., Sander, D., & Scherer, K. R. (2013). Levels of valence. *Front Psychol*, *4*, 261. https://doi.org/10.3389/fpsyg.2013.00261

Siemons, L., Vonkeman, H. E., ten Klooster, P. M., van Riel, P. L., & van de Laar, M. A. (2014). Interchangeability of 28-joint disease activity scores using the erythrocyte sedimentation rate or the C-reactive protein as inflammatory marker. *Clin Rheumatol*, *33*(6), 783-789. https://doi.org/10.1007/s10067-014-2538-x

Sieper, J., Rudwaleit, M., Khan, M. A., & Braun, J. (2006). Concepts and epidemiology of spondyloarthritis. *Best Pract Res Clin Rheumatol*, *20*(3), 401-417. https://doi.org/10.1016/j.berh.2006.02.001

Sierakowski, S., & Cutolo, M. (2011). Morning symptoms in rheumatoid arthritis: a defining characteristic and marker of active disease. *Scand J Rheumatol Suppl*, *125*, 1-5. https://doi.org/10.3109/03009742.2011.566433

Silman, A. J. (2002). The changing face of rheumatoid arthritis: why the decline in incidence? *Arthritis Rheum*, *46*(3), 579-581. https://doi.org/10.1002/art.508

Silman, A. J., MacGregor, A. J., Thomson, W., Holligan, S., Carthy, D., Farhan, A., & Ollier, W. E. (1993). Twin concordance rates for rheumatoid arthritis: results from a nationwide study. *Br J Rheumatol*, *32*(10), 903-907. https://doi.org/10.1093/rheumatology/32.10.903

Silva, M. J., & Kelly, Z. (2020). The escalation of the opioid epidemic due to COVID-19 and resulting lessons about treatment alternatives. *Am J Manag Care*, *26*(7), e202-e204. https://doi.org/10.37765/ajmc.2020.43386

Singh, J. A., Christensen, R., Wells, G. A., Suarez-Almazor, M. E., Buchbinder, R., Lopez-Olivo, M. A., . . . Tugwell, P. (2009). A network meta-analysis of randomized controlled trials of biologics for rheumatoid arthritis: a Cochrane overview. *CMAJ*, *181*(11), 787-796. https://doi.org/10.1503/cmaj.091391

Sirois, F. M. (2014). Positive psychological qualities and adjustment to arthritis. *OA Arthritis*, *2*(1).

Sliwerski, A., Kossakowska, K., Jarecka, K., Switalska, J., & Bielawska-Batorowicz, E. (2020). The Effect of Maternal Depression on Infant Attachment: A Systematic Review. *Int J Environ Res Public Health*, *17*(8). https://doi.org/10.3390/ijerph17082675

Smith, B. W., & Zautra, A. J. (2002). The role of personality in exposure and reactivity to interpersonal stress in relation to arthritis disease activity and negative affect in women. *Health Psychol*, *21*(1), 81-88.

Smith, B. W., & Zautra, A. J. (2008a). The effects of anxiety and depression on weekly pain in women with arthritis. *Pain*, *138*(2), 354-361. https://doi.org/10.1016/j.pain.2008.01.008

Smith, B. W., & Zautra, A. J. (2008b). Vulnerability and resilience in women with arthritis: test of a two-factor model. *J Consult Clin Psychol*, *76*(5), 799-810. https://doi.org/10.1037/0022-006X.76.5.799

Smith, H. S., Smith, A. R., & Seidner, P. (2011). Painful rheumatoid arthritis. *Pain Physician*, *14*(5), E427-458.

Smith, T. (2017). "On their own": social isolation, loneliness and chronic musculoskeletal pain in older adults. *Quality in Ageing and Older Adults*, *18*(2), 87-92. https://doi.org/https://doi.org/10.1108/QAOA-03-2017-0010

Smolen, J. S., & Aletaha, D. (2015). Rheumatoid arthritis therapy reappraisal: strategies, opportunities and challenges. *Nat Rev Rheumatol*, *11*(5), 276-289. https://doi.org/10.1038/nrrheum.2015.8

Smyth, J. M., & Stone, A. A. (2003). Ecological Momentary Assessment research in behavioral medicine. *Journal of Happiness Studies*, *4*(1), 35-52. https://doi.org/http://dx.doi.org/10.1023/A:1023657221954

Snijders, T. (2005). Power and Sample Size in Multilevel Linear Models. *Encyclopedia of Statistics in Behavioral Science*. https://doi.org/https://doi.org/10.1002/0470013192.bsa492

Society, N. R. A. (2021). *Steriods*. National Rheumatoid Arthritis Society. Retrieved May from

Sokka, T. (2010). Assessment of Rheumatoid Arthritis in Clinical Care. *Archives of Rheumatology*, *25*(1), 1-11. https://doi.org/10.5152/tjr.2010.01

Sokolove, J., Johnson, D. S., Lahey, L. J., Wagner, C. A., Cheng, D., Thiele, G. M., . . . Robinson, W. H. (2014). Rheumatoid factor as a potentiator of anti-citrullinated protein

antibody-mediated inflammation in rheumatoid arthritis. *Arthritis Rheumatol*, *66*(4), 813-821. https://doi.org/10.1002/art.38307

Sommerlad, A., Marston, L., Huntley, J., Livingston, G., Lewis, G., Steptoe, A., & Fancourt, D. (2021). Social relationships and depression during the COVID-19 lockdown: longitudinal analysis of the COVID-19 Social Study. *Psychol Med*, 1-10. https://doi.org/10.1017/S0033291721000039

Spector, T. D., & Hochberg, M. C. (1990). The protective effect of the oral contraceptive pill on rheumatoid arthritis: an overview of the analytic epidemiological studies using meta-analysis. *J Clin Epidemiol*, *43*(11), 1221-1230. https://doi.org/10.1016/0895-4356(90)90023-i

Spitzer, R. L., Kroenke, K., Williams, J. B., & Lowe, B. (2006). A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med*, *166*(10), 1092-1097. https://doi.org/10.1001/archinte.166.10.1092

Staples, L. G., Dear, B. F., Gandy, M., Fogliati, V., Fogliati, R., Karin, E., . . . Titov, N. (2019). Psychometric properties and clinical utility of brief measures of depression, anxiety, and general distress: The PHQ-2, GAD-2, and K-6. *Gen Hosp Psychiatry*, *56*, 13-18. https://doi.org/10.1016/j.genhosppsych.2018.11.003

Staud, R., Robinson, M. E., Vierck, C. J., Jr., Cannon, R. C., Mauderli, A. P., & Price, D. D. (2003). Ratings of experimental pain and pain-related negative affect predict clinical pain in patients with fibromyalgia syndrome. *Pain*, *105*(1-2), 215-222. https://doi.org/10.1016/s0304-3959(03)00208-2

Stawski, R. S., Sliwinski, M. J., & Smyth, J. M. (2006). Stress-related cognitive interference predicts cognitive function in old age. *Psychol Aging*, *21*(3), 535-544. https://doi.org/10.1037/0882-7974.21.3.535

Steptoe, A., Leigh, E. S., & Kumari, M. (2011). Positive affect and distressed affect over the day in older people. *Psychol Aging*, *26*(4), 956-965. https://doi.org/10.1037/a0023303

Stoll, M. L., Zurakowski, D., Nigrovic, L. E., Nichols, D. P., Sundel, R. P., & Nigrovic, P. A. (2006). Patients with juvenile psoriatic arthritis comprise two distinct populations. *Arthritis Rheum*, *54*(11), 3564-3572. https://doi.org/10.1002/art.22173

Stolwijk, C., Boonen, A., van Tubergen, A., & Reveille, J. D. (2012). Epidemiology of spondyloarthritis. *Rheum Dis Clin North Am*, *38*(3), 441-476. https://doi.org/10.1016/j.rdc.2012.09.003

Stone, A. A., Broderick, J. E., Porter, L. S., & Kaell, A. T. (1997). The experience of rheumatoid arthritis pain and fatigue: Examining momentary reports and correlates over one week. *Arthritis and Rheumatism*, *10*(3), 185-193.

Stone, A. A., & Shiffman, S. (2002). Capturing momentary, self-report data: A proposal for reporting guidelines. *Annals of Behavioral Medicine*, *24*(3), 236-243. https://doi.org/http://dx.doi.org/10.1207/S15324796ABM2403_09

Stone, A. S., & Shiffman, S. (1994). Ecological Momentary Assessment in Behavioral Medicine. *Annals of Behavioral Medicine*, *16*(3), 199-202.

Strand, E. B., Zautra, A. J., Thoresen, M., Odegard, S., Uhlig, T., & Finset, A. (2006). Positive affect as a factor of resilience in the pain-negative affect relationship in patients with rheumatoid arthritis. *J Psychosom Res*, *60*(5), 477-484. https://doi.org/10.1016/j.jpsychores.2005.08.010

Straub, R. H., & Cutolo, M. (2007). Circadian rhythms in rheumatoid arthritis: implications for pathophysiology and therapeutic management. *Arthritis Rheum*, *56*(2), 399-408. https://doi.org/10.1002/art.22368

Strober, B., Gooderham, M., de Jong, E., Kimball, A. B., Langley, R. G., Lakdawala, N., . . . Menter, A. (2018). Depressive symptoms, depression, and the effect of biologic therapy among patients in Psoriasis Longitudinal Assessment and Registry (PSOLAR). *J Am Acad Dermatol*, *78*(1), 70-80. https://doi.org/10.1016/j.jaad.2017.08.051

Stucki, G., Cieza, A., Geyh, S., Battistella, L., Lloyd, J., Symmons, D., . . . Schouten, J. (2004). ICF Core Sets for rheumatoid arthritis. *J Rehabil Med*(44 Suppl), 87-93. https://doi.org/10.1080/16501960410015470

Studenic, P., Radner, H., Smolen, J. S., & Aletaha, D. (2012). Discrepancies between patients and physicians in their perceptions of rheumatoid arthritis disease activity. *Arthritis Rheum*, *64*(9), 2814-2823. https://doi.org/10.1002/art.34543

Su, J. A., Yeh, D. C., Chang, C. C., Lin, T. C., Lai, C. H., Hu, P. Y., . . . Gossop, M. (2017). Depression and family support in breast cancer patients. *Neuropsychiatr Dis Treat*, *13*, 2389-2396. https://doi.org/10.2147/NDT.S135624

Sullivan, G. M., & Feinn, R. (2012). Using Effect Size-or Why the P Value Is Not Enough. *J Grad Med Educ*, *4*(3), 279-282. https://doi.org/10.4300/JGME-D-12-00156.1

Sweeney, M., Carpenter, L., Souza, S., Chaplin, H., Tung, H. Y., Caton, E., . . . Norton, S. (2021). The impact of COVID-19 lockdown on mental health and quality of life in patients with inflammatory arthritis. *Rheumatology*, *60*. https://doi.org/https://doi.org/10.1093/rheumatology/keab246.024

Sweeney, S. E., & Firestein, G. S. (2004). Rheumatoid arthritis: regulation of synovial inflammation. *Int J Biochem Cell Biol*, *36*(3), 372-378. https://doi.org/10.1016/s1357-2725(03)00259-0

Symmons, D. P. (2005). Looking back: rheumatoid arthritis--aetiology, occurrence and mortality. *Rheumatology (Oxford)*, *44 Suppl 4*, iv14-iv17. https://doi.org/10.1093/rheumatology/kei055

Tamiya, N., Araki, S., Ohi, G., Inagaki, K., Urano, N., Hirano, W., & Daltroy, L. H. (2002). Assessment of pain, depression, and anxiety by visual analogue scale in Japanese women with rheumatoid arthritis. *Scand J Caring Sci*, *16*(2), 137-141. https://doi.org/10.1046/j.1471-6712.2002.00067.x

Tennen, H., Affleck, G., & Zautra, A. (2006). Depression history and coping with chronic pain: A daily process analysis. *Health Psychology*, *25*(3), 370-379. https://doi.org/http://dx.doi.org/10.1037/0278-6133.25.3.370

Teo, A. R., Chan, B. K., Saha, S., & Nicolaidis, C. (2019). Frequency of social contact in-person vs. on Facebook: An examination of associations with psychiatric symptoms in military veterans. *J Affect Disord*, *243*, 375-380. https://doi.org/10.1016/j.jad.2018.09.043

Teo, A. R., Choi, H., Andrea, S. B., Valenstein, M., Newsom, J. T., Dobscha, S. K., & Zivin, K. (2015). Does Mode of Contact with Different Types of Social Relationships Predict Depression in Older Adults? Evidence from a Nationally Representative Survey. *J Am Geriatr Soc*, *63*(10), 2014-2022. https://doi.org/10.1111/jgs.13667

Thota, D. (2020). Evaluating the Relationship Between Fitbit Sleep Data and Self-Reported Mood, Sleep, and Environmental Contextual Factors in Healthy Adults: Pilot Observational Cohort Study. *JMIR Form Res*, *4*(9), e18086. https://doi.org/10.2196/18086

Tierney, M., Fraser, A., & Kennedy, N. (2012). Physical activity in rheumatoid arthritis: a systematic review. *J Phys Act Health*, *9*(7), 1036-1048. https://doi.org/10.1123/jpah.9.7.1036

Tiller, J. W. (2013). Depression and anxiety. *Med J Aust*, *199*(S6), S28-31. https://doi.org/10.5694/mja12.10628

Tobon, G. J., Youinou, P., & Saraux, A. (2010). The environment, geo-epidemiology, and autoimmune disease: Rheumatoid arthritis. *J Autoimmun*, *35*(1), 10-14. https://doi.org/10.1016/j.jaut.2009.12.009

Tolentino, J. C., & Schmidt, S. L. (2018). DSM-5 Criteria and Depression Severity: Implications for Clinical Practice. *Front Psychiatry*, *9*, 450. https://doi.org/10.3389/fpsyt.2018.00450

Tolin, D. (2010). Is cognitive–behavioral therapy more effective than other therapies?: A meta-analytic review. *Clinical Psychology Review*, *30*(6), 710-720.

Tommasi, M., Toro, F., Arno, S., Carrieri, A., Conte, M. M., Devastato, M. D., . . . Saggino, A. (2020). Physical and Psychological Impact of the Phase One Lockdown for COVID-19 on Italians. *Front Psychol*, *11*, 563722. https://doi.org/10.3389/fpsyg.2020.563722

Toonen, E. J., Barrera, P., Fransen, J., de Brouwer, A. P., Eijsbouts, A. M., Miossec, P., . . . Coenen, M. J. (2012). Meta-analysis identified the TNFA -308G > A promoter polymorphism as a risk factor for disease severity in patients with rheumatoid arthritis. *Arthritis Res Ther*, *14*(6), R264. https://doi.org/10.1186/ar4110

Topp, C. W., Ostergaard, S. D., Sondergaard, S., & Bech, P. (2015). The WHO-5 Well-Being Index: a systematic review of the literature. *Psychother Psychosom*, *84*(3), 167-176. https://doi.org/10.1159/000376585

Treharne, G. J., Kitas, G. D., Lyons, A. C., & Booth, D. A. (2005). Well-being in rheumatoid arthritis: the effects of disease duration and psychosocial factors. *J Health Psychol*, *10*(3), 457-474. https://doi.org/10.1177/1359105305051416

Tronick, E., & Reck, C. (2009). Infants of depressed mothers. *Harv Rev Psychiatry*, *17*(2), 147-156. https://doi.org/10.1080/10673220902899714

Tung, H. Y., Galloway, J., Matcham, F., Hotopf, M., & Norton, S. (2021). High-frequency follow-up studies in musculoskeletal disorders: a scoping review. *Rheumatology (Oxford)*, *60*(1), 48-59. https://doi.org/10.1093/rheumatology/keaa487

Turesson, C., O'Fallon, W. M., Crowson, C. S., Gabriel, S. E., & Matteson, E. L. (2003). Extra-articular disease manifestations in rheumatoid arthritis: incidence trends and risk factors over 46 years. *Ann Rheum Dis*, *62*(8), 722-727. https://doi.org/10.1136/ard.62.8.722

Uguz, F., Akman, C., Kucuksarac, S., & Tufekci, O. (2009). Anti-tumor necrosis factor-alpha therapy is associated with less frequent mood and anxiety disorders in patients with rheumatoid arthritis. *Psychiatry Clin Neurosci*, *63*(1), 50-55. https://doi.org/10.1111/j.1440-1819.2008.01905.x

Uhlig, T., Kvien, T. K., Glennas, A., Smedstad, L. M., & Forre, O. (1998). The incidence and severity of rheumatoid arthritis, results from a county register in Oslo, Norway. *J Rheumatol*, *25*(6), 1078-1084.

Uhlig, T., Moe, R. H., & Kvien, T. K. (2014). The burden of disease in rheumatoid arthritis. *Pharmacoeconomics*, *32*(9), 841-851. https://doi.org/10.1007/s40273-014-0174-6

Ulus, Y., Akyol, Y., Tander, B., Durmus, D., Bilgici, A., & Kuru, O. (2011). Sleep quality in fibromyalgia and rheumatoid arthritis: associations with pain, fatigue, depression, and disease activity. *Clin Exp Rheumatol*, *29*(6 Suppl 69), S92-96.

Vallerand, I. A., Lewinson, R. T., Frolkis, A. D., Lowerison, M. W., Kaplan, G. G., Swain, M. G., . . . Barnabe, C. (2018). Depression as a risk factor for the development of rheumatoid arthritis: a population-based cohort study. *RMD Open*, *4*(2), e000670. https://doi.org/10.1136/rmdopen-2018-000670

Vallerand, I. A., Patten, S. B., & Barnabe, C. (2019). Depression and the risk of rheumatoid arthritis. *Curr Opin Rheumatol*, *31*(3), 279-284. https://doi.org/10.1097/BOR.0000000000000597

van de Sande, M. G., de Hair, M. J., van der Leij, C., & Klarenbeek, P. L. (2011). Different stages of rheumatoid arthritis: features of the synovium in the preclinical phase. *Annals of the Rheumatic Diseases*, *70*(5), 772-777.

Van de Velde, S., Bracke, P., & Levecque, K. (2010). Gender differences in depression in 23 European countries. Cross-national variation in the gender gap in depression. *Soc Sci Med*, *71*(2), 305-313. https://doi.org/10.1016/j.socscimed.2010.03.035

van den Berg-Emons, R. J., Schasfoort, F. C., de Vos, L. A., Bussmann, J. B., & Stam, H. J. (2007). Impact of chronic pain on everyday physical activity [Empirical Study; Quantitative Study]. *European Journal of Pain*, *11*(5), 587-593. https://doi.org/http://dx.doi.org/10.1016/j.ejpain.2006.09.003

van den Hoek, J., Boshuizen, H. C., Roorda, L. D., Tijhuis, G. J., Nurmohamed, M. T., Dekker, J., & van den Bos, G. A. (2016). Association of Somatic Comorbidities and Comorbid Depression With Mortality in Patients With Rheumatoid Arthritis: A 14-Year Prospective Cohort Study. *Arthritis Care Res (Hoboken)*, *68*(8), 1055-1060. https://doi.org/10.1002/acr.22812

van der Heijde, D. M., van 't Hof, M. A., van Riel, P. L., Theunisse, L. A., Lubberts, E. W., van Leeuwen, M. A., . . . van de Putte, L. B. (1990). Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score. *Ann Rheum Dis*, *49*(11), 916-920.

van der Helm-van Mil, A. H., Wesoly, J. Z., & Huizinga, T. W. (2005). Understanding the genetic contribution to rheumatoid arthritis. *Curr Opin Rheumatol*, *17*(3), 299-304. https://doi.org/10.1097/01.bor.0000160780.13012.be

Van Loey, N. E., Klein-Konig, I., de Jong, A. E. E., Hofland, H. W. C., Vandermeulen, E., & Engelhard, I. M. (2018). Catastrophizing, pain and traumatic stress symptoms following burns: A prospective study. *Eur J Pain*, *22*(6), 1151-1159. https://doi.org/10.1002/ejp.1203

van Middendorp, H., & Evers, A. W. (2016). The role of psychological factors in inflammatory rheumatic diseases: From burden to tailored treatment. *Best Pract Res Clin Rheumatol*, *30*(5), 932-945. https://doi.org/10.1016/j.berh.2016.10.012

van Riel, P. L. (2014). The development of the disease activity score (DAS) and the disease activity score using 28 joint counts (DAS28). *Clin Exp Rheumatol*, *32*(5 Suppl 85), S-65-74.

van Steenbergen, H. W., Tsonaka, R., Huizinga, T. W., Boonen, A., & van der Helm-van Mil, A. H. (2015). Fatigue in rheumatoid arthritis; a persistent problem: a large longitudinal study. *RMD Open*, *1*(1), e000041. https://doi.org/10.1136/rmdopen-2014-000041

van Zanten, J., Fenton, S. A. M., Brady, S., Metsios, G. S., Duda, J. L., & Kitas, G. D. (2020). Mental Health and Psychological Wellbeing in Rheumatoid Arthritis during COVID-19 - Can Physical Activity Help? *Mediterr J Rheumatol*, *31*(Suppl 2), 284-287. https://doi.org/10.31138/mjr.31.3.284

Verhoeven, F., Tordi, N., Prati, C., Demougeot, C., Mougin, F., & Wendling, D. (2016). Physical activity in patients with rheumatoid arthritis. *Joint Bone Spine*, *83*(3), 265-270. https://doi.org/10.1016/j.jbspin.2015.10.002

Verma, A., Rajput, R., Verma, S., Balania, V. K. B., & Jangra, B. (2020). Impact of lockdown in COVID 19 on glycemic control in patients with type 1 Diabetes Mellitus. *Diabetes Metab Syndr*, *14*(5), 1213-1216. https://doi.org/10.1016/j.dsx.2020.07.016

Vollmayr, B., & Gass, P. (2013). Learned helplessness: unique features and translational value of a cognitive depression model. *Cell Tissue Res*, *354*(1), 171-178. https://doi.org/10.1007/s00441-013-1654-2

von Baeyer, C. L. (2009). Numerical rating scale for self-report of pain intensity in children and adolescents: recent progress and further questions. *Eur J Pain*, *13*(10), 1005-1007. https://doi.org/10.1016/j.ejpain.2009.08.006

von Baeyer, C. L., Spagrud, L. J., McCormick, J. C., Choo, E., Neville, K., & Connelly, M. A. (2009). Three new datasets supporting use of the Numerical Rating Scale (NRS-11) for children's self-reports of pain intensity. *Pain*, *143*(3), 223-227. https://doi.org/10.1016/j.pain.2009.03.002

Vriezekolk, J. E., van Lankveld, W. G., Geenen, R., & van den Ende, C. H. (2011). Longitudinal association between coping and psychological distress in rheumatoid arthritis: a systematic review. *Ann Rheum Dis*, *70*(7), 1243-1250. https://doi.org/10.1136/ard.2010.143271

Vuori, I. M., Lavie, C. J., & Blair, S. N. (2013). Physical activity promotion in the health care system. *Mayo Clin Proc*, *88*(12), 1446-1461. https://doi.org/10.1016/j.mayocp.2013.08.020

Walsh, D. A., & McWilliams, D. F. (2012). Pain in rheumatoid arthritis. *Curr Pain Headache Rep*, *16*(6), 509-517. https://doi.org/10.1007/s11916-012-0303-x

Walsh, D. A., & McWilliams, D. F. (2014). Mechanisms, impact and management of pain in rheumatoid arthritis. *Nat Rev Rheumatol*, *10*(10), 581-592. https://doi.org/10.1038/nrrheum.2014.64

Wang, Z., Huang, M., Yu, B., Huang, Y., Zheng, S., Yang, X., & Ning, H. (2021). Comparison of the efficacy and safety indicators of DMARDs for rheumatoid arthritis: A network meta-analysis. *Medicine (Baltimore)*, *100*(29), e26524. https://doi.org/10.1097/MD.0000000000026524

Waters, R. P., Rivalan, M., Bangasser, D. A., Deussing, J. M., Ising, M., Wood, S. K., . . . Summers, C. H. (2015). Evidence for the role of corticotropin-releasing factor in major depressive disorder. *Neurosci Biobehav Rev*, *58*, 63-78. https://doi.org/10.1016/j.neubiorev.2015.07.011

Watson, D., Clark, L. A., & Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: the PANAS scales. *J Pers Soc Psychol*, *54*(6), 1063-1070. https://doi.org/10.1037//0022-3514.54.6.1063

Watson, D., Clark, L. A., Weber, K., Assenheimer, J. S., Strauss, M. E., & McCormick, R. A. (1995). Testing a tripartite model: II. Exploring the symptom structure of anxiety and depression in student, adult, and patient samples. *J Abnorm Psychol*, *104*(1), 15-25.

Watson, D., & Tellegen, A. (1985). Toward a consensual structure of mood. *Psychol Bull*, *98*(2), 219-235. https://doi.org/10.1037//0033-2909.98.2.219

Weatherall, J., Paprocki, Y., Meyer, T. M., Kudel, I., & Witt, E. A. (2018). Sleep Tracking and Exercise in Patients With Type 2 Diabetes Mellitus (Step-D): Pilot Study to Determine

Correlations Between Fitbit Data and Patient-Reported Outcomes. *JMIR Mhealth Uhealth*, *6*(6), e131. https://doi.org/10.2196/mhealth.8122

Wells, G., Becker, J. C., Teng, J., Dougados, M., Schiff, M., Smolen, J., . . . van Riel, P. L. (2009). Validation of the 28-joint Disease Activity Score (DAS28) and European League Against Rheumatism response criteria based on C-reactive protein against disease progression in patients with rheumatoid arthritis, and comparison with the DAS28 based on erythrocyte sedimentation rate. *Ann Rheum Dis*, *68*(6), 954-960. https://doi.org/10.1136/ard.2007.084459

Welsing, P. M., Landewe, R. B., van Riel, P. L., Boers, M., van Gestel, A. M., van der Linden, S., . . . van der Heijde, D. M. (2004). The relationship between disease activity and radiologic progression in patients with rheumatoid arthritis: a longitudinal analysis. *Arthritis Rheum*, *50*(7), 2082-2093. https://doi.org/10.1002/art.20350

Wen, C. K. F., Schneider, S., Stone, A. A., & Spruijt-Metz, D. (2017). Compliance With Mobile Ecological Momentary Assessment Protocols in Children and Adolescents: A Systematic Review and Meta-Analysis. *J Med Internet Res*, *19*(4), e132. https://doi.org/10.2196/jmir.6641

Westbrook, D., Kennerley, H., & Kirk, J. (2011). *An Introduction to Cognitive Behaviour Therapy: Skills And Applications*. SAGE.

Whibley, D., AlKandari, N., Kristensen, K., Barnish, M., Rzewuska, M., Druce, K. L., & Tang, N. K. Y. (2019). Sleep and Pain: A Systematic Review of Studies of Mediation. *Clin J Pain*, *35*(6), 544-558. https://doi.org/10.1097/AJP.0000000000000697

Whibley, D., Williams, D. A., Clauw, D. J., Sliwinski, M. J., & Kratz, A. L. (2022). Within-day rhythms of pain and cognitive function in people with and without fibromyalgia: synchronous or syncopated? *Pain*, *163*(3), 474-482. https://doi.org/10.1097/j.pain.0000000000002370

WHO. (2001). *International classification of functioning, disability and health : ICF* (W. H. Organization, Ed.)

WHO. (2005). *Preventing chronic diseases : a vital investment : WHO global report*.

WHO. (2020a). *Statement on the second meeting of the International Health Regulations (2005) Emergency Committee regarding the outbreak of novel coronavirus (2019-nCoV)*. WHO. https://www.who.int/news/item/30-01-2020-statement-on-the-second-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-(2019-ncov)

WHO. (2020b). *WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020*. World Health Organzation. https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020

Wichers, M., Peeters, F., Rutten, B. P., Jacobs, N., Derom, C., Thiery, E., . . . van Os, J. (2012). A time-lagged momentary assessment study on daily life physical activity and affect. *Health Psychol*, *31*(2), 135-144. https://doi.org/10.1037/a0025688

Williams, C. M., Maher, C. G., Hancock, M. J., McAuley, J. H., Lin, C. W., & Latimer, J. (2014). Recruitment rate for a clinical trial was associated with particular operational procedures and clinician characteristics. *J Clin Epidemiol*, *67*(2), 169-175. https://doi.org/10.1016/j.jclinepi.2013.08.007

Willner, P. (2017). The chronic mild stress (CMS) model of depression: History, evaluation and usage. *Neurobiol Stress*, *6*, 78-93. https://doi.org/10.1016/j.ynstr.2016.08.002

Wilson-Mendenhall, C. D., Barrett, L. F., & Barsalou, L. W. (2013). Neural evidence that human emotions share core affective properties. *Psychol Sci*, *24*(6), 947-956. https://doi.org/10.1177/0956797612464242

Wirz-Justice, A. (2008). Diurnal variation of depressive symptoms. *Dialogues Clin Neurosci*, *10*(3), 337-343.

Wolfe, F., Clauw, D. J., Fitzcharles, M. A., Goldenberg, D. L., Katz, R. S., Mease, P., . . . Yunus, M. B. (2010). The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care Res (Hoboken)*, *62*(5), 600-610. https://doi.org/10.1002/acr.20140

Wolfe, F., Michaud, K., Gefeller, O., & Choi, H. K. (2003). Predicting mortality in patients with rheumatoid arthritis. *Arthritis Rheum*, *48*(6), 1530-1542. https://doi.org/10.1002/art.11024

Wu, Z., & McGoogan, J. M. (2020). Asymptomatic and Pre-Symptomatic COVID-19 in China. *Infect Dis Poverty*, *9*(1), 72. https://doi.org/10.1186/s40249-020-00679-2

Yan, X. Y., Huang, S. M., Huang, C. Q., Wu, W. H., & Qin, Y. (2011). Marital status and risk for late life depression: a meta-analysis of the published literature. *J Int Med Res*, *39*(4), 1142-1154. https://doi.org/10.1177/147323001103900402

Yazici, Y., Pincus, T., Kautiainen, H., & Sokka, T. (2004). Morning stiffness in patients with early rheumatoid arthritis is associated more strongly with functional disability than with joint swelling and erythrocyte sedimentation rate. *J Rheumatol*, *31*(9), 1723-1726.

Yelin, E., & Wanke, L. A. (1999). An assessment of the annual and long-term direct costs of rheumatoid arthritis: the impact of poor function and functional decline. *Arthritis Rheum*, *42*(6), 1209-1218. https://doi.org/10.1002/1529-0131(199906)42:6<1209::AID-ANR18>3.0.CO;2-M

Yellen, S. B., Cella, D. F., Webster, K., Blendowski, C., & Kaplan, E. (1997). Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. *J Pain Symptom Manage*, *13*(2), 63-74. https://doi.org/10.1016/s0885-3924(96)00274-6

Yohn, C. N., Gergues, M. M., & Samuels, B. A. (2017). The role of 5-HT receptors in depression. *Mol Brain*, *10*(1), 28. https://doi.org/10.1186/s13041-017-0306-y

Young, A., & Koduri, G. (2007). Extra-articular manifestations and complications of rheumatoid arthritis. *Best Pract Res Clin Rheumatol*, *21*(5), 907-927. https://doi.org/10.1016/j.berh.2007.05.007

Zautra, A. J., Affleck, G. G., Davis, M. C., Tennen, H., & Fasman, R. (2007). Assessing the ebb and flow of daily life with an accent on the positive. In *Oxford handbook of methods in positive psychology* (pp. 487-500). Oxford University Press; US.

Zautra, A. J., Johnson, L. M., & Davis, M. C. (2005). Positive affect as a source of resilience for women in chronic pain. *J Consult Clin Psychol*, *73*(2), 212-220. https://doi.org/10.1037/0022-006X.73.2.212

Zhang, Z., Lion, A., Chary-Valckenaere, I., Loeuille, D., Rat, A. C., Paysant, J., & Perrin, P. P. (2015). Diurnal variation on balance control in patients with symptomatic knee osteoarthritis. *Arch Gerontol Geriatr*, *61*(1), 109-114. https://doi.org/10.1016/j.archger.2015.03.009

Ziarko, M., Mojs, E., Sikorska, D., & Samborski, W. (2020). Coping and Life Satisfaction: Mediating Role of Ego-Resiliency in Patients with Rheumatoid Arthritis. *Med Princ Pract*, *29*(2), 160-165. https://doi.org/10.1159/000503708

Zimmerman, M., Martinez, J. H., Young, D., Chelminski, I., & Dalrymple, K. (2013). Severity classification on the Hamilton Depression Rating Scale. *J Affect Disord*, *150*(2), 384-388. https://doi.org/10.1016/j.jad.2013.04.028

Zou, C., Denby, K. J., & Feng, J. (2009). Granger causality vs. dynamic Bayesian network inference: a comparative study. *BMC Bioinformatics*, *10*, 122. https://doi.org/10.1186/1471-2105-10-122

Zyrianova, Y., Kelly, B. D., Gallagher, C., McCarthy, C., Molloy, M. G., Sheehan, J., & Dinan, T. G. (2006). Depression and anxiety in rheumatoid arthritis: the role of perceived social support. *Ir J Med Sci*, *175*(2), 32-36. https://doi.org/10.1007/BF03167946

Öztaş Ayhan, H., & Işiksal, S. (2005). Memory recall errors in retrospective surveys: A reverse record check study. *Quality & Quantity*, *38*, 475-493. https://doi.org/https://doi.org/10.1007/s11135-005-2643-7

A. Appendix to Questionnaires in Methodology

Table A.1: FACIT-F Scale

Questions	Not at all	A little bit	Somewhat	Quite a bit	Very much
I feel fatigued	4	3	2	1	0
I feel weak all over	4	3	2	1	0
I feel listless (washed out)	4	3	2	1	0
I feel tired	4	3	2	1	0
I have trouble starting things because I am tired	4	3	2	1	0
I have trouble finishing things because I am tired	4	3	2	1	0
I have energy	0	1	2	3	4
I am able to do my usual activities	0	1	2	3	4
I need to sleep during the day	4	3	2	1	0
I am too tired to eat	4	3	2	1	0
I need help doing my usual activities	4	3	2	1	0
I am frustrated by being too tired to do the things I want to do	4	3	2	1	0
I have to limit my social activity because I am too tired	4	3	2	1	0

Table A.2: Scoring Criteria for PHQ9

PHQ-9	Over the last two weeks, how often have you been bothered by any of the problems?
Little interest or pleasure in doing things?	0) Not at all 1) Several Days 2) More than half the days 3) Nearly every day
Feeling down, depressed or hopeless?	0) Not at all 1) Several Days 2) More than half the days 3) Nearly every day
Trouble falling or staying asleep, or sleeping too much?	0) Not at all 1) Several Days 2) More than half the days 3) Nearly every day
Feeling tired or having little energy?	0) Not at all 1) Several Days 2) More than half the days 3) Nearly every day
Poor appetite or overeating?	0) Not at all 1) Several Days 2) More than half the days 3) Nearly every day
Feeling bad about yourself – or that you are a failure or have let yourself or your family down?	0) Not at all 1) Several Days 2) More than half the days 3) Nearly every day
Trouble concentrating on things, such as reading the newspaper or watching the television?	0) Not at all 1) Several Days 2) More than half the days 3) Nearly every day

Moving or speaking so slowly that other people could have noticed? Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual	0) Not at all 1) Several Days 2) More than half the days 3) Nearly every day
Thoughts that you would be better off dead, or of hurting yourself in some way?	0) Not at all 1) Several Days 2) More than half the days 3) Nearly every day

Table A.3: Scoring Criteria for GAD-7

GAD-7	Over the last two weeks, how often have you been bothered by any of the problems?
Feeling nervous, anxious, or on edge?	4) Not at all 5) Several Days 6) More than half the days 7) Nearly every day
Not being able to stop or control worrying?	4) Not at all 5) Several Days 6) More than half the days 7) Nearly every day
Worrying too much about different things?	4) Not at all 5) Several Days 6) More than half the days 7) Nearly every day
Trouble relaxing?	4) Not at all 5) Several Days 6) More than half the days 7) Nearly every day

Being so restless that it is hard to sit still?	4) Not at all 5) Several Days 6) More than half the days 7) Nearly every day
Becoming easily annoyed or irritable?	4) Not at all 5) Several Days 6) More than half the days 7) Nearly every day
Feeling afraid as if something awful might happen?	4) Not at all 5) Several Days 6) More than half the days 7) Nearly every day

Table A.4: Scoring Criteria for HAQ-DI

Questions	Without any difficulty (0)	With some difficulty (1)	With much difficulty (2)	Unable to do (3)
Dressing & Grooming				
Dress yourself, including tying shoelaces and doing buttons?				
Shampoo your hair?				
Arising				
Stand up from an armless chair?				
Get in and out of bed?				
Eating				
Cut up your own meat?				
Lift a full cup or glass to your mouth?				

Open a new carton of milk (or soap powder)?				
Walking				
Walk outdoors on flat ground?				
Climb up five steps?				
Hygiene				
Wash and dry your entire body?				
Take a bath?				
Get on and off the toilet?				
Reach				
Reach and get down a 5 lb object (e.g. a bag of potatoes) from just above your head?				
Bend down to pick up clothing off the floor?				
Grip				
Open car doors?				
Open jars which have been previously opened?				
Turn taps on and off?				
Activities				
Run errands and shop?				
Get in and out of a car?				
Do chores such as vacuuming, housework or light gardening?				

B. Appendix to TITRATE-US & IMPARTS Studies

Table B.1: Short codes for each symptom node

Symptom	Short code
Feeling nervous, anxious or on edge	Anxious
Not being able to stop or control worrying	ControlWorry
Worrying too much about different things	MuchWorry
Trouble relaxing	TroubleRelaxing
Being so restless that it is hard to sit still	Restless
Becoming easily annoyed or irritable	Annoyed
Feeling afraid as if something awful might happen	Afraid
Little interest or pleasure in doing things	Anhedonia
Feeling down, depressed, or hopeless	Dysphoria
Trouble falling or staying asleep, or sleeping too much	Sleep
Feeling tired or having little energy	Tired
Poor appetite or overeating	Appetite
Feeling bad about yourself — or that you are a failure or have let yourself or your family down	Failure

Trouble concentrating on things, such as reading the newspaper or watching television	Concentration
Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	Slow
Thoughts that you would be better off dead or of hurting yourself in some way	Ideation
Functional Assessment of Chronic Illness Therapy (FACIT)	Fatigue
Widespread Pain Index	WPI
Health Assessment Questionnaire	HAQ
28 tender joints score	TenderJnts
PainVAS	PnVAS
28 swollen joints score	SwollenJnts
Total Power Doppler	PDUS
Erythrocyte Sedimentation Rate	ESR
C-Reactive Protein	CRP

Table B.2: Centrality Scores for Simplified TITRATE

Variable	Degree Centrality	Closeness Centrality	Betweenness Centrality	Expected Influence
Total PD	2.3	0.015	30	0.52
Swollen Joints	1.7	0.016	8	1.2
Tender joints	3.3	0.021	24	3.3
ESR	1.4	0.011	0	0.92
CRP	1.95	0.011	0	1.58
PainVAS	2.6	0.017	0	2.5
Widespread Pain Index	3.5	0.022	26	2.8
HAQ	3.3	0.019	2	2.9
GAD1	3.9	0.02	4	3.6
GAD2	3.8	0.018	0	3.1
PHQ1	3.8	0.018	0	3.5
PHQ2	4.2	0.02	0	4.0
Fatigue	3.1	0.017	0	2.5

Table B.3: Centrality Scores for Expanded TITRATE

Variable	Degree Centrality	Closeness Centrality	Betweenness Centrality	Expected Influence
Total PD	4.0	0.0076	52	-1.2
Swollen Joints	2.5	0.0075	8	0.83
Tender Joints	6.5	0.011	12	6.5
ESR	2.3	0.0057	0	0.12
CRP	2.8	0.0055	0	1.24
PainVAS	5.4	0.0090	0	5.3
WPI	7.7	0.012	10	7.1
Fatigue	7.6	0.011	0	7.0
HAQ	7.0	0.011	4	6.6
GAD1	11	0.014	14	10.3
GAD2	10	0.013	0	9.4
GAD3	10	0.013	0	9.0
GAD4	11	0.014	0	9.9
GAD5	9.8	0.014	6	9.2
GAD6	9.5	0.013	20	8.8
GAD7	9.6	0.013	24	8.6
PHQ1	10	0.014	0	9.9
PHQ2	11	0.015	4	10.9
PHQ3	8.0	0.012	0	7.5
PHQ4	9.1	0.013	0	8.4
PHQ5	8.5	0.012	0	8.4
PHQ6	10	0.014	6	10.1
PHQ7	9.3	0.014	352	8.2
PHQ8	8.1	0.012	0	8.0
PHQ9	6.7	0.010	0	6.2

Table B.D: Bridge Centrality Scores for Expanded TITRATE

Variable	Bridge Strength Centrality
Total PD	0.94
Swollen Joints	0.76
Tender joints	1.8
ESR	0.41
CRP	0.68
PainVAS	1.2
Widespread Pain Index	1.7
HAQ	1.6
GAD1	2.0
GAD2	1.8
PHQ1	1.9
PHQ2	2.1
Fatigue	2.1

C. Appendix for IA-COVID Study

EMQ Questionnaire for 9am, 11am, 1pm, 3pm, 5pm measurement times.

Please answer the following 4 questions thinking about what you were doing for the past hour.

Q1. What were you doing? Please tick all undertaken for 15 minutes or more.

- ☐ Resting or sleeping (1)
- ☐ Working or studying (2)
- ☐ Household activities (housework, gardening, cooking, etc) (3)
- ☐ Leisure Activities (watching TV, reading, meditation, etc) (4)
- ☐ Exercise and sports (5)
- ☐ Caring activities (children or adults) (6)
- ☐ Socialising (in person, on the phone or online) (7)
- ☐ Eating and drinking (8)
- ☐ Personal care (showering, etc) (9)
- ☐ Shopping (10)
- ☐ Travelling (11)
- ☐ Voluntary activities (12)

Q2 Who were you with?

- [ ] By myself (1)
- [ ] Household members (2)
- [ ] Family (not in your household) (3)
- [ ] Friends (not in your household) (4)
- [ ] Neighbours (5)
- [ ] Colleagues (6)
- [ ] Others (7)

Q3 Were you with them virtually (inclusive of emailing or texting) or in person?

- [ ] Virtually (1)
- [ ] In person (2)
- [ ] Mixed (3)
- [ ] Not applicable (8)

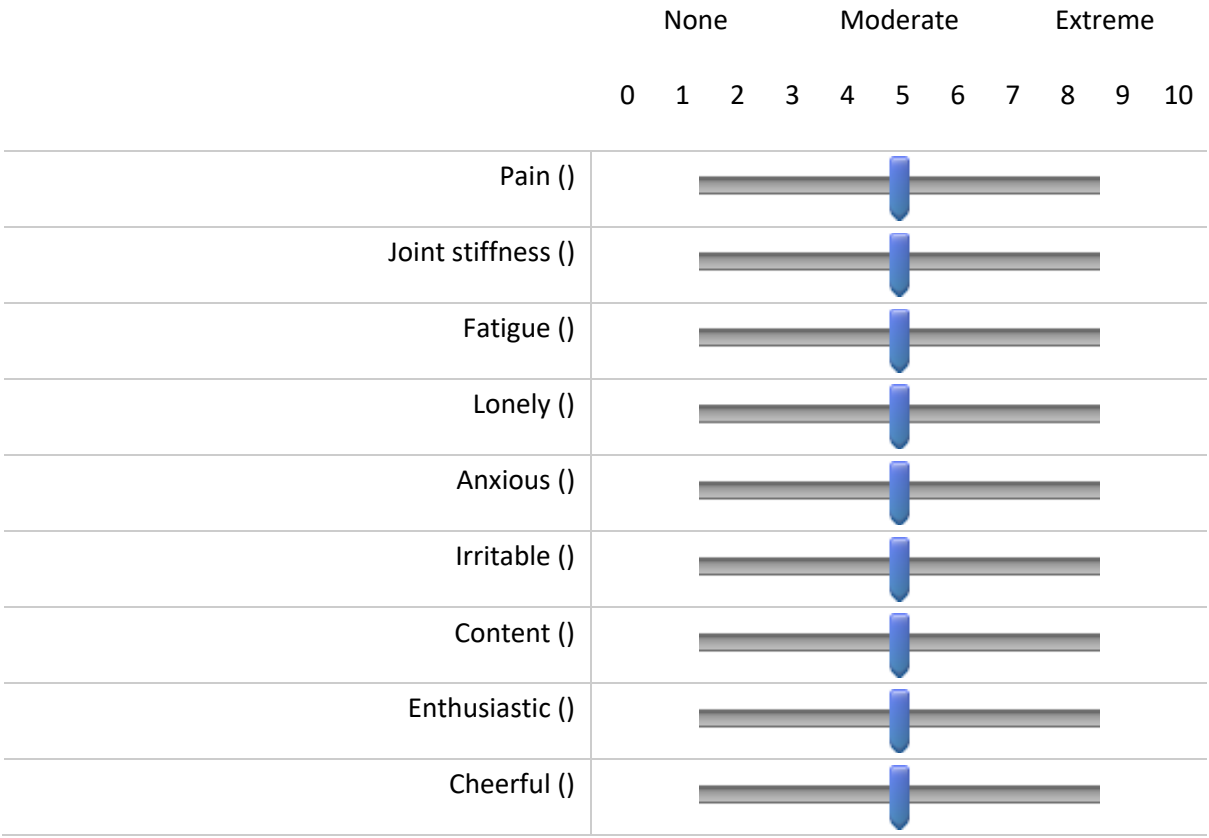
Q4 Were you mainly at home? (mainly defined as more than 30 minutes of the past hour)

- ○ At home (1)
- ○ Away from home (2)

Q5 What was your highest level of physical activity (for at least 10 minutes) ?

- ○ Resting (e.g. napping) (1)
- ○ Sitting (e.g. watching tv, working) (2)
- ○ Standing (e.g. cooking) (3)
- ○ Walking slowly (e.g. doing housework, gardening, yoga) (4)
- ○ Walking briskly (e.g. fast walk as a form of exercise outside, cycling) (5)
- ○ Moderate intensity exercise (e.g. carrying light loads, jogging or social tennis) (6)
- ○ Vigorous or high intensity exercise (e.g. Swimming, HIIT (high intensity interval training) workouts, sprints) (7)

Please rate how much you felt each of the following in the last hour. Responses are all 0-10 scale, with 0 = none and 10 = Extreme.



Daily questionnaire at 8pm measurement period

Please answer the following 4 questions thinking about what you were doing for the past hour.

Q1 What were you doing? Please tick all undertaken for 15 minutes or more.

- ☐ Resting or sleeping (1)
- ☐ Working or studying (2)
- ☐ Household activities (housework, gardening, cooking, etc) (3)
- ☐ Leisure activities (watching TV, reading, meditation, etc) (4)
- ☐ Exercise and sports (5)
- ☐ Caring activities (children or adults) (6)
- ☐ Socialising (in person, on the phone or online) (7)
- ☐ Eating and drinking (8)
- ☐ Personal care (showering, etc) (9)
- ☐ Shopping (10)
- ☐ Travelling (11)
- ☐ Voluntary activities (12)

Q2 Who were you with?

- [ ] By myself (1)
- [ ] Household members (2)
- [ ] Family (not in your household) (3)
- [ ] Friends (not in your household) (4)
- [ ] Neighbours (5)
- [ ] Colleagues (6)
- [ ] Others (7)

Q3 Were you with them virtually (inclusive of emailing or texting) or in person?

- [ ] Virtually (1)
- [ ] In person (2)
- [ ] Mixed (3)
- [ ] Not applicable (8)

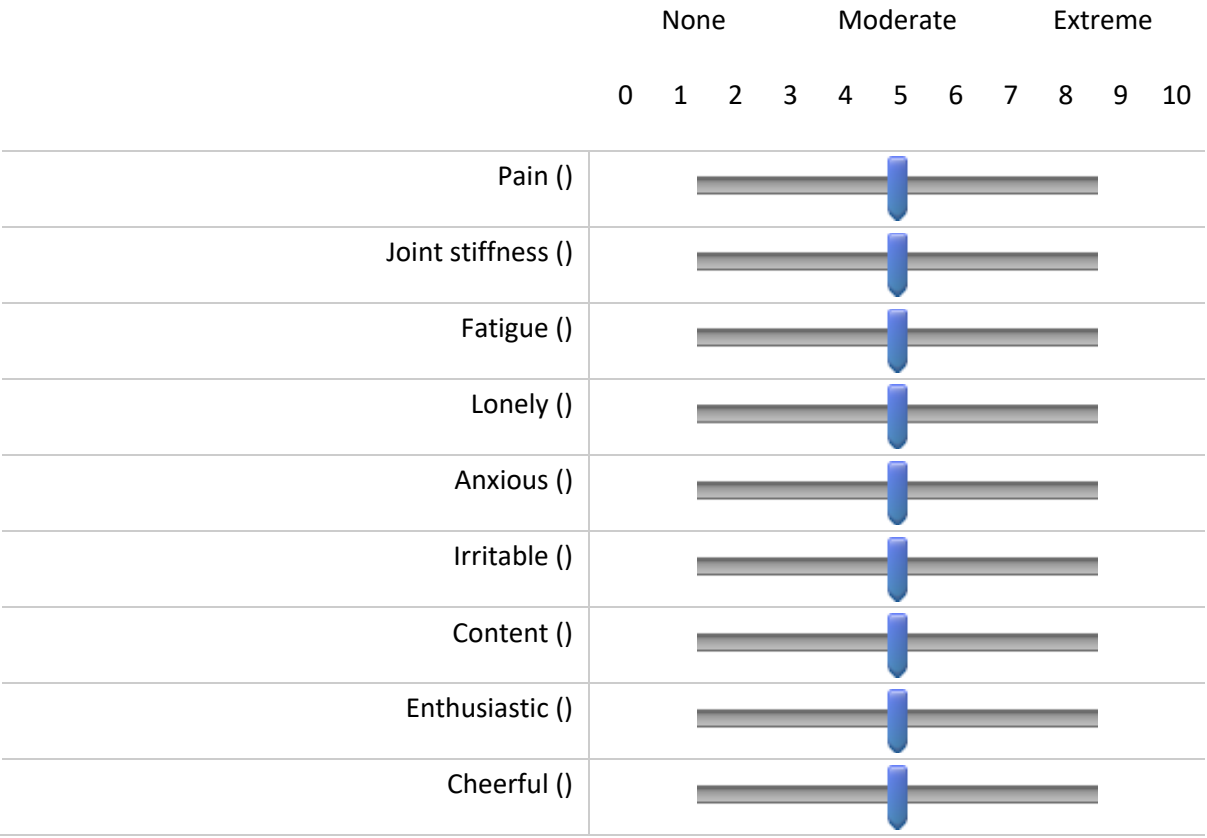
Q4 Were you mainly at home? (mainly defined as more than 30 minutes of the past hour)

- ○ At home (1)
- ○ Away from home (2)

Q5 What was your highest level of physical activity?

- ○ Resting (e.g. napping) (1)
- ○ Sitting (e.g. watching tv, working) (2)
- ○ Standing (e.g. cooking) (3)
- ○ Walking slowly (e.g. doing housework, gardening, yoga) (4)
- ○ Walking briskly (e.g. fast walk as a form of exercise outside, cycling) (5)
- ○ Moderate intensity exercise (e.g. carrying light loads, jogging or social tennis) (6)
- ○ Vigorous or high intensity exercise (e.g. swimming, HIIT (high intensity interval training) workouts, sprints) (7)

Q6 Please rate how much you felt each of the following in the last hour. Responses are all 0-10 scale, with 0 = none and 10 = Extreme.



For the next section, there will be questions about your daily well-being, COVID19 symptoms and sleep quality.

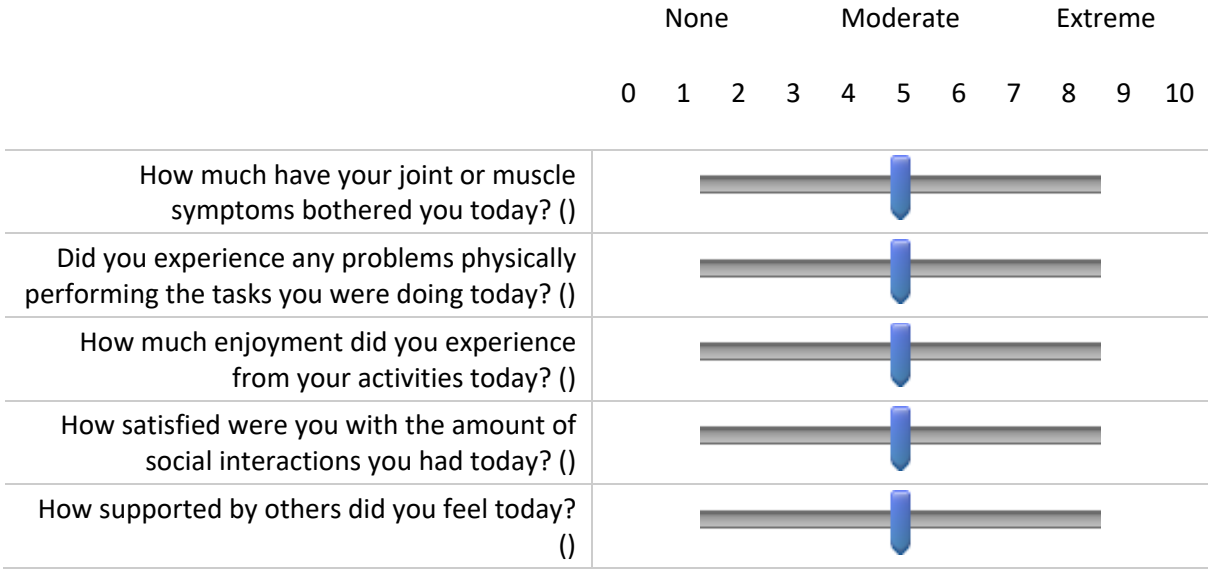
Q7 Do you suspect you might currently have COVID19?

- ○ Yes (1)
- ○ No (2)

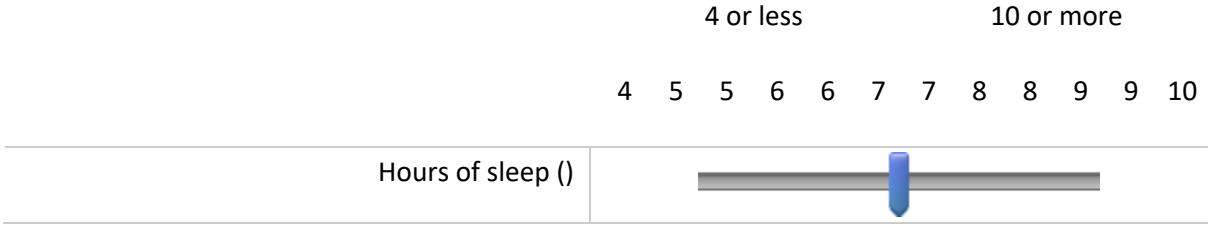
Q8 Irrespective of whether you might have COVID19, have you experienced any symptoms consistent with this condition today? (You may choose more than one symptom)

- ☐ Fever/high temperature (1)
- ☐ Difficulty breathing (2)
- ☐ Coughing (3)
- ☐ Headache (4)
- ☐ Body ache (5)
- ☐ Sore throat (6)
- ☐ Fatigue (7)
- ☐ Loss of taste or smell (8)
- ☐ No symptom at all (9)

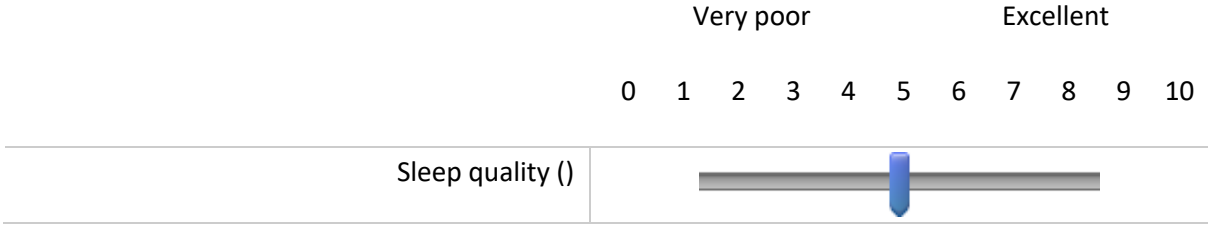
Q9 The following scale will be regarding your well-being today. The response is from a score of 0 to 10, with 0 being none and 10 being extreme



Q10 How many hours did you sleep last night? (4 indicates 4 or less hours and 10 indicates 10 or more hours)



Q11 What was the quality of your sleep last night?



Q12 Did you nap during the day?

- ○ Yes (1)
- ○ No (2)

Figure C.1: Line Plot of symptoms for four participants chosen for network modelling.
PID28358 = Stable low severity PID 16110 = Stable high severity
PID79729 = Flare in symptoms PID 82588 = Fluctuant symptoms

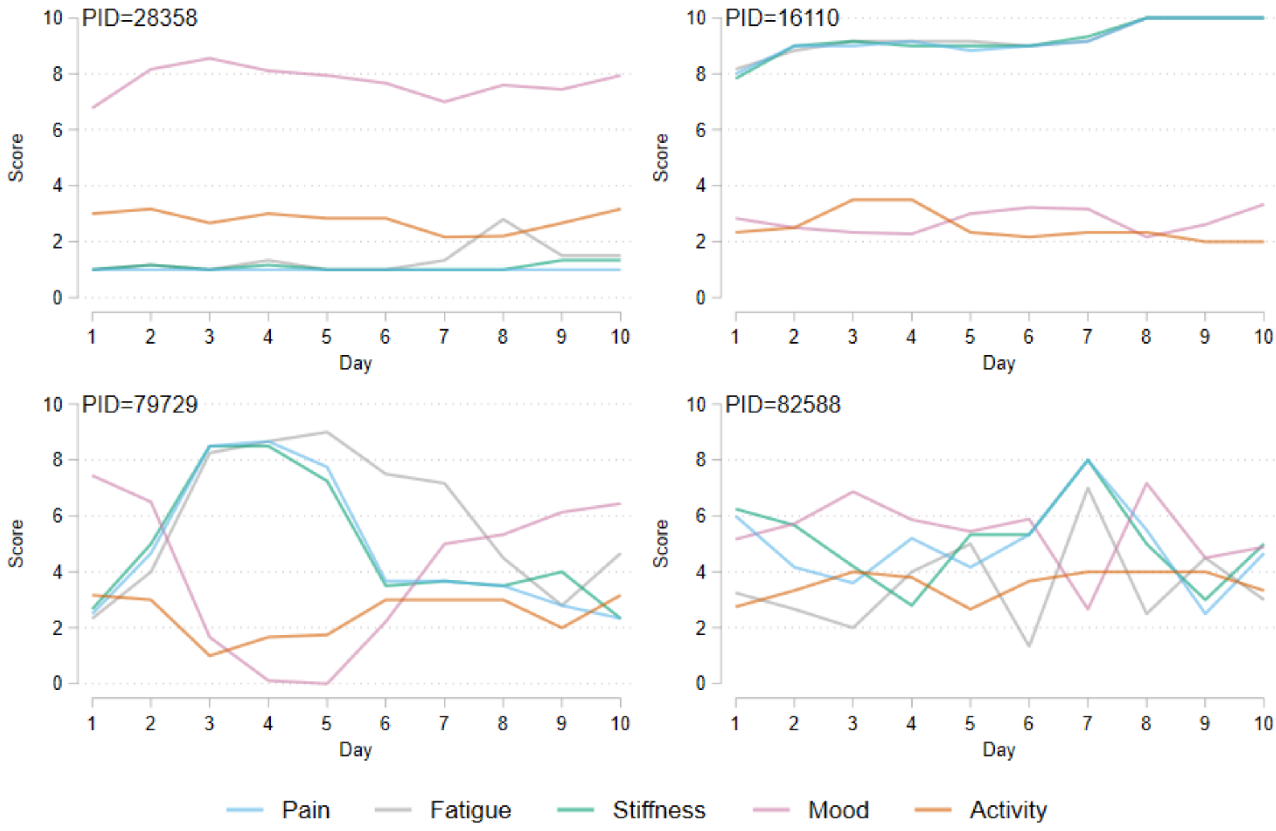


Table C.1: Autocorrelation of positive affect and its lagged components in Chapter 6

	L1 paffect	L2 paffect	L3 paffect	L4 paffect	L5 paffect	L6 paffect
L1 paffect	1					
L2 paffect	0.79	1				
L3 paffect	0.76	0.78	1			
L4 paffect	0.74	0.76	0.79	1		
L5 paffect	0.72	0.72	0.75	0.80	1	
L6 paffect	0.70	0.72	0.73	0.77	0.80	1

Table C.2: Autocorrelation of negative affect and its lagged components in Chapter 6

	L1 naffect	L2 naffect	L3 naffect	L4 naffect	L5 naffect	L6 naffect
L1 naffect	1					
L2 naffect	0.72	1				
L3 naffect	0.64	0.68	1			
L4 naffect	0.61	0.62	0.67	1		
L5 naffect	0.56	0.56	0.60	0.68	1	
L6 pnffect	0.58	0.59	0.60	0.63	0.69	1

Table C.3: Autocorrelation of physical symptoms and its lagged components in Chapter 6

	L1 physymp	L2 physymp	L3 physymp	L4 physymp	L5 physymp	L6 physymp
L1 physymp	1					
L2 physymp	0.90	1				
L3 physymp	0.88	0.90	1			
physymp	0.87	0.88	0.90	1		
L5 physymp	0.87	0.86	0.89	0.90	1	
L6 physymp	0.87	0.87	0.87	0.89	0.91	1

Table C.4: Autoregressive mixed effects dynamic modelling for physical symptom in Chapter 6

Physical Symptom	Coefficient	p-value	95% Conf. Interval
L1 negative affect	0.34	0.020	0.0053, 0.062
L1 positive affect	-0.13	0.59	-0.062, 0.035
L1 physical activity	0.0017	0.88	-0.021, 0.024
L1 physical symptom	-0.10	0.001	-0.16, -0.045

Table C.5: Autoregressive mixed effects dynamic modelling for physical activity in Chapter 6

Physical Activity	Coefficient	p-value	95% Conf. Interval
L1 negative affect	-0.036	0.36	-0.11, 0.041
L1 positive affect	-0.17	0.006	-0.30, -0.050
L1 physical activity	0.013	0.72	-0.056, 0.081
L1 physical symptom	0.030	0.73	-0.14, 0.20

Table C.6: Autoregressive mixed effects dynamic modelling for negative affect in Chapter 6

Negative Affect	Coefficient	p-value	95% Conf. Interval
L1 negative affect	0.47	0.001	0.37, 0.57
L1 positive affect	0.14	0.001	0.064, 0.22
L1 physical activity	-0.36	0.093	-0.077, 0.0060
L1 physical symptom	0.0078	0.89	-0.097, 0.0090

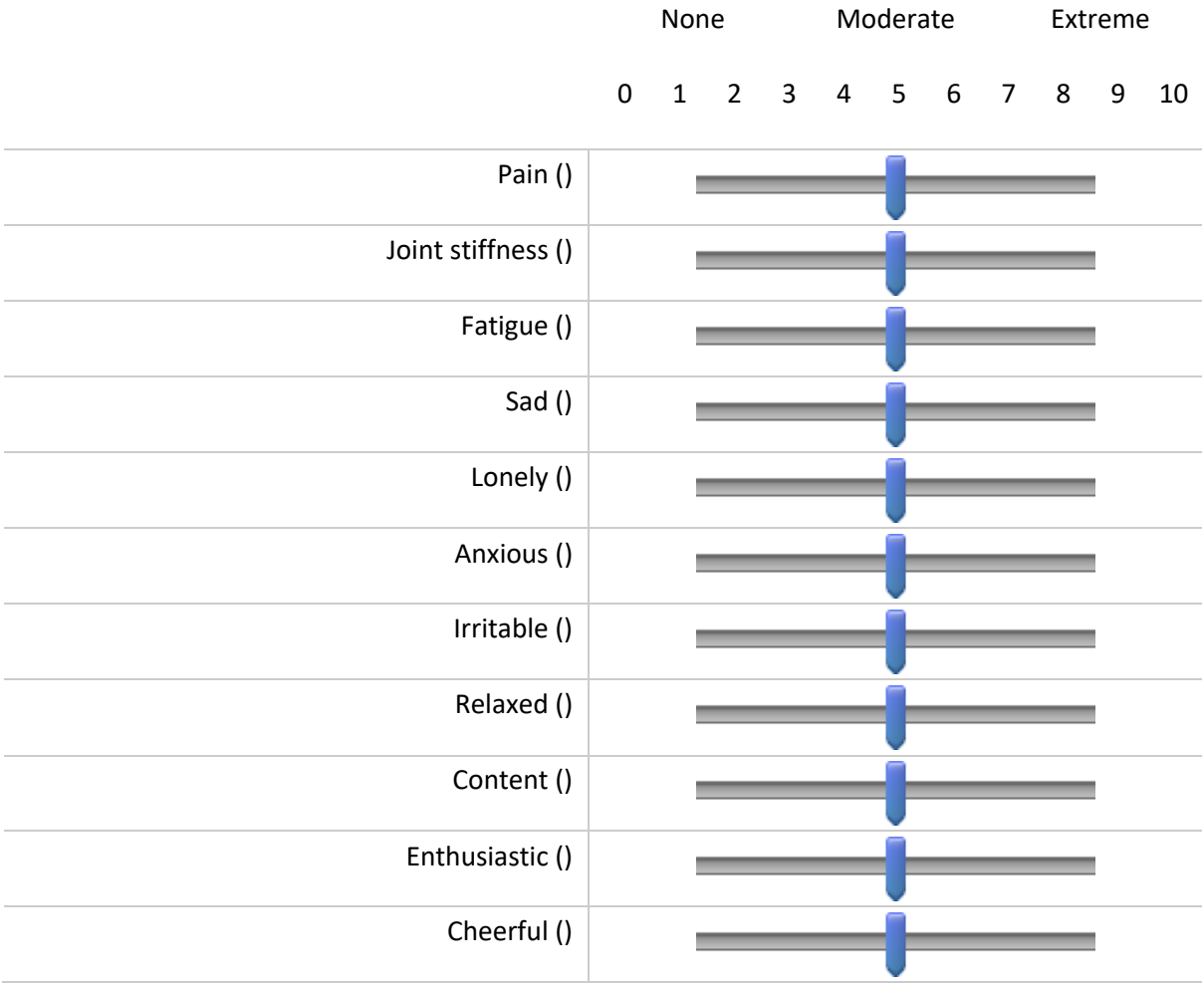
Table C.7: Autoregressive mixed effects dynamic modelling for positive affect in Chapter 6

Positive Affect	Coefficient	p-value	95% Conf. Interval
L1 negative affect	0.14	0.001	0.82, 0.20
L1 positive affect	0.61	0.001	0.51, 0.71
L1 physical activity	-0.068	0.001	-0.096, -0.040
L1 physical symptom	0.15	0.008	0.041, 0.27

D. Appendix to APPro Study

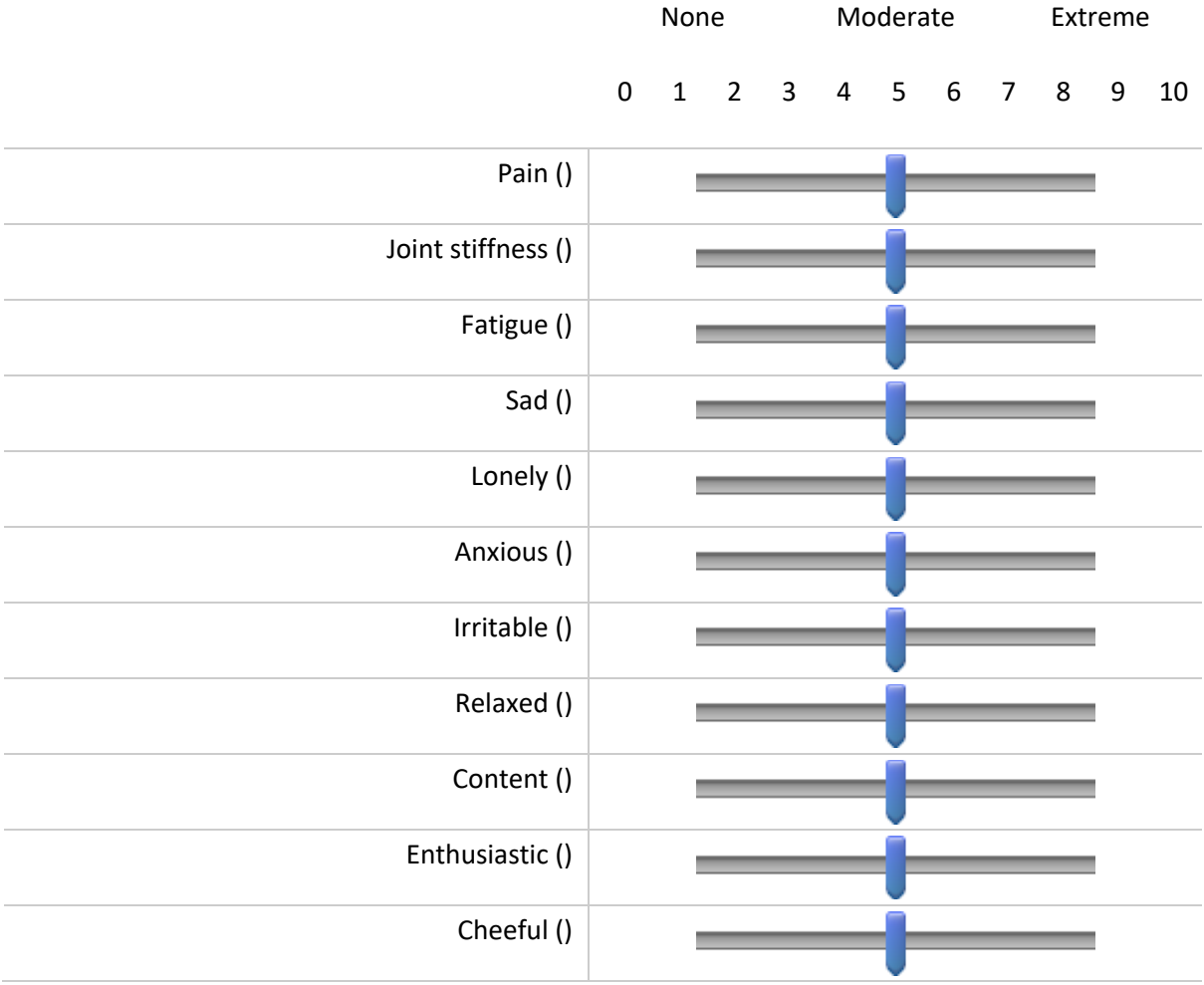
EMA Assessment for the first 16 days

Q1 Please rate how much you felt each of the following in the last hour. Responses are all 0-10 scale, with 0 = none and 10 = extreme

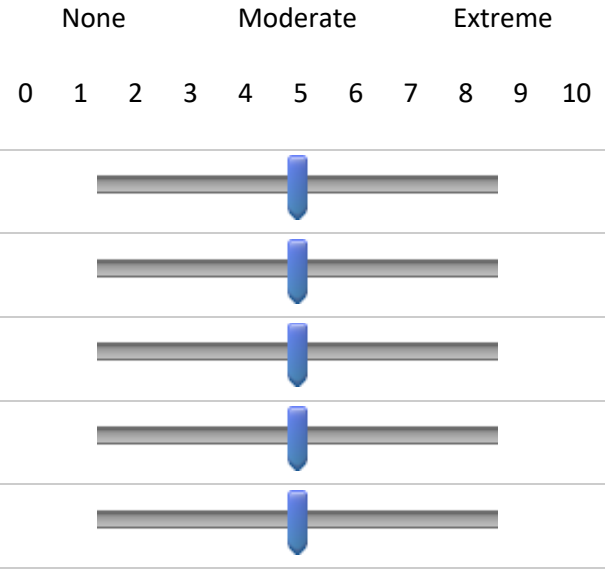


Daily Assessment at 8pm and for the last 16 days

Q1 Please rate how much you felt each of the following in the last hour. Responses are all 0-10 scale, with 0 = none and 10 = extreme



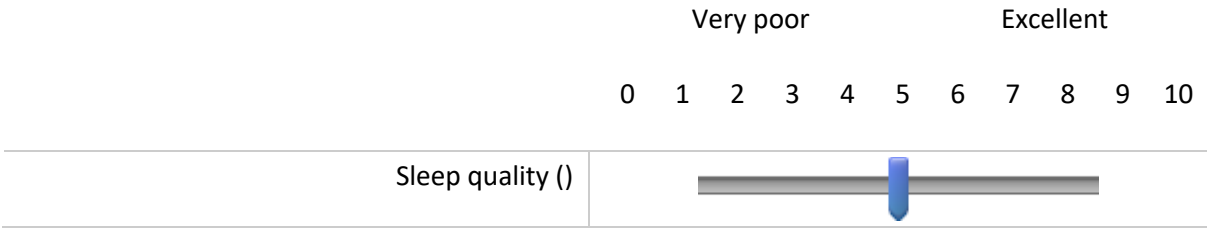
Q2 The following scale will be regarding your well-being today. The response is from a score of 0 to 10, with 0 being none and 10 being extreme.



Q3 How many hours did you sleep last night?

- ○ 4 hours or less (1)
- ○ 4.5 hours (2)
- ○ 5 hours (3)
- ○ 5.5 hours (4)
- ○ 6 hours (5)
- ○ 6.5 hours (6)
- ○ 7 hours (7)
- ○ 7.5 hours (8)
- ○ 8 hours (9)
- ○ 8.5 hours (10)
- ○ 9 hours (11)
- ○ 9.5 hours (12)
- ○ 10 hours or more (13)

Q4 What was the quality of your sleep last night?



Q5 Did you nap during the day?

- ○ Yes (1)
- ○ No (2)

Q6 What was your highest level of physical activity today?

- ○ Resting (e.g. napping) (1)
- ○ Sitting (e.g. watching tv, working) (2)
- ○ Standing (e.g. cooking) (3)
- ○ Walking slowly (e.g. doing housework, gardening, yoga) (4)
- ○ Walking briskly (e.g. fast walk as a form of exercise outside, cycling) (5)
- ○ Moderate intensity exercise (e.g. carrying light loads, jogging, social tennis) (6)
- ○ Vigorous or high intensity exercise (e.g. swimming, HIIT (high intensity interval training) workouts, sprints) (7)

Q7 For how long did you wear your fitbit today?

- ○ Less than 1 hour or not at all (1)
- ○ 1 hour to 3 hours (2)
- ○ 3 hours to 6 hours (3)
- ○ 6 hours to 9 hours (4)
- ○ More than 9 hours (5)

Q8 Did you undertake any strenuous physical activity today while not wearing your Fitbit?

- ○ Yes (1)
- ○ No (2)

Please remember to sync your FitBit with your smartphone today, thank you!

Baseline Survey for APPro study (inclusive of the MSK-HQ)

Q1 About you:

This section is to collect some basic information, so we can have demographic information that can help us understand how these demographics affect disease activity.

Q2 Please indicate your age in years

_____

Q3 What is your gender?

- ○ Male (1)
- ○ Female (2)
- ○ Non Binary (4)
- ○ Other (5)

Q4 Please indicate your highest education level

- ○ No formal qualifications (4)
- ○ O level, GCSE, or equivalent (5)
- ○ A level, or equivalent (6)
- ○ Undergraduate degree, or equivalent (7)
- ○ Postgraduate degree, or equivalent (8)

Q5 Please let us know in which year you are diagnosed with Rheumatoid Arthritis, e.g. 2015

_____

Q6 MUSCULOSKELETAL HEALTH QUESTIONNAIRE (MSK-HQ)

This questionnaire is about your joint, back, neck, bone and muscle symptoms such as aches, pains and/or stiffness.

Q7

Pain/stiffness during the day: How severe was your usual joint or muscle pain and/or stiffness overall during the day in the last 2 weeks?

	Very severe	Fairly severe	Moderately	Slightly	Not at all
	0	1	2	3	4
Pain/stiffness during day ()					

Q9

Pain/stiffness during the night: How severe was your usual joint or muscle pain and/or stiffness overall during the night in the last 2 weeks?

	Very severe	Fairly severe	Moderately	Slightly	Not at all
	0	1	2	3	4
Pain/stiffness at night ()					

Q10

Walking: How much have your symptoms interfered with your ability to walk in the last 2 weeks?

	Unable to walk	Severely	Moderately	Slightly	Not at all
	0	1	2	3	4

Walking ()	

Q11

Washing/Dressing: How much have your symptoms interfered with your ability to wash or dress yourself in the last 2 weeks?

	Unable to wash/dress myself	Severely	Moderately	Slightly	Not at all
	0	1	2	3	4
Washing/Dressing ()					

Q12

Physical activity levels: How much has it been a problem for you to do physical activities (e.g. going for a walk or jogging) to the level you want because of your joint or muscle symptoms in the last 2 weeks?

	Unable to do much	Very much	Moderately	Slightly	Not at all
	0	1	2	3	4
Physical Activity Levels ()					

Q13

Work/daily routine: How much have your joint or muscle symptoms interfered with your work or daily routine in the last 2 weeks (including work & jobs around the house)?

	Extremely	Severely	Moderately	Slightly	Not at all
	0	1	2	3	4

Work/Daily Routine ()	

Q14

Social activities and hobbies: How much have your joint or muscle symptoms interfered with your social activities and hobbies in the last 2 weeks?

Extremely Severely Moderately Slightly Not at all

0 1 2 3 4

Social Activities and Hobbies ()	

Q15

Needing help: How often have you needed help from others (including family, friends or carers) because of your joint or muscle symptoms in the last 2 weeks?

All the time Frequently Sometimes Rarely Not at all

0 1 2 3 4

Needing Help ()	

Q16

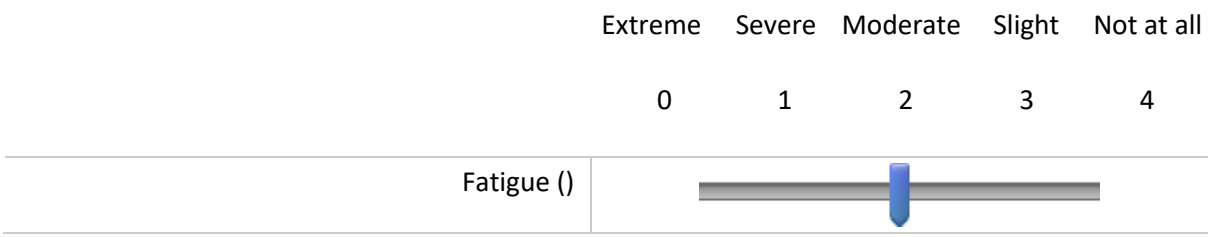
Sleep: How often have you had trouble with either falling asleep or staying asleep because of your joint or muscle symptoms in the last 2 weeks?

Every night Frequently Sometimes Rarely Not at all

0 1 2 3 4

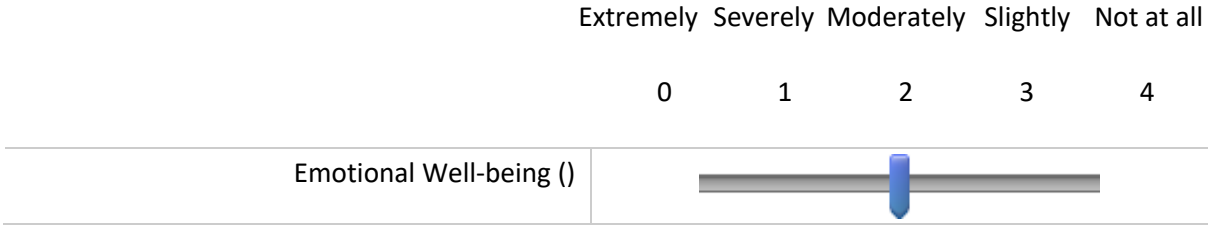
Sleep ()	

Q17 Fatigue or low energy: How much fatigue or low energy have you felt in the last 2 weeks?



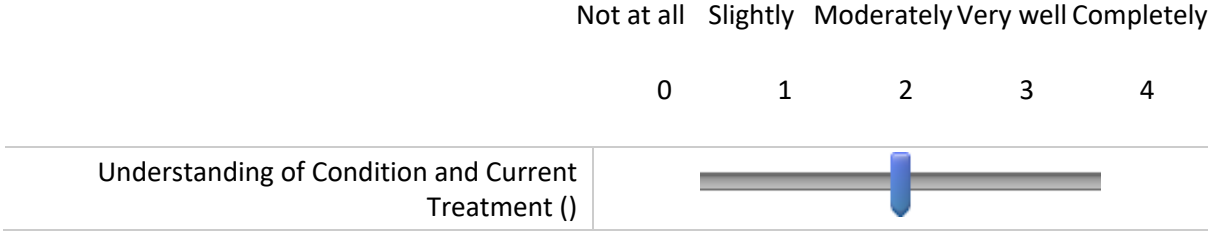
Q18

Emotional well-being: How much have you felt anxious or low in your mood because of your joint or muscle symptoms in the last 2 weeks?



Q19

Understanding of your condition and any current treatment: Thinking about your joint or muscle symptoms, how well do you feel you understand your condition and any current treatment (including your diagnosis and medication)?



Q20

Confidence in being able to manage your symptoms: How confident have you felt in being

able to manage your joint or muscle symptoms by yourself in the last 2 weeks (e.g. medication, changing lifestyle)?

	Not at all	Slightly	Moderately	Very	Extremely
	0	1	2	3	4
Confidence in Managing Symptoms ()					

Q21

Overall impact: How much have your joint or muscle symptoms bothered you overall in the last 2 weeks?

	Extremely	Very Much	Moderately	Slightly	Not at all
	0	1	2	3	4
Overall Impact ()					

Q22 Physical activity levels In the past week, on how many days have you done a total of 30 minutes or more of physical activity, which was enough to raise your heart rate? This may

include sport, exercise and brisk walking or cycling for recreation or to get to and from places, but should not include housework or physical activity that is part of your job.

- None (1)
- 1 Day (2)
- 2 Days (3)
- 3 Day (4)
- 4 Days (5)
- 5 Days (6)
- 6 Days (7)
- 7 Days (8)

Q23 Emotional and Psychological Health. This section includes 4 questions that are scored from 0 to 3 that provide an indication of key symptoms of depression and anxiety.

Q24 Over the past 2 weeks, how often have you been bothered by the following problems?

	Not at all	Several days	More than half the days	Nearly every day
	0	1	2	3

Feeling nervous, anxious or on edge ()	
Not being able to stop or control worrying ()	
Little interest or pleasure in doing things ()	
Feeling down, depressed, or hopeless ()	

Table D.1: Centrality values for symptom plot before biologic

	Degree Centrality	Closeness Centrality	Betweenness Centrality	Expected Influence
Pain	2.18	00195	0	2.60
Joint Stiffness	2.23	0.0195	0	2.22
Fatigue	2.73	0.0257	14	2.04
Sad	4.44	0.0363	10	1.54
Lonely	3.53	0.0288	0	2.06
Anxious	4.21	0.0332	10	2.05
Irritable	4.44	0.0359	18	1.85
Relaxed	3.59	0.0274	0	0.991
Content	4.07	0.0282	6	1.07
Enthusiastic	3.52	0.0242	0	1.58
Cheerful	3.81	0.0254	0	1.43

Table D.2: Centrality values for symptom plot after biologic

	Degree Centrality	Closeness Centrality	Betweenness Centrality	Expected Influence
Pain	3.62	0.0322	14	1.09
Joint Stiffness	3.22	0.0279	0	1.56
Fatigue	2.91	0.0277	0	2.40
Sad	4.14	0.0329	18	1.94
Lonely	3.71	0.0281	0	2.19
Anxious	3.85	0.0298	4	2.65
Irritable	4.13	0.0307	4	2.84
Relaxed	3.62	0.0248	0	1.35
Content	3.90	0.0277	2	1.33
Enthusiastic	3.89	0.0264	0	1.36
Cheerful	4.38	0.0321	14	0.826