King's Research Portal

Title: Duration of untreated eating disorder and relationship to outcomes: A systematic review of the literature

Authors: Amelia Austin[1], Michaela Flynn[1], Katie Richards[1], John Hodsoll[2], Tiago Antunes Duarte[3], Paul Robinson[4], Jonathan Kelly[5], Ulrike Schmidt[1,6]

1: Section of Eating Disorders, Institute of Psychiatry, Psychology and Neuroscience, London, King's College London, UK

2: Department of Biostatistics, Institute of Psychiatry, Psychology and Neuroscience, London, King's College London, UK

3: Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte, EPE, Lisboa, PT

4: University College London, London, UK

5: Beat, 1 Chalk Hill House, 19 Rosary Road, Norwich, UK

6: South London and Maudsley NHS Foundation Trust, London, UK

Corresponding author: Ulrike Schmidt, Section of Eating Disorders, PO Box 59, Institute of Psychiatry, Psychology and Neuroscience, De Crespigny Park, London, SE5 8AF, email address: ulrike.schmidt@kcl.ac.uk

Conflicts of interest: None

Abstract:

Objective: This systematic review assesses the average duration of untreated eating disorder (DUED) in help-seeking populations at the time of first eating disorder (ED) treatment and investigates the relationship between DUED and symptom severity/clinical outcomes.

Method: PRISMA guidelines were followed throughout. Selected studies provided information on either: a) length of DUED, b) components of DUED, c) cross-sectional associations between DUED and symptom severity, d) associations between DUED and clinical outcomes, or e) experimental manipulation of DUED. Study quality was assessed.

Results: Fourteen studies from seven countries were included. Across studies, average DUED weighted by sample size was 29.9 months for anorexia nervosa, 53.0 months for bulimia nervosa and 67.4 months for binge eating disorder. A younger age at time of first treatment was indicative of shorter DUED. Retrospective studies suggest that a shorter DUED may be related to a greater likelihood of remission. Manipulation of DUED by shortening service-related delays may improve clinical outcomes.

Conclusions: Data on length of DUED provide a benchmark for early intervention in EDs. Preliminary evidence suggests DUED may be a modifiable factor influencing outcomes in EDs. To accurately determine the role of DUED, definition and measurement must be uniformly operationalised.

Highlights:

- This systematic review is the first to examine duration of untreated eating disorder (DUED) across different eating disorders. Definitions and measurement of DUED and its components vary considerably between studies.

- Across different eating disorders average DUED weighted by sample size ranges from approximately two and a half years (for anorexia nervosa) to nearly 6 years (for binge eating disorder).

- DUED appears to be related to age such that younger patients have shorter DUED.

Key words: eating disorder; anorexia nervosa; bulimia nervosa, duration of untreated illness; early intervention

1.0 Introduction

The principles of early intervention and associated stage models of disease are widely accepted in medicine. Early intervention has been defined as early detection followed by stage-specific or proportionate intervention, for as long as necessary and effective (McGorry, Ratheesh, & O'Donoghue, 2018). This approach has led to improved survival rates and better outcomes in many disorders, from cancer to cardiovascular disease. In relation to mental health, these ideas have been most enthusiastically taken up by the psychosis field and have influenced research and policy. Early intervention services for psychosis are now 'mainstream' in many countries (McGorry & Mei, 2018). These developments are underpinned by a solid evidence-base from randomised controlled trials, finding that early intervention is superior to treatment as usual (Correll et al., 2018). In this context, attempts to reduce the duration of untreated psychosis, i.e. the time from onset of symptoms to the start of treatment, have been a key strategy of early intervention programmes for promoting favourable long-term outcomes of first-episode psychosis (Penttilä, Jääskeläinen, Hirvonen, Isohanni, & Miettunen, 2014; Oliver et al., 2018; Sullivan et al., 2018). This is with the aim of preventing neuroprogression, i.e. neurobiological changes associated with psychosis symptoms which unfavourably affect the illness trajectory (Moylan, Maes, Wray, & Berk, 2013; Gama, Kunz, Magalhaes, & Kapczinski, 2013).

Many of the arguments made in relation to psychosis also apply to eating disorders (EDs). As in psychosis, the peak onset of EDs spans adolescence into emerging adulthood, about age 15 to 25 (Schmidt, Adan, et al., 2016), with new EDs rarely presenting after age 30 (Micali, Hagberg, Petersen, & Treasure, 2013). It has been known for some time that longer illness duration is a key predictor of poor outcome in EDs (Steinhausen, 2002). In addition, and similar to psychosis and bipolar disorder, converging data support the idea that neurobiological changes associated with disordered eating unfavourably affect the illness trajectory of EDs (O'Hara, Campbell, & Schmidt, 2015; Steinglass & Walsh, 2016). Provisional staging models for EDs have been developed, suggesting that illness stage at diagnosis is predictive of later outcomes (Maguire et al., 2017). Evidence suggests that early stage EDs

can be defined as less than three years illness duration, beyond which the treatment response becomes more muted (Ambwani et al., 2020; Treasure, Stein, & Maguire, 2015). A service model for early intervention in EDs has been developed and tested in the UK (Schmidt, Brown, McClelland, Glennon, & Mountford, 2016; Brown et al., 2018; McClelland et al., 2018; Fukutomi et al., 2020) and is included in national guidance as a positive practice example (National Collaborating Centre for Mental Health [NCCMH], 2019).

Despite the parallels to psychosis and the availability of a plausible rationale for early intervention, the ED field has been slow to adopt early intervention approaches. Existing efforts have been piecemeal, and hampered by a number of problems, with traditional service designs, separating services for children and adolescents from those for adults, being just one of them (see Davey & McGorry [2019] for discussion of these issues in relation to depression).

Nonetheless, national guidance is now increasingly supporting the need for early intervention approaches in EDs (e.g. National Institute for Health and Care Excellence [NICE], 2017). However, if successful strategies for early intervention for EDs are to be developed, a clear understanding of duration of untreated ED (DUED), pathways into care, and delays in accessing specialist treatments during a first episode ED, are necessary. This goes beyond documenting overall DUED and involves identifying specific sources of delay in different ED diagnoses and populations (e.g. adolescents or adults). Previously, duration of untreated psychosis has been divided into three components (Birchwood et al., 2013): 1) a period where an individual experiences symptoms, but doesn't recognise that they have a problem, 2) a period where an individual recognises that they have a problem, but are not yet ready to seek help, and 3) a period where an individual has sought help, and is waiting for treatment. Similar components could plausibly be applied to EDs.

The overall aim of this review is to better understand DUED, its component delays and its impact on outcome in different ED diagnoses and populations, and to provide a benchmark for early intervention.

1.1 Objectives:

This review aims to answer the following questions:

What is the typical length of DUED for different ED diagnoses (anorexia nervosa [AN], bulimia

nervosa [BN], binge eating disorder [BED], otherwise specified eating disorder [OSFED]

and populations (children, adolescents, adults, male or female)?

What are the different components of DUED?

Is DUED cross-sectionally associated with symptom severity?

Is DUED associated with long-term clinical outcomes?

Is experimental manipulation of DUED associated with improved outcomes?

2.0 Method

A systematic review (i.e. an organised and transparent method of gathering, evaluating, and synthesizing data applicable to specific research questions) was conducted. While a traditional meta-analysis (e.g. calculating a pooled measure of effect from multiple RCTs) was not conducted, a meta-analytic approach, whereby quantitative results from multiple studies are combined into a summary statistic, was used.

PRISMA guidelines for conducting systematic reviews were applied (http://prisma-statement.org/). The search strategy was designed by two reviewers (M.F. and A.A.). The protocol was registered with PROSPERO (CRD42018110884). Relevant literature was identified by searching PubMed, World of Science, and PsycINFO. We used the following search terms: ("duration of untreated" OR DUED OR "illness duration" OR "duration of illness" OR "early intervention" OR "first episode") AND (eating disorder* OR anorexia nervosa OR bulimi* OR binge eat*). The terms were used to search all fields and no language or publication date restrictions were imposed at this point.

Detailed information on search strategy, eligibility criteria, data extraction, quality assessment, and data synthesis are available in Supplementary Methods. The search was conducted from inception until December 17, 2019. Average DUED was calculated for each population group (i.e. diagnosis, age) in two

ways: 1) A simple mean weighted by sample size and 2) meta-analytic estimates weighted by the inverse variance of the DUED. The meta-analytic approach allows statistically efficient 95% CI intervals to be calculated for the pooled average incorporating both sampling and between study heterogeneity. Here we use the IVHet approach which arguably corrects the under-estimation of statistical error which can result from a random effects model under conditions of high heterogeneity (Doi et al, 2015). We present both sample size weighted means in addition to meta-analytic means as estimations of variance are subject to sampling error. The MetaXL plugin for Microsoft Excel was used which is freely available to download and install from www.epigear.com. As the Beat (2017) report was potentially less methodologically robust than the other studies (i.e. used self-report data for illness onset, treatment start, and diagnosis), used a broader definition of onset than the other studies, and had the longest DUEDs across different EDs, a sensitivity analysis was run to explore it's influence on the overall pooled estimate.

3.0 Results:

3.1 Characteristics of included studies

The results of the study search are detailed in the PRISMA diagram in Figure 1. The search produced 1862 articles, of which 865 were duplicates. Based on the abstracts, 30 articles were eligible for full-text screening, and 13 of these were excluded as they either did not report on DUED or it was unclear whether study participants were experiencing a first episode. We identified two previous systematic reviews on early intervention in AN (Schoemaker, 1997) and BN (Reas, Schoemaker, Zipfel, & Williamson, 2001). The Schoemaker (1997) review used duration of illness as a proxy for "time between onset and first admission," stating, "duration of illness is the only indirect estimate available at this time" (p. 2). None of the papers from this review met our inclusion criteria. Likewise, Reas et al. (2001) used duration of illness as an approximation of DUED and thus did not meet our criteria.

Table 1 summarises the characteristics of the 14 included studies. These were from seven countries, i.e. Australia, Canada, Germany, Republic of Ireland, Singapore, Spain and the UK. All studies reported

DUED using a statistic of central tendency. Four studies (*n*=2246) reported a component breakdown of DUED, (Beat, 2017; Brown et al., 2018; Gumz, Weigel, Wegscheider, Romer, & Löwe, 2018, Schlegl et al., 2019), two (*n*=787) reported DUED and its cross-sectional association with symptom severity (Bühren et al., 2013; Flynn et al., in preparation), and one (*n*=38) reported associations between DUED and long term clinical outcomes (Andrés-Pepiñá et al., 2019). Three studies (*n*=721) attempted to experimentally manipulate DUED (Brown et al., 2018; Flynn et al, in preparation; Gumz et al., 2018), one of which (*n*=142) also reported the prospective associations between DUED and clinical outcomes (McClelland et al., 2018).

3.1.1 Participants:

Overall, 5032 patients were included in the selected studies. Information on patient diagnosis and age by study can be found in Table 1 and summary information in Supplementary Results.

3.1.2 Methodological characteristics and quality:

Details on study characteristics can be found in Table 1 and details on methodological quality can be found in Supplementary Material. Three studies (*n*=275) measured the onset of EDs, and therefore start of DUED, through a clinical interview using Diagnostic and Statistical Manual of Mental Disorders (DSM; American Psychiatric Association, 2000, 2013) or International Classification of Diseases (ICD; World Health Organization, 1992) diagnostic criteria (Gumz et al., 2018; Neubauer et al., 2014; Weigel et al., 2014). Two studies (*n*=644) used a clinical interview plus an additional research assessment with an adapted version of the Eating Disorder Diagnostic Scale (EDDS; Stice, Telch, & Rizvi, 2000) to confirm onset date (Brown et al., 2018; Flynn et al., in preparation). Two studies (*n*=2027) measured onset date using participant self-report (Beat, 2017; Schlegl et al., 2019), one (*n*=285) reported that this was "assessed at admission," (Bühren et al., 2013), three (*n*=1298) relied on young person and/or parental self-report (Lieberman et al., 2019; Kwok et al., 2019; Shu et al., 2015), and three (*n*=503) did not define how onset was determined (Andrés-Pepiñá et al., 2019; Ng et al., 2018; Nicholls et al., 2011). To measure

the start of treatment, or end of DUED, five studies (n=1736) used the date of entrance into specialised treatment (Bühren et al., 2013; Brown et al., 2018; Flynn et al., in preparation; Kwok et al., 2019; Lieberman et al., 2019; Nicholls et al., 2011; Weigel et al., 2014), two (n=2027) used self-reported dates for start of treatment (Beat, 2017), and three (n=1091) did not explicitly define how start of treatment date was measured (Gumz et al., 2018; Ng et al., 2018; Shu et al., 2015).

3.2 Length of DUED

3.2.1 Studies comparing DUED by diagnosis

3.2.1.1 Anorexia Nervosa

Eleven studies explored the duration of untreated AN (Andrés-Pepiñá et al., 2019; Beat, 2017; Bühren et al., 2013; Flynn et al., in preparation; Gumz et al., 2018; Kwok et al., 2019; Lieberman et al., 2019; Neubauer at el., 2014; Ng et al., 2018; Schlegl et al., 2019; Weigel et al., 2014). As shown in Figure 2, the average DUED in these studies ranged from 6.39 – 39.96 months, with a simple average of 29.9. Meta-analytic estimation found a mean DUED of 14.6 months (99% CI [5.1, 24.0]). Heterogeneity was high with I^2 at 99% (95% CI [98.6, 99.1]. A sensitivity analysis was run excluding the Beat (2017) study (M=11.4, 95% CI [4.5, 18.3], I^2=97.2%, 95% CI [96.2, 97.9]).

3.2.1.2 Bulimia Nervosa

A total of four studies assessed DUED for BN (Beat, 2017; Flynn et al., in preparation; Ng et al., 2018, Schlegl et al., 2019). The average DUED ranged from 23.05 – 58.56 months, with a simple average of 53.0 months (see Supplementary Figure 1). Meta-analytic estimation found a mean DUED of 34.3 months, (95% CI [3.6, 65.0]). Heterogeneity was high with I^2 at 98% (95% CI [97.3, 99.0]). A sensitivity analysis was run excluding the Beat (2017) study (M=26.6, 95% CI [-16.1, 69.4], I^2=96.7%, 95% CI [93.2, 98.4]).

3.2.1.3 Binge Eating Disorder

Only one study analysed DUED for BED (Beat, 2017), which revealed an average of 67.4 months (*SD*=39.7).

3.2.1.4 OSFED/EDNOS

Three studies assessed DUED for OSFED/EDNOS (Beat, 2017; Flynn et al., in preparation; Ng et al., 2018). As shown in Supplementary Figure 2, the average DUED ranged from 19.9-53.0 months with a simple average of 43.8. Meta-analytic estimation found a mean DUED of 29.5 months, (95% CI [7.5, 51.6.0]). Heterogeneity was high with I^2 at 95% (95% CI [89.2, 97.9]). A sensitivity analysis was run excluding the Beat (2017) study (*M*=21.5, 95% CI [-20.1, 63.1], I^2=89.6%, 95% CI [61.6, 97.2]).

3.2.2 Studies Comparing Age at First Treatment

As shown in Supplementary Figures 3 and 4, average DUED varies strongly between age groups. All studies reporting mean duration by age for either children (≤ 12 years old) or adolescents/adults (≥ 12 years old) at first treatment are included in these figures. The categories of adolescents and adults were collapsed, as several studies included participants both below and above 18 years of age. A simple mean DUED weighted by sample size was calculated for children (9.8 months) and adolescents/adults (34.7 months). Meta-analytic estimation found a mean of 7.5 months for children (95% CI, [4.8, 10.2], I^2=86.9%, 95% CI [62.5, 95.4]]), and 21.3 months (Supplementary Figure 4) for adults (95% CI, [12.3, 30.3], I^2=96.0%, 95% CI [92.9, 97.2]). DUED appears to increase with age.

Two studies analysed DUED information for separate age groups at first treatment (child/adolescent vs. adults [Beat, 2017] and adolescents vs. emerging adults vs. adults [Weigel et al., 2014]): again, DUED increase reflects an age increase.

3.2.3. Studies Comparing Gender

One study examined the role of gender in DUED (Shu et al., 2015). Gender was not related to length of DUED in their paediatric population.

3.3 Components of DUED

While all studies measured the time between illness onset and treatment, the component breakdown of this time varied (See Figure 3). Three studies explicitly identified components of DUED. Brown (2018) measured DUED as the time of onset to the start of evidence-based treatment, defined as any treatment recommended by the NICE guidelines (NICE, 2017). One component of this was the duration until specialised service contact (DUSC) which represents the time between illness onset and assessment.

Gumz (2014) defined DUED similarly but included duration until first contact (DUC) with any healthcare professional for eating related symptoms as a component. Schlegl et al. (2019) took a related approach by again measuring DUED from onset to treatment but further breaking this down into two distinct periods: pre and post general practitioner (GP) diagnosis.

One study (Beat, 2017) deconstructed DUED most thoroughly, breaking it down into several components: A) the time before realisation of being ill, B) the time between realisation and seeking help, C) time between first GP visit and referral, D) time between referral and assessment, and E) time between assessment and start of treatment.

As can be seen in Figure 3, DUED can be conceptualised in different ways but in all cases broadly includes patient-related delays (i.e. time before seeking help) as well as service-related delays (i.e. time to starting treatment after seeking help).

3.4 Cross-sectional association with symptom severity

Bühren et al. (2013) investigated the role of DUED in children and adolescents with AN. These authors found that age-adjusted BMI was not significantly influenced by DUED. Flynn et al. (in preparation) investigated the role of DUED in emerging adults with a range of ED diagnoses. Baseline analysis of participants diagnosed with AN suggests that there was no significant relationship between DUED and BMI at assessment.

3.5 Association with long-term clinical outcome

Andrés-Pepiñá et al. (2019) retrospectively investigated the long-term outcome of patients with AN an average of 22 years (range, 17-29) after initial diagnosis and treatment. Patients who still had an ED diagnosis at follow-up were significantly more likely to have had a longer DUED (*m*=18 months, *SD*=10.8) compared to those in remission (*m*=8.4 months, *SD*=8.4) with an odds ratio of 3.33 (95% CI: 1.3-8.7; P < 0.014).

3.6 Experimental manipulation of DUED

Using a pre-post design, a quasi-experimental study from the UK compared DUED following the introduction of an early intervention service model/care pathway for emerging adults with recent ED onset (FREED: First episode rapid early intervention for EDs) with that of similar patients (age, illness duration, diagnosis) previously having received treatment as usual (TAU) in the same service (Brown et al., 2018; McClelland et al., 2018). For details of the FREED model see Allen et al., 2019 and Supplementary Table 2. For patients able to access FREED under optimal conditions (i.e. without gate-keeping barriers) DUED was 6 months shorter than for TAU patients. Patients offered FREED took up treatment significantly more than those offered TAU (100% versus 73%) and had significant improvement in ED and other symptoms over time. FREED participants diagnosed with AN on average gained weight between clinical assessment and start of treatment whereas the comparison group lost weight in the same interval. By 12 months, 59% of the FREED AN group had returned to normal BMI compared to only 17% of the TAU group. These improvements were maintained up to 24 months after start of treatment (Fukutomi et al., 2020). A second ongoing multi-centre study using a similar design found comparable reductions in DUED between participants receiving FREED under optimal conditions and those assigned to TAU (Flynn et al., in preparation).

A study from Germany also used a pre-post design, to evaluate the impact of a multi-faceted public health intervention (including an awareness raising campaign, school-based prevention, treatment resources and

a network of services providing early intervention) on DUED in AN patients of all ages across a large

metropolitan catchment area (Gumz et al., 2018). There was no significant change in DUED from before

(m=36.5 months, SD=68.2) to after (m=40.1, SD=89.4) the introduction of the intervention. There was

also no significant difference between BMI and EDE-Q scores for the before and after participant

samples.

4.0 Discussion

4.1 Principal findings:

The first aim of this review was to determine the typical length of DUED for different ED populations.

Studies from seven countries indicate that, across different disorders, DUEDs are lengthy. Simple average

DUED weighted by sample size ranged from 29.9 months for AN to 38.9 months for BN, with OSFED in

between. A meta-analytic approach accounting for heterogeneity estimated a lower mean DUED, giving

14.6 months for AN, 34.3 months for BN, and 29.5 months for OSFED. The large difference between the

mean weighted by sample size and the meta-analytic estimate weighted by inverse variance for AN is due

to low variance in samples of younger patients. The meta-analytic estimate for AN highly weighted

smaller studies with children, and younger age is a confounding factor for shorter DUED, thus lowering

overall estimates for DUED. However, the simple average mean weighted by sample size did not devalue

studies based on large variance, therefore giving just as much weight to outliers, and likely being more

reflective of clinical reality.

The lengthy time periods as measured by simple average DUED found here appear longer than that found

in a recent care pathway study from Italy (Volpe et al., 2019). This study found that this took

approximately 26 months across disorders. These patients did not necessarily have a first episode of their

ED and it is likely that during a later illness episode patients may ask for help more quickly.

Our findings, both within study comparisons (Beat, 2017; Weigel, 2014) and cross study comparisons

(Figure 3), suggest that there is variability in DUED relating to age, with a younger age relating to a

shorter DUED. This age-related increase in length of DUED is likely to be related to several factors. Firstly, the younger the child the more likely the parents are able to identify the illness earlier. Longer DUED as age increases may be explained by living independently, leaving the individual in charge of seeking help and navigating the health care system. Additionally, despite the fact that peak onset of EDs ranges from age 15 to 25 (Schmidt, Adan, et al., 2016), many countries have separate child/adolescent and adult ED services, which may add to delays and disruptions in accessing first episode specialist mental health care. Secondly, studies of younger participants tend to mainly include AN, which is a highly visible disorder, whereas studies of adults often include a mixture of AN and those with bulimic EDs, which are more hidden. For example, parents are often unaware of bulimic symptoms in their adolescent children (Bartholdy et al., 2017). Thirdly, it may also matter who reports on DUED. Where parents report DUED, a self-serving bias may be operative, i.e. with parents not wishing to admit they left symptoms unchallenged for a period of time. Conversely, where DUED is defined by patients, an 'effort after meaning' bias may mean that people date the onset of their symptoms back to mild body image concerns.

Average DUED weighted by sample size found here for children was 9.8 months (see Figure 3). DUEDs for adolescents and adults (M=34.7) were longer than duration of illness in recent large scale clinical trials in adolescents with EDs (e.g. AN: Agras et al. [2014] 13.5 months; Hodsoll et al. [2017] median 12-15 months; Eisler et al. [2017] 9.6-11.4 months; Herpertz-Dahlmann et al. [2014] 9.8-12.4 months; BN: Le Grange et al. [2015] 18.4-19.6 months; Schmidt et al. [2007] 2.5-2.6 years) and shorter than in trials in adults (e.g. AN: Attia et al. [2019] 10.5-12.6 years; Schmidt et al. [2015] 8.3 years; BN/EDNOS/BED: Fairburn et al. [2009] 9.9 years; BED: de Zwaan et al. [2017] 7.9-10.4 years). While this is certainly due in part to the conflation of the average DUED for adolescents and adults, there is still another factor: DUED measures time to first treatment whereas duration of illness measures time to current treatment, including any previous treatments. For the majority of adolescents, this likely constitutes their first ever treatment.

The second aim of this review was to delineate components of DUED. The evidence suggests that the largest delays are patient-related (i.e. from start of illness to help-seeking; see Figure 3). Likewise, in the Italian care pathway study by Volpe et al. (2019), the larger component delay was prior to starting help-seeking. Nonetheless, the time between help-seeking and accessing specialist care was substantial (28 weeks).

These findings have implications for early intervention programmes. Waiting for weeks or months from the point of help-seeking is distressing. As such, reducing service-related delays is important. These efforts need to be joined with attempts to intervene earlier e.g. through indicated prevention in high-risk groups.

In relation to our third aim, overall, studies failed to find cross-sectional associations between BMI at the commencement of treatment and length of DUED (Bühren et al., 2013; Flynn et al., in preparation). This may be explained by the limited variability in DUED in these two studies. However, the Bühren et al. (2013) study found that older adolescents had a longer DUED and lower age-adjusted BMI at admission than younger adolescents, which the authors attributed to a lessening of parental influence on older teens.

The fourth aim of the review was to investigate the relationships of DUED and long-term clinical outcomes. Andrés-Pepiñá et al.'s (2019) retrospective study suggests that a longer DUED may play a role in persistence of AN many years after initial treatment. No other studies assessed the influence of DUED on long-term clinical outcomes, and thus these findings cannot be generalised to the wider group of patients with EDs, although they do bolster the rationale for early intervention.

The final aim was to investigate experimental manipulations of DUED. Three studies, all using pre-post designs, attempted this, one through an ambitious public health intervention (Gumz et al., 2018). The other two attempted to reduce DUED through a novel service intervention (FREED) designed to reduce service-related delays specialist ED services in the UK (McClelland et al., 2018; Flynn et al., in preparation). For details of the FREED model see Allen et al., 2019 and Supplementary Table 2. The

public health intervention did not reduce DUED, whereas the novel service intervention did reduce DUED by several months. Clinical (BMI)/weight recovery outcomes for FREED patients with AN were much better than for those receiving TAU with differences in rate of improvement maintained up to 24 months (Fukutomi et al., 2020). This evidence suggests that FREED is a promising early intervention model for reducing DUED across all EDs, and for improving clinical outcomes in AN. Its impact on clinical outcomes in other EDs is yet to be demonstrated. In contrast, efforts to intervene with a prominent focus on prevention of onset of AN and/or raising awareness about early help seeking may not be enough to reduce DUED, as indicated by the disappointing findings of Gumz et al. (2018). Similarly, indicated prevention efforts focusing exclusively on AN have also had disappointing results (Jacobi et al., 2018).

4.2 Strengths and Limitations

A strength of this review is that it assesses DUED across different EDs, and as such provides a benchmark for future research, clinical practice, and health policy. The data included were from a range of countries with different health care systems, yet findings seemed to be consistent, and thus appear generalisable across high-income Western countries.

This review also has several limitations. First, the search excluded papers not written in English, Portuguese, or German and many types of grey literature. Second, DUED was not operationalised in the same way across studies. Studies differed markedly in their definitions of illness onset and treatment start. A recent systematic review on the duration of untreated psychosis (DUP) cited similar difficulties with heterogeneous definitions of DUP (Oliver et al., 2018). This suggests that other mental health fields, even those in a more advanced stage of research on duration of untreated illness, are facing similar problems. Likewise, the components of DUED have been conceptualised differently by different authors (see Figure 3). For example, Pinhas, Wong, and Woodside (2014) have segmented DUED into several components for both mental and physical health pathways and have also taken into consideration the role of duration of untreated ED to first psychotropic medication (DUPMed) as being a relevant period of time, but do not provide any data.

Third, we were not able to separate out the influence of age at presentation and diagnosis, given very limited data on children and adolescents with bulimic EDs. Finally, the variable of DUED may be confounded by other factors. Research in psychosis lists the following potential confounders: mode-of-onset, pre-morbid functioning, and acuteness of illness at assessment (Sullivan et al., 2018). These variables may also affect DUED.

4.3 Implications for research, practice and policy

Future studies should aim to adopt a common definition of DUED, including its components, and standardised measurement tools. For research purposes it is desirable to use in-depth interview measures allowing retrospective assessment of symptoms, anchored in key autobiographical events. This methodology has been tested across many different disorders (e.g. depression: Brown, Adler, & Bifulco, 1988; psychosis: Bebbington et al., 1993; eating disorders: Schmidt, Tiller, Blanchard, Andrews, & Treasure, 1997). These studies show that, given biographical anchoring, such details can be accurately remembered going back many years. We used an adapted version of this methodology in our studies, using a graph to create a timeline incorporating patient life events and details of the illness course (Brown et al., 2018; Flynn et al., in preparation). However, this methodology is time consuming and less useful for routine clinical practice. We have developed an abbreviated assessment of DUED for clinical practice. Any such assessment tools should also try to delineate the components of DUED, as this would inform decisions about when it is best to intervene.

In terms of clinical practice and policy, long DUEDs across different countries with different health care systems suggest that we are nowhere near achieving early intervention. In psychosis, early intervention efforts have been organised around shortening duration of untreated psychosis as a key outcome. This requires routine measurement of this variable. Likewise, it would be helpful to routinely measure DUED.

The longest component of DUED is the time before seeking help. Measures to improve early detection of EDs may help to shorten this period. A second key component of DUED is the time people wait between

seeking help (e.g. in the UK an appointment with their GP) and starting specialist treatment. In England, there are nationally binding waiting times targets for EDs in young people below age 18 (Department of Health, 2014). In parallel, self-referrals to specialist services are now allowed for under 18s (NCCMH, 2015). These measures have successfully increased the proportion of under 18s with EDs starting specialist treatment (NHS England, 2019).

It is expected that similar waiting time targets will be brought in for adults in the UK (NCCMH, 2019). These are important steps for shortening DUED. However, measurement of waiting times alone is not sufficient, as a substantial proportion of young people are referred between services (e.g. child to adult services) without ever starting specialist treatment.

Emerging data suggest that a service model/care pathway, such as FREED, can successfully reduce DUED, improve clinical outcomes, and appears to be cost-effective (Brown et al., 2018; McClelland et al., 2018).

4.4 Conclusion

This systematic review is the first to examine DUED across different EDs. Whilst definitions and measurement of DUED and its components vary between studies, there is agreement across different studies internationally that average DUEDs are long, ranging from about two and a half years (for AN) to nearly 6 years (for BED). DUED appears to be shorter in children than in adolescents and adults. Preliminary evidence suggests DUED may be a modifiable factor effecting outcome in EDs. Taken together, these data provide a useful benchmark for early intervention efforts in EDs. To accurately determine the role of DUED, definition and measurement must be uniformly operationalised.

References:

Agras, W. S., Lock, J., Brandt, H., Bryson, S. W., Dodge, E., Halmi, K. A, … & Woodside, B. (2014). Comparison of 2 family therapies for adolescent anorexia nervosa: A randomized parallel trial. *JAMA Psychiatry*, *71*(11), 1279-1286. DOI: 10.1001/jamapsychiatry.2014.1025

Allen, K. L., Mountford, V., Brown, A., Richards, K., Grant, N., Austin, A., ... & Schmidt, U. (2020). First episode rapid early intervention for eating disorders (FREED): From research to routine clinical practice. *Early Intervention in Psychiatry*. Advanced online publication. DOI: 10.1111/eip.12941

Ambwani, S., Cardi, V., Albano, G., Cao, Li, Crosby, R., MacDonald, P., Schmidt, U., & Treasure, J. (2020). A multicenter audit of outpatient care for adult anorexia nervosa: Symptom trajectory, service use, and evidence in support of "early stage" versus "severe and enduring" classification. *International Journal of Eating Disorders.* Advanced online publication. DOI: 10.1002/eat.23246

American Psychiatric Association (2000). *Diagnostic and statistical manual of mental disorders* (4th ed., Text Revision). Washington, DC: American Psychiatric Association.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Washington, DC: American Psychiatric Publishing.

Andrade, R., Gonçalves-Pinho, M., Roma-Torres, A., & Brandão, I. (2017). Treatment of anorexia nervosa: The importance of disease progression in the prognosis. *Acta Medica Portuguesa, 30*(7-8), 517-523. DOI: 0.20344/amp.8963

Andrés-Pepiñá, S., Plana, M. T., Flamarique, I., Romero, S., Borràs, R., Julià, L., ... & Castro-Fornieles, J. (2019). Long-term outcome and psychiatric comorbidity of adolescent-onset anorexia nervosa. *Clinical Child Psychology and Psychiatry*, 1359104519827629. DOI: 10.1177/1359104519827629

Attia, E., Steinglass, J. E., Walsh, B. T., Wang, Y., Wu, P., Schreyer, C., … & Marcus, M. D. (2019). Olanzapine versus placebo in adult outpatients with anorexia nervosa: A randomized clinical trial. *American Journal of Psychiatry*, appi-ajp. DOI: 10.1176/appi.ajp.2018.18101125

Bartholdy, S., Allen, K., Hodsoll, J., O'Daly, O.G., Campbell, I.C., Banaschewski, … & Schmidt, U. (2017). Identifying disordered eating behaviours in adolescents: How do parent and adolescent reports differ by sex and age? *European Child & Adolescent Psychiatry, 26*(6), 691-701. DOI: 10.1007/s00787-016-0935-1

Beat. (2017). *Delaying for years, denied for months.* Norwich, UK: Beat. Retrieved from https://www.beateatingdisorders.org.uk/uploads/documents/2017/11/delaying-for-years-denied-for-months.pdf

Bebbington, P., Wilkins, S., Jones, P., Foerster, A., Murray, R., Toone, B., & Lewis, S. (1993). Life events and psychosis: Initial results from the Camberwell Collaborative Psychosis Study. *The British Journal of Psychiatry*, 162(1), 72-79. DOI: 10.1192/bjp.162.1.72

Birchwood, M., Connor, C., Lester, H., Patterson, P., Freemantle, N., Marshall, M., … & Singh, S.P. (2013). Reducing duration of untreated psychosis: Care pathways to early intervention in psychosis services. *The British Journal of Psychiatry, 203*(1), 58-64. DOI: 10.1192/bjp.bp.112.125500

Brown, A., McClelland, J., Boysen, E., Mountford, V., Glennon, D., & Schmidt, U. (2018). The FREED Project (first episode and rapid early intervention in eating disorders): Service model, feasibility and acceptability. *Early Intervention in Psychiatry*. *12*(2), 250-257. DOI: 10.1111/eip.12382

Brown, G. W., Adler, Z., & Bifulco, A. (1988). Life events and chronic depression. *The British Journal of Psychiatry*, 152(4), 487-498. DOI: 10.1192/bjp.152.4.487

Bühren, K., von Ribbeck, L., Schwarte, R., Egberts, K., Pfeiffer, E., Fleischhaker, C., … & Herpertz-Dahlmann, B. (2013). Body mass index in adolescent anorexia nervosa patients in relation to age, time point and site of admission. *European Child & Adolescent Psychiatry, 22*(7), 395-400. DOI: 10.1007/s00787-013-0376-z

Correll, C.U., Galling, B., Pawar, A., Krivko, A., Bonetto, C., Ruggeri, M., … & Kane, J.M. (2018).
Comparison of early intervention services vs treatment as usual for early-phase psychosis: A
systematic review, meta-analysis, and meta-regression. *JAMA Psychiatry, 75*(6), 555-565. DOI:
10.1001/jamapsychiatry.2018.0623

Davey, C.G. & McGorry, P.D. (2019). Early intervention for depression in young people: A blind spot in
mental health care. *Lancet Psychiatry, 6*(3), 267-272. DOI: 10.1016/S2215-0366(18)30292-X

Department of Health. (2014). *Achieving better access to mental health services by 2020*. Retrieved from
https://www.gov.uk/government/publications/mental-health-services-achieving-better-access-by-
2020

de Zwaan, M., Herpertz, S., Zipfel, S., Svaldi, J., Friederich, H. C., Schmidt, F., … & Hilbert, A. (2017).
Effect of internet-based guided self-help vs individual face-to-face treatment on full or
Subsyndromal binge eating disorder in overweight or obese patients: The INTERBED
randomized clinical trial. *JAMA Psychiatry, 74*(10), 987-995. DOI:
10.1001/jamapsychiatry.2017.2150

Doi, S. A. R., Barendregt, J. J., Khan, S., Thalib, L., & Williams, G. M. (2015). Advances in the meta-
analysis of heterogeneous clinical trials I: The inverse variance heterogeneity model.
Contemporary Clinical Trials, 45, 130–138. DOI: 10.1016/j.cct.2015.05.009

Eijkemans, M., Mommers, M., Jos, M. T., Thijs, C., & Prins, M. H. (2012). Physical activity and asthma:
A systematic review and meta-analysis. *PLoS One, 7*(12), e50775. DOI:
10.1371/journal.pone.0050775

Eisler, I., Simic, M., Hodsoll, J., Asen, E., Berelowitz, M., Connan, F., … & Landau, S. (2016). A
pragmatic randomised multi-centre trial of multifamily and single family therapy for adolescent
anorexia nervosa. *BMC Psychiatry, 16*(1), 422. DOI: 10.1186/s12888-016-1129-6

Fairburn, C. G. & Beglin, S. J. (1994). Assessment of eating disorders: Interview or self-report questionnaire? *International Journal of Eating Disorders, 16*(4), 363-370. DOI: 10.1002/1098-108X(199412)16:4<363::AID-EAT2260160405>3.0.CO;2-%23

Fairburn, C. G., Cooper, Z., Doll, H. A., O'Connor, M. E., Bohn, K., Hawker, D. M., ... & Palmer, R. L. (2009). Transdiagnostic cognitive-behavioral therapy for patients with eating disorders: A two-site trial with 60-week follow-up. *American Journal of Psychiatry*, 166(3), 311-319. DOI: 10.1176/appi.ajp.2008.08040608

Flynn, M., Austin, A., Allen, K., Grant, N., Mountford, V., Glennon, D., …, & Schmidt, U. (2019). *Does introduction of a novel early intervention service reduce duration of untreated eating disorder in emerging adults with first episode illness?* Manuscript in preparation.

Fukutomi, A., Austin, A., McClelland, J., Brown, A., Mountford, V., Grant, N., …, & Schmidt, U. (2020). First episode rapid early intervention for eating disorders: A two-year follow-up. *Early Intervention in Psychiatry, 14*(1), 137-141. DOI: 10.1111/eip.12881

Gama, C.S., Kunz, M., Magalhaes, P.V., & Kapczinski, F. (2013). Staging and neuroprogression in bipolar disorder: A systematic review of the literature. *Revista Brasileira de Psiquiatria, 35*(1), 70-74. DOI: 10.1016/j.rbp.2012.09.001

Gumz, A., Weigel, A., Wegscheider, K., Romer, G., & Löwe, B. (2018). The psychenet public health intervention for anorexia nervosa: A pre-post-evaluation study in a female patient sample. *Primary Health Care Research & Development, 19*(1), 42-52. DOI: 10.1017/S1463423617000524

Gumz, A., Uhlenbusch, N., Weigel, A., Wegscheider, K., Romer, G., & Löwe, B. (2014). Decreasing the duration of untreated illness for individuals with anorexia nervosa: Study protocol of the evaluation of a systemic public health intervention at community level. *BMC Psychiatry 14*(1), 300. DOI: 10.1186/s12888-014-0300-1

Herpertz-Dahlmann, B., Schwarte, R., Krei, M., Egberts, K., Warnke, A., Wewetzer, C., ... & Dempfle, A. (2014). Day-patient treatment after short inpatient care versus continued inpatient treatment in adolescents with anorexia nervosa (ANDI): A multicentre, randomised, open-label, non-inferiority trial. *The Lancet*, 383(9924), 1222-1229. DOI: 10.1016/S0140-6736(13)62411-3

Herzog, R., Álvarez-Pasquin, M. J., Díaz, C., Del Barrio, J. L., Estrada, J. M., & Gil, Á. (2013). Are healthcare workers' intentions to vaccinate related to their knowledge, beliefs and attitudes? A systematic review. *BMC Public Health, 13*(1), 154. DOI: 10.1186/1471-2458-13-154

Hodsoll, J., Rhind, C., Micali, N., Hibbs, R., Goddard, E., Nazar, B. P., … & Treasure, J. (2017). A pilot, multicentre pragmatic randomised trial to explore the impact of carer skills training on carer and patient behaviours: Testing the cognitive interpersonal model in adolescent anorexia nervosa. *European Eating Disorders Review*, 25(6), 551-561. DOI: 10.1002/erv.2540

Jaite, C., Bühren, K., Dahmen, B., Dempfle, A., Becker, K., Correll, C. U., ... & Herpetz-Dahlmann, B. (2019). Clinical Characteristics of Inpatients with Childhood vs. Adolescent Anorexia Nervosa. *Nutrients*, 11(11), 2593.

Jacobi, C., Hütter, K., Völker, U., Möbius, K., Richter, R., Trockel, M., ... & Taylor, C. B. (2018). Efficacy of a parent-based, indicated prevention for anorexia nervosa: Randomized controlled trial. *Journal of Medical Internet Research*, 20(12), e296. DOI: 10.2196/jmir.9464

Kwok, C., Kwok, V., Lee, H. Y., & Tan, S. M. (2019). Clinical and socio-demographic features in childhood vs adolescent-onset anorexia nervosa in an Asian population. *Eating and Weight Disorders-Studies on Anorexia, Bulimia and Obesity*, 1-6.

Le Grange, D., Lock, J., Agras, W. S., Bryson, S. W., & Jo, B. (2015). Randomized clinical trial of family-based treatment and cognitive-behavioral therapy for adolescent bulimia nervosa. *Journal of the American Academy of Child & Adolescent Psychiatry, 54*(11), 886-894. DOI: 10.1016/j.jaac.2015.08.008

Lieberman, M., Houser, M. E., Voyer, A. P., Grady, S., & Katzman, D. K. (2019). Children with avoidant/restrictive food intake disorder and anorexia nervosa in a tertiary care pediatric eating disorder program: A comparative study. *International Journal of Eating Disorders, 52*(3), 239-245.

Luchini, C., Stubbs, B., Solmi, M., & Veronese, N. (2017). Assessing the quality of studies in meta-analyses: advantages and limitations of the Newcastle Ottawa Scale. *World Journal of Meta-Analysis, 5*(4), 80-84. DOI: 10.13105/wjma.v5.i4.80

Maguire, S., Surgenor, L.J., Le Grange, D., Lacey, H., Crosby, R.D., Engel, S.G., … , Touyz, S. (2017). Examining a staging model for anorexia nervosa: Empirical exploration of a four stage model of severity. *Journal of Eating Disorders, 5*(41). DOI: 10.1186/s40337-017-0155-1

McClelland, J., Hodsoll, J., Brown, A., Lang, K., Boysen, E., Flynn, M., … & Schmidt, U. (2018) A pilot evaluation of a novel First Episode and Rapid Early Intervention service for Eating Disorders (FREED). *European Eating Disorder Review 26*(2), 129-140. DOI: 10.1002/erv.2579

McGorry P.D. & Mei C. (2018). Early intervention in youth mental health: Progress and future directions. *Evidence Based Mental Health, 21*(4), 182-184. DOI: 10.1136/ebmental-2018-300060

McGorry, P.D., Ratheesh, A., & O'Donoghue, B. (2018). Early intervention-An implementation challenge for 21st century mental health care. *JAMA Psychiatry, 75*(6), 545-546. DOI: 10.1001/jamapsychiatry.2018.0621

Micali, N., Hagberg, K. W., Petersen, I., & Treasure, J. L. (2013). The incidence of eating disorders in the UK in 2000–2009: Findings from the General Practice Research Database. *BMJ Open*, *3*(5), e002646. DOI: 10.1136/bmjopen-2013-002646

Moylan, S., Maes, M., Wray, N. R., & Berk, M. (2013). The neuroprogressive nature of major depressive disorder: Pathways to disease evolution and resistance, and therapeutic implications. *Molecular Psychiatry*, 18(5), 595-606. DOI: 10.1038/mp.2012.33

National Collaborating Centre for Mental Health. (2015). *Access and waiting time standard for children and young people with an eating disorder.* Retrieved from https://www.england.nhs.uk/wp-content/uploads/2015/07/cyp-eating-disorders-access-waiting-time-standard-comm-guid.pdf

National Collaborating Centre for Mental Health (2019). *Adult eating disorders: Community, inpatient and intensive day patient care*. Guidance for commissioners and providers.

National Institute for Health and Care Excellence. (2017). Eating disorders: Recognition and treatment. NICE Guideline NG 69. https://www.nice.org.uk/guidance/ng69

Neubauer, K., Weigel, A., Daubmann, A., Wendt, H., Rossi, M., Löwe, B., & Gumz A. (2014). Paths to first treatment and duration of untreated illness in anorexia nervosa: Are there differences according to age of onset? *European Eating Disorders Review, 22*(4), 292-8. DOI: 10.1002/erv.2300

Ng, K. W., Kuek, A., & Lee, H. Y. (2018). Eating psychopathology and psychosocial impairment in patients treated at a Singapore eating disorders treatment programme. *Singapore Medical Journal, 59*(1), 33. DOI: 10.11622/smedj.2017042

NHS England. (2019). *Children and young people with an eating disorder waiting times*. Retrieved from https://www.england.nhs.uk/statistics/statistical-work-areas/cyped-waiting-times/

Nicholls D.E., Lynn R., Viner R.M. (2011). Childhood eating disorders: British national surveillance study. *British Journal of Psychiatry, 198*(4), 295-301. DOI: 10.1192/bjp.bp.110.081356

O'Hara, C.B., Campbell, I.C., & Schmidt, U. (2015), A reward-centred model of anorexia nervosa: A focussed narrative review of the neurological and psychophysiological literature. *Neuroscience and Biobehavioral Reviews, 52*, 131-52. DOI: 10.1016/j.neubiorev.2015.02.012

Oliver, D., Davies, C., Crossland, G., Lim, S., Gifford, G., McGuire, P., & Fusar-Poli, P. (2018). Can we reduce the duration of untreated psychosis? *Schizophrenia Bulletin, 44*(6), 1362-1372. DOI: 10.1093/schbul/sbx166

Peterson, J., Welch, V., Losos, M., & Tugwell, P. (2011). The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. *Ottawa: Ottawa Hospital Research Institute*.

Petkova, H., Simic, M., Nicholls, D., Ford, T., Prina, A. M., Stuart, R., ... & Gowers, S. (2019). Incidence of anorexia nervosa in young people in the UK and Ireland: a national surveillance study. *BMJ Open, 9*(10), e027339.

Penttilä, M., Jääskeläinen, E., Hirvonen, N., Isohanni, M., & Miettunen, J. (2014) Duration of untreated psychosis as predictor of long-term outcome in schizophrenia: Systematic review and meta-analysis. *British Journal of Psychiatry, 205*(2), 88-94. DOI: 10.1192/bjp.bp.113.127753

Pinhas, L, Wong, J., & Woodside, B. (2014). Early intervention in eating disorders. In P. Byrne & A. Rosen (Eds.), Early intervention in psychiatry: EI of nearly everything for better mental health (pp.288-304). Chichester, UK: John Wiley & Sons Ltd.

Reas, D.L., Schoemaker, C., Zipfel, S., Williamson, D.A. (2001) Prognostic value of duration of illness and early intervention in bulimia nervosa: A systematic review of the outcome literature. *International Journal of Eating Disorders, 30*(1), 1-10. DOI: 10.1002/eat.1049

Schlegl, S., Hupe, K., Hessler, J. B., Diedrich, A., Huber, T., Rauh, E., ... & Voderholzer, U. (2019). Pathways to Care and Duration of Untreated Illness of Inpatients with Anorexia and Bulimia nervosa. *Psychiatrische Praxis*. DOI:10.1055/a-0922-5651

Schmidt, U., Adan, R., Böhm, I., Campbell, I. C., Dingemans, A., Ehrlich, S., … & Zipfel, S. (2016). Eating disorders: The big issue. *The Lancet Psychiatry*, *3*(4), 313-315. DOI: 10.1016/S2215-0366(16)00081-X

Schmidt, U., Brown, A., McClelland, J., Glennon, D., & Mountford V.A. (2016). Will a comprehensive, person-centered, team-based early intervention approach to first episode illness improve outcomes in eating disorders? *International Journal of Eating Disorders, 49*(4), 374-7. DOI: 10.1002/eat.22519

Schmidt, U., Lee, S., Beecham, J., Perkins, S., Treasure, J., Yi, I., ... & Johnson-Sabine, E. (2007). A randomized controlled trial of family therapy and cognitive behavior therapy guided self-care for adolescents with bulimia nervosa and related disorders. *American Journal of Psychiatry, 164*(4), 591-598.

Schmidt, U., Magill, N., Renwick, B., Keyes, A., Kenyon, M., Dejong, H., … & Watson, C. (2015). The Maudsley outpatient study of treatments for anorexia nervosa and related conditions (MOSAIC): Comparison of the Maudsley Model of Anorexia Nervosa Treatment for Adults (MANTRA) with specialist supportive clinical management (SSCM) in outpatients with broadly defined anorexia nervosa: A randomized controlled trial. *Journal of Consulting and Clinical Psychology, 83*(4), 796. DOI: 10.1037/ccp0000019

Schmidt, U., Tiller, J., Blanchard, M., Andrews, B., & Treasure, J. (1997). Is there a specific trauma precipitating anorexia nervosa? *Psychological Medicine*, 27(3), 523-530. DOI: 10.1017/S0033291796004369

Schoemaker, C. (1997). Does early intervention improve the prognosis in anorexia nervosa? A systematic review of the treatment-outcome literature. *International Journal of Eating Disorders, 21*(1), 1-15. DOI: 10.1002/(SICI)1098-108X(199701)21:1<1::AID-EAT1>3.0.CO;2-R

Shu, C. Y., Limburg, K., Harris, C., McCormack, J., Hoiles, K. J., Hamilton, M. J., & Watson, H. J. (2015). Clinical presentation of eating disorders in young males at a tertiary setting. *Journal of Eating Disorders, 3*(1), 39. DOI: 0.1186/s40337-015-0075-x

Stice, E., Telch, C. F., & Rizvi, S. L. (2000). Development and validation of the Eating Disorder

    Diagnostic Scale: A brief self-report measure of anorexia, bulimia, and binge-eating disorder.

    Psychological Assessment, 12(2), 123. DOI: 10.1037/1040-3590.12.3.252

Steinhausen, H.C. (2002). The outcome of anorexia nervosa in the 20th century. *American Journal of*

    Psychiatry, 159(8), 1284-1293. DOI: 10.1176/appi.ajp.159.8.1284

Steinglass, J.E. & Walsh, B.T. (2016). Neurobiological model of the persistence of anorexia nervosa.

    Journal of Eating Disorders, 4(1), 19. DOI: 10.1186/s40337-016-0106-2

Sullivan, S.A., Carroll, R., Peters, T.J., Amos, T., Jones, P.B., Marshall, M., … & Tilling, K. (2018).

    Duration of untreated psychosis and clinical outcomes of first episode psychosis: An

    observational and an instrumental variables analysis. *Early Intervention in Psychiatry*. Advanced

    online publication. DOI: 10.1111/eip.12676.

Treasure, J., Stein, D., & Maguire, S. (2015). Has the time come for a staging model to map the course of

    eating disorders from high risk to severe enduring illness? An examination of the evidence. *Early*

    Intervention in Psychiatry, *9*(3), 173-184. DOI: 10.1111/eip.12170

Volpe, U., Monteleone, A.M., Ricca, V., Corsi, E., Favaro, A., Santonastaso, P., … & Maj, M. (2019).

    Pathways to specialist care for eating disorders: An Italian multicentre study. *European Eating*

    Disorders Review, [Epub ahead of print] PubMed PMID: 30848056. DOI: 10.1002/erv.2669.

Weigel, A., Rossi, M., Wendt, H., Neubauer, K., von Rad, K., Daubmann, A., … & Gumz, A. (2014)

    Duration of untreated illness and predictors of late treatment initiation in anorexia nervosa.

    Journal of Public Health, 22(6), 519-527. DOI: 10.1007/s10389-014-0642-7

World Health Organization. (1992). *The ICD-10 classification of mental and behavioural disorders:*

    Clinical descriptions and diagnostic guidelines. Geneva: World Health Organization.

Table 1. Study characteristics

Author, Location	N	Sample	Design	Measures	Assessment of DUED	Components of DUED	Length DUED	Symptoms/ Clinical outcomes	Other findings/comments
Studies in AN									
Andrés-Pepiñá et al., 2019 (Spain)	38	All females diagnosed with AN between 1987-1993 (age M=14.4 years, SD=1.6). At 22-year follow-up mean age was 37.03 (SD=4.01).	Retrospective, cohort	Questionnaires: EDI-2, BDI, ASQ Clinical Interview: SCID-I	DUI: Time between illness onset and first contact with services. Onset: Not described.	N/A	M=13.05 months (SD=9.80) Remission group M=8.4 (SD =8.4) Current ED group M = 18 (SD = 10.8)	Longer DUED was significantly associated with an increased risk of ED status at 22-year follow-up (OR=3.3).	No other measured variables were significantly related to ED status at follow-up.
Bühren et al., 2013 (Germany)	285	All females between age 11-18 years old referred between 2001 and 2009. All diagnosed with AN (DSM-IV) with BMI below 10th percentile. Local sample- Aachen, Germany n=116 (age M=15.2 years, SD=1.7), multisite sample n=127 (age M=15.1 years, SD=1.5), included in both samples n=42 (age M=15.6 years, SD=1.5).	Cross-sectional	Age adjusted BMI scores	"The time between beginning of weight loss and admission to hospital" (p. 396).	N/A	Local sample M=10.8 months (SD=8.2) Multi-site sample M=11.1 (SD=8.6) Included in both samples M=11.9 (SD=8.8)	DUED was not a significant influence on age-adjusted BMI at admission.	Older patients were significantly more likely to have a longer DUED and lower age-adjusted BMI at admission than younger patients.

Author, Location	N	Sample	Design	Measures	Assessment of DUED	Components of DUED	Length DUED	Symptoms/ Clinical outcomes	Other findings/comments
Gumz et al., 2014, 2018 (Germany)	77	Pre-intervention (*n*=59) and post intervention (*n*=18). All females between 10-60 years old (*M*=22.2, *SD*=7.2). All diagnosed with AN or atypical AN (DSM-IV). All receiving first ED-specific treatment.	Pre/post between-subjects intervention evaluation	Questionnaires: EDE-Q or Ch-EDE-Q, PHQ-9, GAD-7, date of first contact with healthcare. Clinical interview: SCID-I	DUI: Time between AN onset and initiation of ED-specific guideline-based treatment. Onset: Date when all AN criteria were first met.	DUC: Duration until first contact with healthcare system for ED related issues.	Pre-intervention *M*=36.5 months (*SD*=68.2) Post-intervention *M*=40.1 (*SD*=89.4)	N/A	Intervention was a systemic public health intervention, no effect was found. GP/paediatrician was typically the first healthcare professional consulted about ED symptoms. Study is limited by small sample size.
Kwok et al., 2019 (Singapore)	435	Female (*n*=415) and male (*n*=20) adolescents between age 13-18 years old (*M*=16.26, *SD*=1.85). All diagnosed with AN (DSM-IV-TR) between Jan. 1, 2003 and Dec. 31, 2014. Child (< 13 years) onset (*n*=36) and adolescent (13-18 years) onset (*n*=399).	Cross-sectional	Retrospective chart review: sociodemographic variables, clinical characteristics, treatment details	Duration of illness prior to presentation	N/A	*M*=33.60 months (*SD*=34.32) Childhood-onset *M*=57.0 (*SD*=64.68) Adolescent onset *M*=31.44 (*SD*=29.40)	Those with childhood-onset had longer DUED than those with adolescent onset when presenting at adolescent ED services.	Those with childhood-onset had subsequently longer inpatient stays and more admissions.
Neubauer et al., 2014 (Germany)	140	All females between 10-60 years old (*M*=17.51, *SD*=5.81). Early	Cross-sectional	Questionnaires: EDE-Q or Ch-EDE-Q, PHQ-9, FTQ)	DUI: Time between onset and presentation to first ED-	N/A	*M*=25.14 months (*SD*=36.76)	N/A	Longer DUED was associated with internal rather than external motivation

Author, Location	N	Sample	Design	Measures	Assessment of DUED	Components of DUED	Length DUED	Symptoms/ Clinical outcomes	Other findings/comments
		onset (≤14 years) (*n*=40), intermediate onset (15-18 years) (*n*=53), late onset (>19 years) (*n*=47). All diagnosed with AN or subsyndromal AN (DSM-IV or ICD-10) with onset 1990 or later.		Clinical Interview: SCID-I	specific treatment. Onset: Date when all AN criteria were met simultaneously for the first time (or all criterion except one for subsyndromal AN)		Early onset *M*=38.35 (*SD*=45.92) Intermediate onset *M*=20.57 (*SD*=31.97) Late onset *M*=19.04 (*SD*=30.44)		to initiate treatment. GP/paediatrician was typically the first to diagnose AN and provide ED-specific treatment information.
Weigel et al., 2014 (Germany)	58	All females between age 10-60 years old (*M*=22.3, *SD*=7.8). Adolescents <18 years old (*n*=19), emerging adults 18-25 years old (*n*=25), adults ≥26 years old (*n*=14). All diagnosed with AN or atypical AN (DSM-IV or provisional DSM-V).	Cross-sectional	Questionnaires: FTQ, PSSIK, sociodemographic Clinical Interview: SCID-I	DUI: Time between date of illness onset and date of first treatment reported in FTQ. Onset: Date of illness onset reported in SCID-I.	N/A	*M*=31.8 months (*SD*=71.4) Adolescents *M*=14.1 (*SD*=34.7) Emerging adults *M*=20.7 (*SD*=24.8) Adults *M*=83.2 (*SD*=122.9)		Significant predictors of longer DUED: Statutory health insurance, healthcare system-related factors (e.g. waiting times), low insight into the disorder, low self-motivation to initiate treatment, higher paternal education, having a romantic partner, separated parents, immigrant background, one-point lower BMI, and certain personality characteristics (depressive, rhapsodic, schizoid,

Author, Location	N	Sample	Design	Measures	Assessment of DUED	Components of DUED	Length DUED	Symptoms/ Clinical outcomes	Other findings/comments
									obsessive-compulsive, paranoid and dependent).
Studies in mixed diagnostic groups									
Beat, 2017 (United Kingdom)	1821	Female (*n*=1741), male (*n*=54), non-binary (*n*=18), and other gender (*n*=8). Rates of self-reported diagnosis: AN *n*=1330, BN *n*=261, BED *n*=63, atypical ED (i.e. OSFED/EDNOS) *n*=154, unknown *n*=13. Age: *M*=20.77, *SD*=8.43. Up to 18 years old (*n*=831), 19+ years old (*n*=717), age not given (*n*=273). All participants began treatment in the UK between 2000 and 2017.	Cross-sectional	Questionnaire (online self-report)	Time spent waiting for treatment.	Time waiting for treatment = 1. Time between symptom onset and realising they had an ED, 2. Between realising and seeking help, 3. Between 1st GP visit and referral, 4. Between referral and assessment, 5. Between assessment and start of treatment.	*M*=39.24 months (*SD*=33.39) AN *M*=34.54 (*SD*=30.39) BN *M*=55.06 (*SD*=36.42) BED *M*=67.39 (*SD*=39.70) Atypical *M*=42.40 (*SD*=36.02) Children & adolescents: *M*=117.29 (*SD*=95.92) Adults: *M*=246.74 (*SD*=163.92)	N/A	Overall, those with AN had a shorter wait time than those with other diagnoses. The longest component of DUED was the time between symptom onset and realisation of having an ED.

Author, Location	N	Sample	Design	Measures	Assessment of DUED	Components of DUED	Length DUED	Symptoms/ Clinical outcomes	Other findings/comments
Brown et al., 2018; Fukutomi et al., 2020; McClelland et al., 2018 (United Kingdom)	142	Female (*n*=139) and male (*n*=3) aged 16-25 years old (control group: *M*=20.4, *SD*=2.0, treatment *M*=20.4, *S*=2.4). Diagnosed ED (AN *n*=57, BN *n*=42, BED *n*=5, OSFED *n*=38). All with DUED ≤ 3 years.	Historical controlled intervention study	Questionnaires: EDE-Q, CORE-10, DASS-21, WSAS, LEE, CIA Novel structured onset interview plus life chart (including items from the EDDS and EDE)	DUED: Time from onset to evidence-based treatment. Onset: The time at which DSM-5 criteria for an ED was first met.	DUSC: Time from ED onset to assessment.	Audit group (*n*=89): *M*=19.09 months (*SD*=11.67) Treatment group with minimal gate-keeping (*n*=14): *M*=13.04 (*SD*=9.29) Treatment group with complex gate keeping (*n*=37): *M*=17.66 (*SD*=10.20)	Treatment group had significant decrease in ED symptoms from 0 to 12 months with 70% below clinical cut-off by 12-months. Between assessment and treatment, BMI decreased in the audit group but increased in the treatment group.	DUED was successfully reduced using an early intervention model/care pathway.
Flynn et al., in preparation, (United Kingdom)	502	Female (*n*=475) and male (*n*=27) aged 16-25 years old (*M*=20.56, *SD*=2.35). All diagnosed with ED using criteria	Cross-sectional	Questionnaires: EDE-Q, CORE-10, DASS-21, WSAS, LEE, CIA Clinical assessment	DUED: Time from onset to evidence-based treatment.	DUSC: Time from onset to assessment.	TAU (*n*=160): *M*=19.98 months, *SD*=11.13, AN (*n*=84) *M*=18.57,	DUED was not related to BMI at assessment for those	DUED was successfully reduced using an early intervention model/care pathway.

Author, Location	N	Sample	Design	Measures	Assessment of DUED	Components of DUED	Length DUED	Symptoms/ Clinical outcomes	Other findings/comments
		from DSM-5 (AN n=233, BN n=131, BED n=9, OSFED n=129) †		Research interview (EDDS adapted for onset, life chart) BMI	Onset: The time at which DSM-5 criteria for an ED were first met.		SD=11.27, BN (n=42) M=23.05, SD=9.35, OSFED (n=29) M=19.90, SD=12.64 Treatment (n=272): M=17.85, SD=10.38, AN (n=114) M=17.50, SD=10.62, BN (n=68) M=20.26, SD=10.45, OSFED (n=82), M=16.30, SD=9.84 Optimal treatment* (n=153): M=15.96, SD=9.74 AN (n=56) M=14.02, SD=9.08, BN (n=47) M=19.72, SD=10.76, OSFED (n=41)	diagnosed with AN	

Author, Location	N	Sample	Design	Measures	Assessment of DUED	Components of DUED	Length DUED	Symptoms/ Clinical outcomes	Other findings/comments
							M=14.05, SD=8.37		
Lieberman et al., 2019 (Canada)	106	Females (n=88) and males (n=18) between the ages of 8 and 13 years old (M=11.27, SD=0.9). All assessed between May 2013 and Jan 2017 and diagnosed using DSM-V with either AN (n=77) or ARFID (n=29).	Cross-sectional	Questionnaires: (ChEAT, EDI-C, CDI-2, MASC-2) Clinical interview: unspecified	Duration of illness in months since onset Onset: Symptom onset	N/A	ARFID: M=29.28 months (SD=40.6) AN: M=6.39 months (SD=4.7)	Children with ARFID had a significantly longer DUED than children with AN.	Patients with ARFID were significantly younger and more likely to be male.
Nicholls et al., 2011, (United Kingdom and Republic of Ireland)	208	Female (n=171) and male (n=37) aged 5-12 years old (M=11.5, SD=1.3). All diagnosed with ED using criteria modified from DSM-IV and ICD-10 (AN n=76, BN n=3, EDNOS n=89 [including BED n=6], 'other' ED n=40).	Prospective, cohort	Questionnaires: Study-specific clinician questionnaire	DUI: Time between illness onset and presentation to secondary care Onset: Not described	N/A	M=8.3 (SD=7.0)	N/A	
Ng et al., 2018 (Singapore)	257	Female (n=238) and male (n=19) ≥ 12 years old (M=20.52, SD=7.14). Diagnosed ED	Cross-sectional	Questionnaires: EDE-Q, CIA, demographic info	Not described	N/A	Total M=43.6 months (SD=63.0)		Those with AN had shorter DUED than those with BN or EDNOS.

Author, Location	N	Sample	Design	Measures	Assessment of DUED	Components of DUED	Length DUED	Symptoms/ Clinical outcomes	Other findings/comments
		using DSM-IV (AN n=107, BN n=76, EDNOS n=74).					AN M=26.9 (SD=35.3) BN M=57.8 (SD=57.4) EDNOS M=53.0 (SD=89.2)		
Schlegl et al., 2019 (Germany)	206	Females (n=200) and males (n=6) diagnosed using ICD-10 with AN (n=140) or BN (n=66). All between 12-58 years old at diagnosis (AN M=24.28, SD=7.74, BN M=25.35, SD=8.31). Recruited between Aug. 2011 and Sept. 2012.	Cross-sectional	Specially created questionnaire including demographics, clinical characteristics, illness course	Treatment latency: from start to treatment	1. Period from onset to diagnosis 2. Period from onset to treatment 3. Period from diagnosis (by GP) to treatment	M=48.24 months, SD=64.32 AN M=39.96 (SD=54.96) BN M=58.56 (SD=70.68)	Those with AN had approx. 1.5 years shorter DUED than those with BN.	Age of onset did not differ between AN and BN. A BN diagnosis, a higher current age and not perceiving the eating disorder as a problem were significant predictors of a longer DUED latency.
Shu et al., 2015 (Australia)	757	Females (n=704) and males (n=53) under 18 years old (male M=13.57 years [SD=2.02], female M=14.74 years [SD=1.56]) diagnosed with ED using DSM-V (AN n=286, atypical AN n=179, BN n=71,	Cross-sectional	EDE (adapted versions for child and parent informant)	Self-reported in medical assessment by parent and child.	N/A	Male DUED median=9.00 months ±5-12 Female DUED median=8.00 ±5-12	N/A	No significant difference in DUED between genders. Males had significantly earlier age of onset than females.

Author, Location	N	Sample	Design	Measures	Assessment of DUED	Components of DUED	Length DUED	Symptoms/ Clinical outcomes	Other findings/comments
		BN low frequency/duration *n*=10, BED *n*=3, BED low frequency/duration *n*=5, purging disorder *n*=29, UFED n=174.							

ED = Eating Disorder; AN = Anorexia Nervosa; BN = Bulimia Nervosa; BED = Binge Eating Disorder; EDNOS = Eating Disorder Not Otherwise Specified; OSFED = Other Specified Feeding or Eating Disorder; DUED = Duration of Untreated Eating Disorder; DUI = Duration of Untreated Illness; DUSC = Duration of Untreated to Specialist Service Contact; EDE-Q = Eating Disorder Examination-Questionnaire; Ch-EDE-Q = Child Eating Disorder Examination-Questionnaire; PHQ-9 = Patient Health Questionnaire; GAD-7 = Generalized Anxiety Disorder Scale; SCID-IV = Structured Clinical Interview for DSM-IV; GP = General Practitioner; FTQ = First Treatment Questionnaire; PSSIK = Personality style and disorder inventory; CIA = Clinical Impairment Assessment; CORE-10 = Ten-item version of Clinical Outcomes in Routine Evaluation; DASS-21 = Depression, Anxiety, and Stress Scale 21; WSAS = Work and Social Adjustment Scale; LEE = Level of Expressed Emotion; EDDS = Eating Disorder Diagnostic Scale; EDE = Eating Disorder Examination; MAEDS = Multiaxial Assessment of Eating Disorder Symptoms; EAT = Eating Attitudes Test; ChEAT = Children's Eating Attitudes Test; BDI = Beck Depression Inventory; OR = Odd Ratio; EDI-2 = Eating Disorder Inventory-2; EDI-C = Eating Disorder Inventory for Children; ASQ = Autism Spectrum Quotient; CDI-2 = Children's Depression Inventory-2; MASC-2 = Multidimensional Anxiety Scale for Children-2.

[*] Included as a subgroup of the previous 'treatment' group

[†] 86 patients in the TAU condition were previously included in the study by Brown et al. (2018) and McClelland et al., (2018
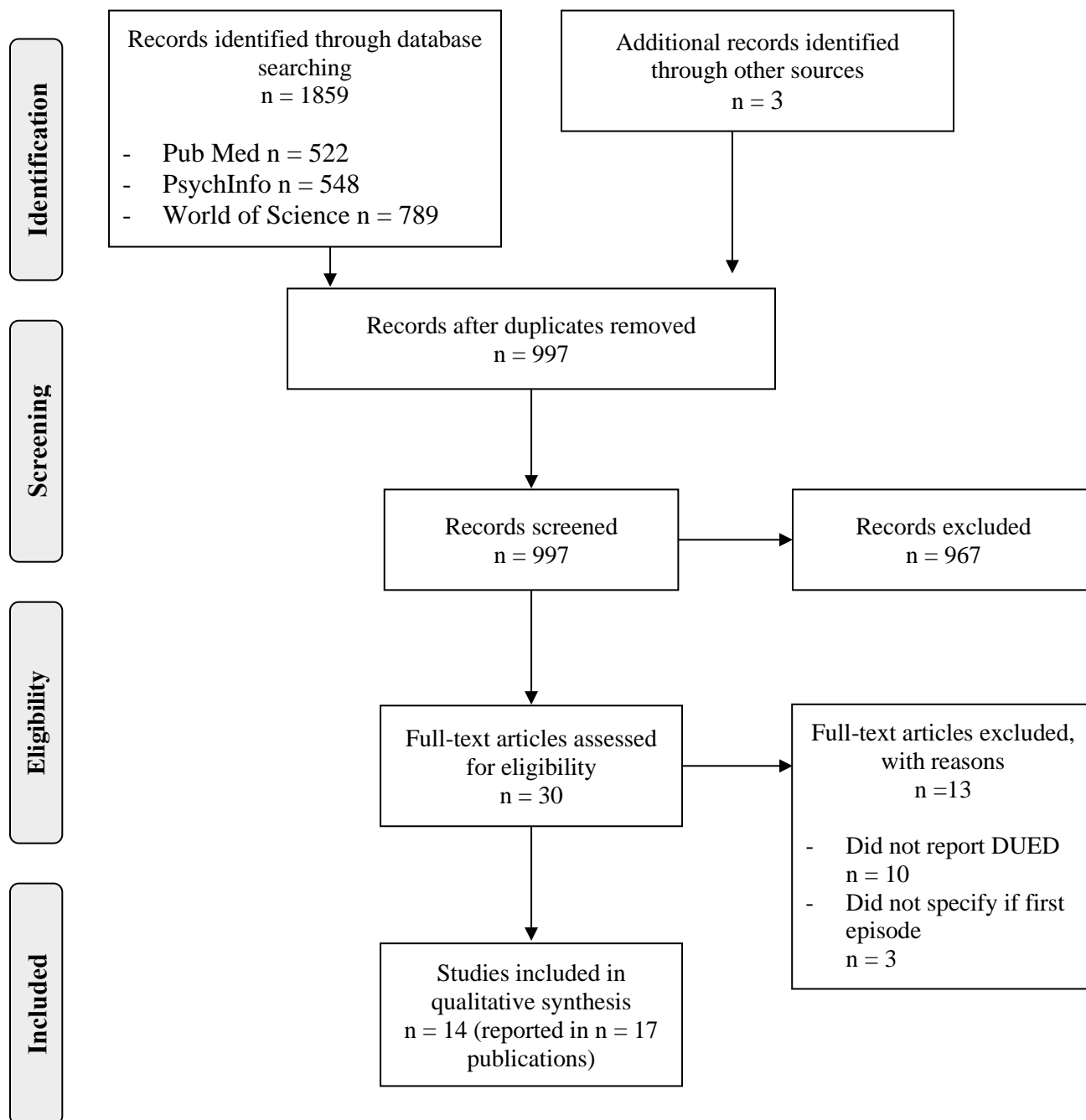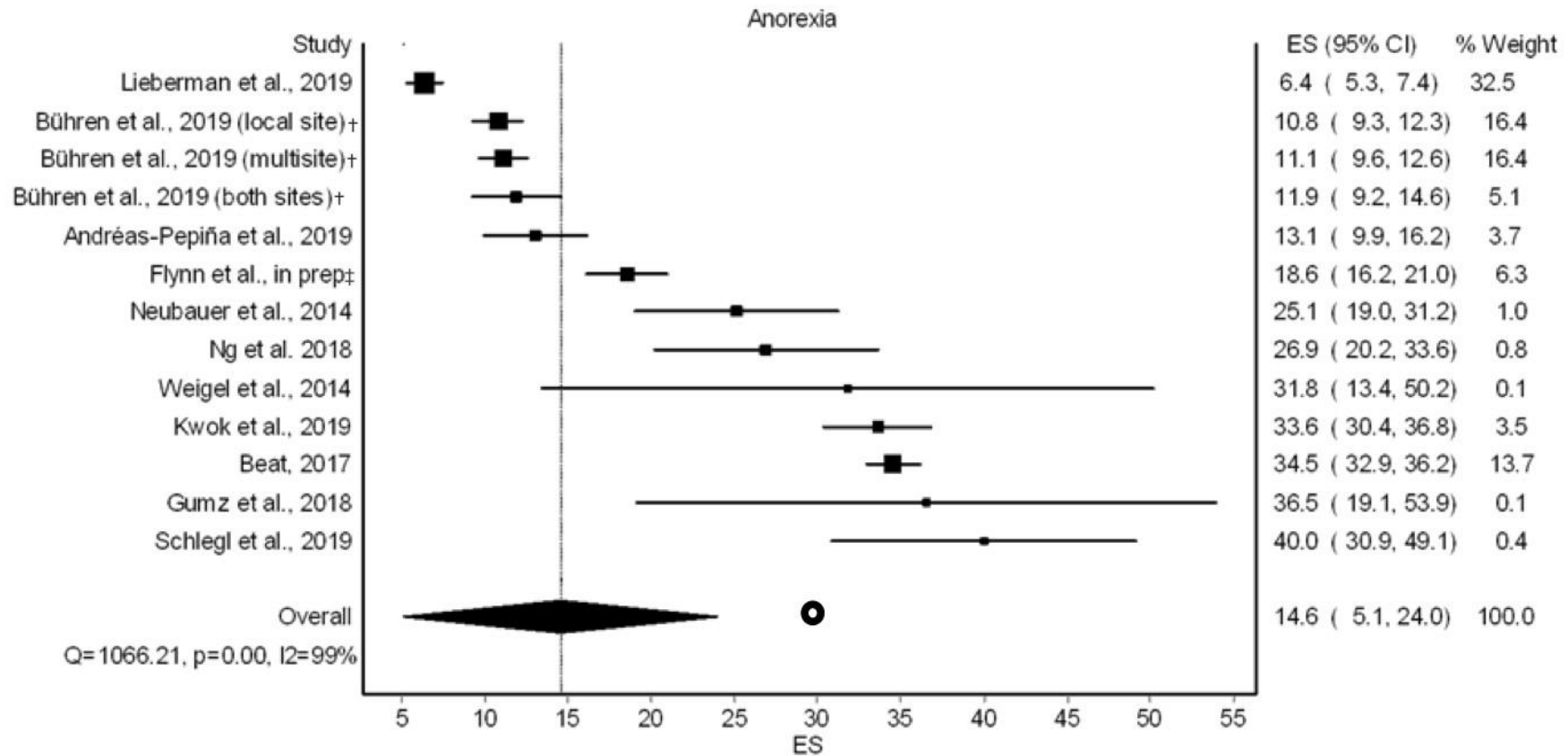
Figure 1. Prisma Flow Diagram

Figure 2. Estimated DUED (in months) for anorexia using the inverse heterogeneity approach with point estimate for simple mean weighted by sample size.
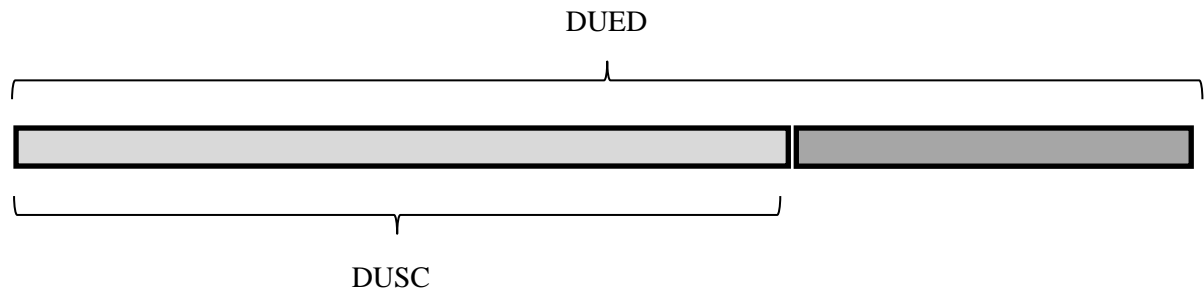

Circle indicates the point estimate for DUED as calculated using a simple mean weighted by sample size (29.9 months)

† Bühren et al. (2013) analysed participants in three separate groups: a local sample in Aachen, Germany, a multisite sample for those outside Aachen, and a third group for participants included in both samples. The corresponding author could not be reached to provide a combined analysis.
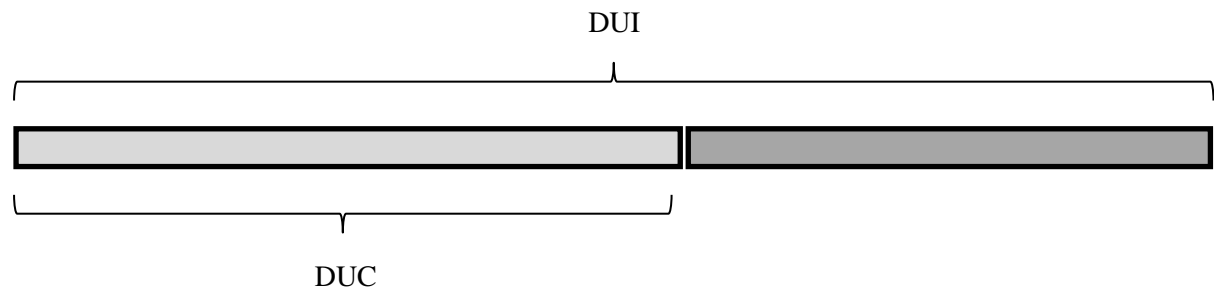
‡ Denotes those in the treatment-as-usual (i.e. non-intervention) condition.

Figure 3. Different conceptualisations of the putative components of DUED
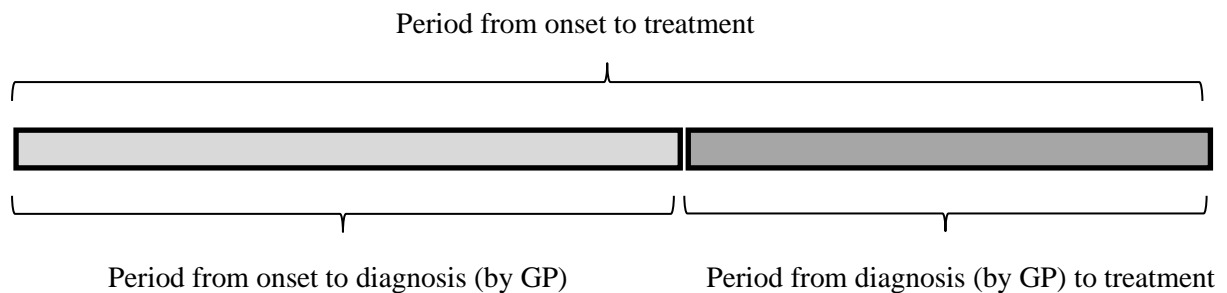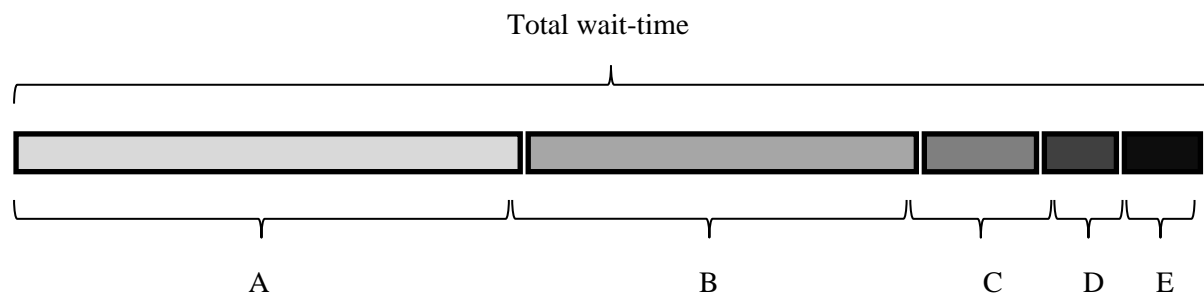
Brown et al., 2018:

DUED

DUSC

Gumz et al., 2018:

DUI

DUC

Schlegl et al., 2019:

Period from onset to treatment

Period from onset to diagnosis (by GP)   Period from diagnosis (by GP) to treatment

Beat, 2017:

Total wait-time

A   B   C   D   E

DUED = Duration of untreated eating disorder (time from onset to evidence-based treatment.); DUSC = Duration until service contact (time from ED onset to assessment.); DUI = Duration of untreated illness (time from onset to initiation of ED-specific evidence-based treatment); DUC = Duration until first contact with healthcare system for ED related issues (measured from onset). A = Time before realising they had an eating disorder; B = Time between realising they had an eating disorder and seeking help; C = Time between first GP visit and referral; D = Time between referral and assessment; E = Time between assessment and start of treatment.