Using an epidemiological approach to investigate sex differences in the manifestation of ADHD in youth and adulthood

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Abstract

Attention-deficit/hyperactivity disorder (ADHD) is a common and impairing neurodevelopmental disorder, defined by maladaptive levels of inattentive and hyperactive/impulsive behaviours. In youth, more males than females receive a diagnosis and the literature is clear in identifying that females with ADHD may be underdiagnosed compared to males. The sex ratio balances out in adulthood, but the diagnosis in adulthood is less common in comparison to youth and is based on age-appropriate adaptations of behavioural symptom descriptions developed to reflect ADHD in childhood. Research has uncovered a wider range of traits that are characteristic of the disorder and could form part of the core symptomatology, which have the potential to aid diagnosis in adults, such as excessive spontaneous mind wandering.

In this thesis, I capitalise on the strengths of epidemiological datasets to investigate sex differences in ADHD across the lifespan and aim to uncover factors that may influence differential referral and diagnostic rates. The first two empirical chapters examine sex differences in youth. Specifically, I examine whether different factors are associated with meeting diagnostic criteria in females versus males, whether sex-dependent biases in parental perceptions of ADHD symptoms exist, and whether the predictive associations of symptoms on being diagnosed and treated for ADHD differs in males and females. The last two empirical chapters investigate ADHD in adulthood and whether a new measure based on the internal subjective experience of ADHD symptoms - excessive mind wandering - could have clinical utility in ADHD diagnosis and add to our understanding of sex differences in the manifestation of ADHD.

My findings suggest that females' ADHD symptoms may need to be made more prominent by additional behavioural and emotional problems for them to receive clinical recognition for their ADHD, and that in the absence of prominent externalising problems females may be more easily missed in the ADHD diagnostic process. Furthermore, sex differences in parental perceptions of ADHD behaviours and impairment were demonstrated, indicating that parents may be less sensitive to ADHD symptoms and impairment in females which could lead to under-referral. My findings also suggest that excessive mind wandering is a common co-occurring feature of adult ADHD that has specific effects on impairment, and that a newly developed measure of mind wandering - The Mind Excessively Wandering Scale (MEWS) – could have clinical utility as an

additional screening tool in adult ADHD assessment and be used for treatment monitoring. Moreover, that the pattern of sex differences observed for the behavioural symptoms of ADHD in youth and adulthood are also reflected in the internalised and subjective experience of excessive mind wandering in adulthood.

It is a public health concern if individuals with ADHD are being missed and not gaining access to services and treatment that they could benefit from, and thus are at greater risk for the adverse outcomes associated with ADHD. Overall, the results of this thesis highlight the need for a careful approach in the assessment of individuals with symptoms of ADHD, specifically females and adults. More research is needed to interrogate further the reasons why females with ADHD may be under-referred and under-diagnosed.

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Statement of authorship

I confirm that this thesis is my own original work, performed and written by myself. I was responsible for conceptualisation, planning, conducting data analyses, interpretation of results, writing drafts of the studies as papers, and revising based on feedback from co-authors and peer-reviewers. The contribution of co-authors, and all published sources consulted, are acknowledged appropriately.

The research presented in this thesis uses data from several collaborative projects. Specifically, the data used in Chapter 2, 3, and 4 were collected by others prior to the commencement of my PhD. I quality controlled and cleaned the data used in Chapters 2 and 5 prior to analyses. The data used in Chapter 5 was from my own study: I completed the ethics application, obtained permissions for the scales used, created the survey on Qualtrics, carried out piloting, 'recruited' participants, and was responsible for data management.

Publications

Chapter 2 is based on the following:

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Chapter 3 is based on the following:

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Chapter 5 is based on the following:

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Chapter 1: Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterised by developmentally inappropriate and impairing levels of inattention and/or hyperactivity/impulsivity, that often persists into adulthood (Biederman, Petty, Evans, Small, & Faraone, 2010; Faraone, Biederman, Spencer, et al., 2006). ADHD has an estimated worldwide prevalence of 5.3% amongst children and adolescents (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007) and 2.5 – 4.4% in adults (Kessler et al., 2006; Simon, Czobor, Bálint, Mészáros, & Bitter, 2009).

In children and adolescents, ADHD is more commonly diagnosed in males, with the sex ratio ranging from 2:1 to 10:1 (Arnold, 1996; Gaub & Carlson, 1997; Novik et al., 2006; Ramtekkar, Reiersen, Todorov, & Todd, 2010; Willcutt, 2012). However, the sex ratio in childhood and adolescence appears to be dependent on the type of sample, with higher male-to-female ratios found in clinical versus population-based samples. Further, the sex ratio in adulthood tends to be more equal (Biederman, Faraone, Monuteaux, Bober, & Cadogen, 2004; Solberg et al., 2018). This suggests that in youth, ADHD affects a greater proportion of females than reflected in clinical practice and that differences exist in the diagnostic process for males and females with ADHD symptoms (Biederman et al., 1999; Rucklidge, 2010). It also suggests that investigating sex differences in population-based samples could extend and enrich our understanding of the ADHD construct beyond that of clinical samples. Potentially, males and females may manifest their ADHD differently, which could contribute to sex differences in referral and diagnosis of the disorder.

The conceptualisation of ADHD as a disorder of attention and hyperactive/impulsive behaviours is perhaps narrow, in the sense that there are a wider range of traits and impairments shown to be characteristic of the disorder. Further, despite the continuation of the disorder into adulthood being reflected in the latest edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association [APA], 2013), the defining symptom descriptions still very much reflect childhood ADHD. As ADHD does not have a single, simply identifiable form, diagnosing it requires an observer's interpretation of behaviour. In childhood, typically parents and teachers provide information on a child's symptoms, whilst in adolescence and adulthood self-

report is usually the main source of information for the diagnostic process. Although diagnosis is made based on the presence of the core symptoms of inattention and hyperactivity/impulsivity, studies have begun to identify other relevant (potentially core) features of ADHD that could aid the diagnostic process, such as excessive spontaneous mind wandering (Seli, Smallwood, Cheyne, & Smilek, 2015). Enhancing our understanding of the broader range of symptoms and problems associated with ADHD and the phenomenology that underlies ADHD symptomatology, has the potential to aid diagnosis and inform targets for interventions. It may also provide further insight into sex differences in the manifestation of ADHD.

This thesis seeks to further our understanding of the sex differences in youth and adult ADHD which may influence referral and diagnostic rates, by examining whether: 1) different factors are associated with meeting diagnostic criteria in females versus males, 2) sex-dependent biases in parental perceptions of ADHD symptoms exist, and 3) symptoms differentially predict being diagnosed and treated for ADHD in males and females. Furthermore, this thesis investigates whether a new measure based on the internal subjective experience of ADHD symptoms - excessive mind wandering - could have clinical utility in ADHD diagnosis and add to our understanding of sex differences in the manifestation of ADHD.

The following sections provide a more detailed overview of ADHD based on current understanding of the disorder, with specific focus on the aspects of relevance to this body of work. This introductory chapter concludes with an overview of the contents of this thesis.

1.1   Diagnosis and symptoms of ADHD

There are two classification systems used in the diagnosis of psychiatric conditions: the International Classification of Diseases (ICD-10), published by the World Health Organisation (World Health Organisation, 1992), and the Diagnostic and Statistical Manual of Mental Disorders (DSM), published by the American Psychiatric Association (APA) (American Psychiatric Association, 2013). The research in this thesis is based on the DSM-IV or DSM-5 classification of ADHD (the specific edition is detailed in the relevant chapters).

The DSM-5 diagnostic criteria for ADHD sets out 18 symptoms: nine symptoms of inattention, six symptoms of hyperactivity, and three of impulsivity, grouped into the two symptom dimensions of inattention and hyperactivity/impulsivity (Table 1.1). To meet diagnostic criteria for ADHD, a child must present with six or more symptoms from at least one dimension (American Psychiatric Association, 2013). The criteria further specify that the onset of several of these symptoms must have been prior to age 12 years, have been present for at least 6 months to a degree that is inconsistent with the child's developmental level, and that several symptoms must be present in more than one setting. There must also be clear evidence of symptoms interfering with functioning in the social, school, or work realm. If all criteria are met, and the symptoms are not better explained by another psychiatric disorder, then a diagnosis of ADHD can be made. For diagnosis in older adolescents and adults (aged 17 years and older), a slightly lower symptom threshold is implemented, with at least five symptoms required in either symptom domain.

Based on the differential manifestation of the two core dimensions of symptoms, the DSM-5 also distinguishes three presentations of ADHD: the predominately inattentive presentation, met when six or more (five in adults) symptoms of inattention are present; the predominantly hyperactive-impulsive presentation, met when six or more (five in adults) symptoms of hyperactivity/impulsivity are present; and the combined presentation, met when at least six symptoms (five in adults) of both dimensions are present. The DSM-5 also requires the level of severity to be specified (mild, moderate or severe).

The ADHD diagnostic criteria in DSM-5 differs only slightly from the DSM-IV. The most prominent revisions include a change from the *onset of symptoms and impairments* before 7 years of age to *onset of several symptoms* before 12 years of age, age-appropriate changes to the wording of items (giving examples of how symptoms may manifest in adulthood), and allowing for the diagnosis of ADHD in conjunction with other frequently co-occurring disorders such as Autism Spectrum Disorder (ASD) (but the symptoms must not be better explained by this condition). Other subtle but important changes include an alteration from *evidence of impairment* in at least two settings, to *evidence of symptoms* in two or more settings, and that functional impairments should *interfere with, or reduce the quality of* functioning, compared to the previous requirement of showing evidence of *clinically significant impairment*. Such changes reflect a more lenient diagnostic approach.

The ICD-10's equivalent to ADHD as set out in the DSM-5, is 'hyperkinetic disorder' (World Health Organisation, 1992). Fundamentally, the two classification systems describe the same disorder, but with slight differences in item wording. However, the number of symptoms required in each domain differs, with the ICD-10 requiring endorsement of all three types of symptoms for diagnosis, perhaps more akin to the DSM-5 combined presentation of ADHD. In ICD-10, onset also remains at before 7 years of age. For these reasons, ICD-10's hyperkinetic disorder is considered a stricter classification of the disorder, identifying a more severely affected group of individuals (Döpfner et al., 2008; Lee et al., 2008; Sørensen, Mors, & Thomsen, 2005).

In clinical practice neither classification system is used in isolation, and additional guidelines on the diagnosis of ADHD are often provided; for example, in the UK the National Institute for Health and Care Excellence (NICE) provide guidelines for ADHD diagnosis and management (NICE, 2018). NICE recommend that, as well as comprising DSM or ICD assessment, the diagnostic process should also include assessment of the individual's needs, circumstances (social, familial, and educational or occupational), and physical health.

Table 1.1.DSM-5 symptom checklist for ADHD

	Inattention
1.	Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or during other activities (e.g., overlooks or misses details, work is inaccurate)
2.	Often has difficulty sustaining attention in tasks or play activities (e.g., has difficulty remaining focused during lectures, conversations, or lengthy reading)
3.	Often does not seem to listen when spoken to directly (e.g., mind seems elsewhere, even in the absence of any obvious distraction)
4.	Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (e.g., starts tasks but quickly loses focus and is easily sidetracked)
5.	Often has difficulty organizing tasks and activities (e.g., difficulty managing sequential tasks; difficulty keeping materials and belongings in order; messy, disorganized work; has poor time management; fails to meet deadlines)
6.	Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (e.g., schoolwork or homework; for older adolescents and adults, preparing reports, completing forms, reviewing lengthy papers)
7.	Often loses things necessary for tasks or activities (e.g., school materials, pencils, books, tools, wallets, keys, paperwork, eyeglasses, mobile telephones)
8.	Is often easily distracted by extraneous stimuli (for older adolescents and adults, may include unrelated thoughts)
9.	Is often forgetful in daily activities (e.g., doing chores, running errands; for older adolescents and adults, returning calls, paying bills, keeping appointments)
	Hyperactivity and Impulsivity
10.	Often fidgets with or taps hands or feet or squirms in seat
11.	Often leaves seat in situations when remaining seated is expected (e.g., leaves his or her place in the classroom, in the office or other workplace, or in other situations that require remaining in place)
12.	Often runs about or climbs in situations where it is inappropriate (in adolescents or adults, may be limited to feeling restless)
13.	Often unable to play or engage in leisure activities quietly
14.	Is often "on the go," acting as if "driven by a motor" (e.g., is unable to be or uncomfortable being still for extended time, as in restaurants, meetings; may be experienced by others as being restless or difficult to keep up with)
15.	Often talks excessively
16.	Often blurts out an answer before a question has been completed (e.g., completes people's sentences; cannot wait for turn in conversation)
17.	Often has difficulty waiting his or her turn (e.g., while waiting in line)
18.	Often interrupts or intrudes on others (e.g., butts into conversations, games, or activities; may start using other people's things without asking or receiving permission; for adolescents and adults, may intrude into or take over what others are doing)

Note: Items replicated from DSM-5 (American Psychiatric Association, 2013)

1.2   Categorical versus dimensional approaches to ADHD

Diagnostic manuals, including the DSM and ICD, implement categorical classifications of mental health disorders such as ADHD. Such diagnostic classification systems create a division between what is typical or 'normal' behaviour versus pathological and 'abnormal', leading to categorisation of an individual as meeting diagnostic criteria (affected) or not (unaffected). This clearly has utility for clinical practice, enabling the identification of individuals with ADHD that is severe and impairing and whom will likely benefit from access to treatment, equating to a binary treatment decision (Coghill & Sonuga-Barke, 2012). However, there is now much converging evidence that the behavioural symptoms of ADHD are quantitative traits distributed continuously throughout the population, lying on a spectrum of normal trait variation, with clinically significant ADHD representing the extreme of this continuum rather than being qualitatively different (Frazier, Youngstrom, & Naugle, 2007; Haslam et al., 2006; Larsson, Anckarsater, Råstam, Chang, & Lichtenstein, 2012; Levy, Hay, McStephen, Wood, & Waldman, 1997; Lubke et al., 2007; Salum et al., 2014). For example, the genetic and environmental aetiology are shown to be similar for categorical and dimensional definitions of ADHD behaviours (i.e., for both disorder and trait) (Chen et al., 2008; Larsson et al., 2012; Levy et al., 1997). Studies using a polygenic risk score derived from individuals diagnosed with ADHD predicted ADHD traits in the general population, which demonstrates high genetic overlap between the categorical diagnosis of ADHD and the continuous trait in the population (Martin, Hamshere, Stergiakouli, O'Donovan, & Thapar, 2014; Stergiakouli et al., 2015). The implications of such findings are that multiple genes and environmental influences of small effect contribute to the spectrum of symptoms and that no single factor is either necessary or sufficient for diagnosis.

When viewing traits as dimensional, where to implement the cut-off for clinically significant symptoms that warrant diagnosis and treatment becomes a substantial issue. The absence of a distinct point of rarity means that it becomes unclear where to delineate the boundary between normal and pathological. This is further complicated by the considerable heterogeneity of ADHD; for example, two people can be diagnosed with ADHD but have very different manifestations (i.e., present with different combinations of symptoms from the diagnostic criteria). Careful consideration of the diagnostic threshold for ADHD is of great importance. In clinical practice, in

moderate to severe cases the continuous nature of the disorder should not create difficulties with regard to diagnosis, as at the extremes of range it is likely to be apparent who warrants intervention. However, in mild cases or more subtle manifestations of the disorder, it is less clear cut (Asherson, Buitelaar, Faraone, & Rohde, 2016). If the cut-off is too strict, children who would benefit from support may be excluded from this option. Questions also arise around what should happen to individuals presenting at subthreshold to the diagnostic criteria but who may still experience significant functional impairment and whom would benefit from treatment (Coghill & Sonuga-Barke, 2012; Polanczyk, Salum, Sugaya, Caye, & Rohde, 2015). Furthermore, some critics of the categorical approach have raised the issue that the same criteria are applied to males and females, and since the empirical basis for these criteria is derived from research conducted largely among males only, this could be inappropriate and a potential reason why more males than females are diagnosed (Lubke et al., 2007) (this is discussed further in section 1.3.4.2). This highlights the importance of managing diagnostic thresholds effectively, since failure to meet full diagnosis limits access to a range of services, despite the association of subthreshold ADHD with real world impairment (Angold, Costello, Farmer, Burns, & Erkanli, 1999; Balazs & Kereszteny, 2014; Bussing, Mason, Bell, Porter, & Garvan, 2010; Faraone, Biederman, Spencer, et al., 2006; Hong et al., 2014; Noren Selinus et al., 2016). Conversely, if the cut-off is too low then typically developing children could be labelled with ADHD and given unnecessary stimulant medication.

The National Collaborating Centre for Mental Health (NCCMH, 2009) emphasise the importance of linking symptoms to impairment, which may be a better measure of identifying those who would benefit from treatment rather than arbitrary symptom counts. Conceptually, impairment is not the same as severity. In ADHD, severity relates to the frequency, pervasiveness, and intensity of the symptoms, whereas impairment is what results from the symptoms. Consequently, one could have high severity of symptoms but not experience impairment, perhaps due to environmental circumstances being suited to symptoms (for example, an artist who experiences the spontaneous and uncontrolled thoughts as the root of their creativity, or those with high levels of support from significant others). Another individual could have symptoms of less severity but experience high functional impairment, again speaking to the heterogeneity of ADHD.

Both categorical and dimensional approaches to ADHD have value in the investigation of the disorder and its underlying psychopathology. A benefit of the categorical approach is that it offers

a common language between clinicians, healthcare professionals and researchers, and reduces the potential of risky and unethical treatment where not indicated (Coghill & Sonuga-Barke, 2012). However, a dimensional approach to ADHD enables investigation of ADHD in population-based samples unselected for clinical extremes for epidemiological research, reducing the risk of ascertainment bias that is associated with clinical samples. Further, these types of samples include children for whom formal diagnosis is absent or unknown and also enables the study of the clinical need of those who do not meet full diagnosis. The research in this thesis uses both symptom counts - viewing behaviours along a continuum of severity - and clinical cut-off. The approach used is specified in each chapter, with some employing both approaches. The importance of impairment in ADHD is also emphasised.

1.3   Epidemiology of ADHD

1.3.1   Prevalence

Meta-analytic evidence estimates the worldwide prevalence of ADHD in children and adolescents at 3.4 – 7.2% (Polanczyk et al., 2007, 2015; Thomas, Sanders, Doust, Beller, & Glasziou, 2015; Willcutt, 2012), leading it to be considered one of the most common neurodevelopmental disorders in childhood. The evidence suggests that the prevalence has remained constant over the past three decades (Collishaw, 2015; Polanczyk, Willcutt, Salum, Kieling, & Rohde, 2014; Rydell, Lundström, Gillberg, Lichtenstein, & Larsson, 2018; Safer, 2018; Thomas et al., 2015) in both boys and girls (Rydell et al., 2018), and that cross-cultural variability is limited (Polanczyk et al., 2015; Willcutt, 2012), speaking against the view that ADHD is merely a cultural construct. However, as with most mental health disorders, the diagnosis of ADHD is dependent on subjective ratings of symptom clusters as opposed to objective measures of etiological processes or biomarkers. This can lead to wide variability in prevalence estimates, and research shows that heterogeneity in estimates across studies can be attributed to varying study methods, including the diagnostic criteria employed, the diagnostic measures used, inclusion of impairment criterion, source of informant, and sampling methods (Polanczyk et al., 2007, 2014, 2015; Willcutt, 2012). This suggests that methodological differences influence overall prevalence and highlights the importance of establishing pervasiveness of symptoms and impairment. However, evidence does

document that diagnosis and medication rates have increased over time (McCarthy et al., 2012; Rydell et al., 2018; Safer, 2018). This could be attributed to a variety of factors, such as increased awareness of ADHD, changes in clinical practice and ADHD management, parental and public attitudes to diagnosis and treatment, adjustment to the DSM criteria, and/or changes in the impact of symptoms and degree of impairment (which could be influenced by societal and cultural norms and interpretation of ADHD symptoms) (Safer, 2018).

In adulthood, the prevalence of ADHD is estimated at 2.1 – 5.8% (Faraone & Biederman, 2005; Fayyad et al., 2007; Kessler et al., 2006; Matte et al., 2015; Simon et al., 2009; Vitola et al., 2017; Willcutt, 2012). It is not clear if the lower prevalence rates in adulthood compared to those observed in youth reflect true estimates due to remittance of ADHD from childhood (which will be discussed more in section 1.3.2), or lower recognition of ADHD in adults leading to under-diagnosis (Asherson et al., 2016; Deberdt et al., 2015; Faraone & Biederman, 2005; Ginsberg, Quintero, Anand, Casillas, & Upadhyaya, 2014). There are still relatively few diagnostic services for adult ADHD in many regions of the world, and those with ADHD in childhood can also be lost during the transition from child to adult mental health services (Asherson et al., 2016; Ginsberg et al., 2014). Further, adult ADHD symptoms such as emotional lability and restlessness are often mistaken for comorbid disorders and attributed to another disorder altogether (Ginsberg et al., 2014). Under-diagnosis could also result from the employment of different informants in the diagnostic process in adulthood, where ADHD diagnoses relies heavily (often exclusively) on self-report as compared to parent and teacher reports in childhood. In addition, up until the release of the DSM-5 (American Psychiatric Association, 2013), adult ADHD diagnosis was based on behavioural descriptions of ADHD symptoms developed for children, with no adaptation for adult presentations (American Psychiatric Association, 1994, 2000), which is likely to have affected prevalence estimates (Matte et al., 2015; Vitola et al., 2017).

A clear understanding of the prevalence of ADHD is imperative for efficient service planning and resource allocation, which has implications for both the affected individual and society. This may be especially important for clinicians working with adults, as compared to in childhood, screening for ADHD in adults is not commonplace (Faraone & Biederman, 2005). Further, identifying the most effective screening methods and informant, and the most appropriate cut-off thresholds for diagnosis is of great importance (Polanczyk et al., 2015). In adulthood, assessing ADHD symptoms

based on observed behaviours may be less appropriate and subjective reports of mental state changes could be more informative, but limited attempts have been made with regard to a phenomenological approach in ADHD (i.e., an approach based on subjective experience) (Asherson et al., 2016). One objective of this thesis is to examine the value in taking a phenomenological approach to ADHD by evaluating a newly developed measure based on patient reports of their internal experience of ADHD (further information is given in section 1.5.2.2).

1.3.2 Developmental Trajectory

Initially, ADHD was believed to be a disorder confined to childhood, but it is now recognised to frequently persist into adolescence and adulthood (Asherson et al., 2016; Biederman et al., 2010; Faraone, Biederman, & Mick, 2006), with estimates of persistence rates ranging from 15 – 87% (Biederman, Monuteaux, et al., 2006; Cheung et al., 2016; Faraone, Biederman, & Mick, 2006; van Lieshout et al., 2016). A meta-analysis of follow-up studies found that ~15% of children with ADHD retained full diagnostic status (syndromatic persistence) by the age of 25 years, but when including those meeting criteria for partial remission (symptomatic persistence, involving maintenance of partial diagnostic status with impairment) the persistence rate was in the region of 40 - 60% (Faraone, Biederman, & Mick, 2006). More recent follow-up studies have found much higher persistence rates, ranging from 50 – 86.5% for full diagnosis (Cheung et al., 2016; Lara et al., 2009; van Lieshout et al., 2016) and 8.4% maintaining subthreshold symptoms (van Lieshout et al., 2016). The persistence of inattentive symptoms tends to be greater than symptoms of hyperactivity-impulsivity, which have been shown to decline with age (Biederman, Mick, & Faraone, 2000; Larsson, Dilshad, Lichtenstein, & Barker, 2011; Pingault et al., 2015; Sollie, Larsson, & Mørch, 2012; van Lieshout et al., 2016; Willcutt, 2012).

Varying persistence rates could result from differences across studies in the classification of persistence or remittance, the inclusion of impairment criteria, the subtype and severity of the study sample, and the presence of comorbidity (van Lieshout et al., 2016). Limitations also exist in the relatively small sample sizes of existing persistence studies and that follow-up was only into young adulthood. Studies in larger cohorts are needed, as well as those that study later adulthood (i.e., >25 years). Thus, it is hard to deduce clear developmental trajectories of ADHD.

Although findings suggest that ADHD attenuates over time, symptom reduction across the developmental trajectory could reflect developmental insensitivity of earlier versions of the DSM (Faraone, Biederman, & Mick, 2006). The detailed studies were before the introduction of DSM-5, where changes were implemented in the diagnostic criteria to facilitate diagnosis in adults, and so 'true' persistence rates may potentially be higher than the existing estimates. The DSM-5 also allows for the possibility that adults with ADHD may not have met full diagnostic status in childhood, enabling children who had subthreshold levels of symptoms and no impairment to meet diagnostic criteria for ADHD in adolescence and adulthood. Thus, the DSM-5 acknowledges the possibility that full diagnosis of ADHD may emerge at difference stages in the developmental trajectory (Asherson et al., 2016).

Recently, evidence has emerged that raises the possibility of a late-onset form of ADHD in the absence of a history of substantial symptoms in childhood (Agnew-Blais et al., 2016; Caye et al., 2016; Moffitt et al., 2015). Three large-scale longitudinal population-based studies found that around 67.5 – 90% of adults who met diagnostic criteria for ADHD did not meet criteria in childhood. Agnew-Blais et al. (2016) also found that those with late-onset ADHD were more likely to be female and have higher IQ. Such studies propose that ADHD may not always be a continuation of the childhood disorder, but instead emerge in late adolescence or adulthood. They raise the possibility that late-adolescent or adult-onset ADHD could represent a distinct diagnostic entity that differs in onset, developmental trajectory, and aetiology from childhood ADHD (Agnew-Blais et al., 2016; Caye et al., 2016; Moffitt et al., 2015). The studies also speak to the view that the age of onset criteria are based on clinical wisdom and are not yet strongly supported by empirical data (Asherson et al., 2016).

This is currently a topic of considerable debate and it has been suggested that the studies showing late-onset ADHD may have overestimated its prevalence (Asherson et al., 2016; Faraone & Biederman, 2016). These studies had methodological limitations, such as not assessing subthreshold symptoms or using the 18 DSM items in childhood (Caye et al., 2016), and the use of self-report in adulthood instead of informant report (as in childhood diagnosis) (Agnew-Blais et al., 2016; Caye et al., 2016). Another potential explanation for these findings is that in the presence of positive scaffolding or protective factors (e.g., high IQ, well developed executive functioning skills, supportive and structured home and school environment), instead of presenting with the full

diagnostic syndrome some children may manifest subthreshold ADHD symptoms (Asherson et al., 2016; Faraone & Biederman, 2016). Due to this scaffolding they are able to compensate for their symptoms, but once such scaffolding is removed (e.g., when leaving the home or school environment) and new challenges of adult life present, the full syndrome may emerge (Asherson et al., 2016; Faraone & Biederman, 2016). Thus, individuals with childhood-onset and adult-onset may have the same underlying liability for ADHD, but when such protective factors are present in childhood the symptoms may not become impairing and exceed diagnostic thresholds until a later developmental stage when this scaffolding is removed (Agnew-Blais et al., 2016; Kosaka, Fujioka, & Jung, 2018). This highlights the importance of monitoring subthreshold symptoms in childhood (Faraone & Biederman, 2016).

It is also possible for this explanation to work in the converse way, in that children who meet full diagnostic criteria for ADHD in childhood may no longer meet threshold in adulthood due to the selection of environments that are more suited to their symptoms. Thus, symptoms are no longer experienced as impairing (Agnew-Blais et al., 2016; Kosaka et al., 2018).

A recent study has proposed that the symptoms and impairments of those with late-onset ADHD may be better explained by substance use or another mental health disorder (Sibley et al., 2018), and studies in adult ADHD clinics suggest adult-onset to be less frequent (Lopez, Micoulaud-Franchi, Galera, & Dauvilliers, 2017; Solanto, 2018). Thus, these recent findings require replication and further investigation and should be interpreted with caution at this early stage. However, the absence of a childhood diagnosis of ADHD should not preclude adults with ADHD from accessing services if their level of impairment warrants it (Agnew-Blais et al., 2016).

1.3.3   Co-occurring disorders

Studies in both epidemiological and clinical samples show that most individuals with ADHD have multiple co-occurring disorders (Bauermeister et al., 2007; Biederman, Newcorn, & Sprich, 1991; Elia, Ambrosini, & Berrettini, 2008; Ford, Goodman, & Meltzer, 2003; Ghanizadeh, 2009; Jensen & Steinhausen, 2015; Kadesjö & Gillberg, 2001; Kraut et al., 2013; Larson, Russ, Kahn, & Halfon, 2011). A recent study found 52% of children and adolescents diagnosed with ADHD had at least one co-existing psychiatric disorder and 26% had two or more (Jensen & Steinhausen, 2015),

whilst others have found as many as 87% have one or more co-existing diagnoses and 67% have two or more (Kadesjö & Gillberg, 2001). Individuals with subthreshold ADHD symptoms can also experience high rates of comorbidity (Kadesjö & Gillberg, 2001).

Externalising problems such as conduct disorder and oppositional defiant disorder are among the most frequent co-occurring behavioural disorders, found in between 10-67% of youth with ADHD (Bauermeister et al., 2007; Bendiksen et al., 2017; Elia et al., 2008; Ford et al., 2003; Ghanizadeh, 2009; Jensen & Steinhausen, 2015; Kadesjö & Gillberg, 2001; Kraut et al., 2013; Larson et al., 2011; Reale et al., 2017; Steinhausen et al., 2006; Wichstrøm et al., 2012). Internalising problems, such as mood and anxiety problems are also commonly found to co-occur with ADHD. Studies indicate that between 6-44% of youth with ADHD also have a co-occurring anxiety disorder (Bauermeister et al., 2007; Elia et al., 2008; Larson et al., 2011; Reale et al., 2017; Steinhausen et al., 2006; Wichstrøm et al., 2012), and between 3-32% have co-occurring depression (Bauermeister et al., 2007; Elia et al., 2008; Ghanizadeh, 2009; Larson et al., 2011; Steinhausen et al., 2006; Wichstrøm et al., 2012).

ADHD also shows high rates of comorbidity with other neurodevelopmental disorders and specific learning difficulties (Jensen & Steinhausen, 2015; Kadesjö & Gillberg, 2001; Thapar & Cooper, 2016). One of the most commonly co-occurring neurodevelopmental disorders is autism spectrum disorder (ASD), which has been shown in 6-50% of children with ADHD (Jensen & Steinhausen, 2015; Larson et al., 2011; Rommelse, Franke, Geurts, Hartman, & Buitelaar, 2010). Co-existing learning difficulties (such as dyslexia, dyscalculia and writing disorders) have been found in between 3-56% (Carroll, Maughan, Goodman, & Meltzer, 2005; DuPaul, Gormley, & Laracy, 2013; Larson et al., 2011; Reale et al., 2017; Sexton, Gelhorn, Bell, & Classi, 2012).

Co-occurring disorders are also frequent in adulthood, with around 75-90% of those with ADHD believed to have at least one co-existing condition (Ginsberg et al., 2014; Kooij et al., 2010). In this age group, co-occurring conditions also include conduct and oppositional problems, depression, anxiety, ASD, and learning difficulties (Bolea-Alamañac et al., 2014; Friedrichs, Igl, Larsson, & Larsson, 2012; Ginsberg et al., 2014; Hesson & Fowler, 2018; Kessler et al., 2006; Schmidt & Petermann, 2009). Furthermore, bipolar disorder, personality disorders and substance use disorders are also common (Bolea-Alamañac et al., 2014; Gudjonsson, Sigurdsson, Sigfusdottir, &

Young, 2012; Hesson & Fowler, 2018; Jacob et al., 2007; Kessler et al., 2006; Sobanski, 2006; Solberg et al., 2018). For example, studies have estimated that among adults with ADHD, between 5-32% may also have bipolar disorder (Asherson et al., 2014; Halmøy et al., 2010; Solberg et al., 2018), 30% have a co-occurring personality disorder (Huntley & Young, 2014), and between 9-58% have a substance use disorder (Magon & Müller, 2012; Sizoo et al., 2010; Sobanski, 2006; Solberg et al., 2018). Sleep problems are also frequently reported in adults with ADHD (Asherson et al., 2016; Bjorvatn et al., 2017; Díaz-Román, Mitchell, & Cortese, 2018; Van Veen, Kooij, Boonstra, Gordijn, & Van Someren, 2010).

In many cases of those with ADHD and co-existing symptoms of other disorders, diagnostic overshadowing may occur and alternative diagnoses may be given (Asherson et al., 2014; Ginsberg et al., 2014; Kooij et al., 2010; Reale et al., 2017). Co-occurring symptoms and disorders may be associated with greater impairment (Bauermeister et al., 2007; Steinhausen et al., 2006), and as it is so often the case that ADHD is comorbid with other disorders it can be challenging to disentangle which symptoms are leading to the adverse outcomes (Nigg, 2013).

1.3.4 Sex Differences

A striking observation in childhood ADHD, and a well-established feature of the disorder, is the large sex difference in referral and diagnostic rates, in the direction of male dominance. The ratio of males to females with ADHD in youth falls in the realm of 2:1 to 10:1 (Arnett, Pennington, Willcutt, Defries, & Olson, 2015; Biederman et al., 2002; Novik et al., 2006; Ramtekkar et al., 2010; Willcutt, 2012), with the more pronounced male: female ratios found in clinical samples compared to population-based samples. Further, by adulthood the sex ratio of ADHD tends to be closer to equal (Biederman et al., 2004; Solberg et al., 2018). This suggests that in youth, females may be underdiagnosed in the community (Ramtekkar et al., 2010), indicating potential sex differences in the process of referral and diagnosis for those with ADHD symptoms (Arcia & Conners, 1998). More research in non-referred samples is needed to greater understand these issues, facilitate further understanding of the disorder, and ensure that females with ADHD are not being 'missed' in childhood leading to greater risk of negative long-term outcomes. This was a primary objective of this thesis and so a more detailed overview of current understanding of sex differences in ADHD is now provided.

1.3.4.1   Phenotypic and symptom severity sex differences

One explanation for the observed sex differences in referral and diagnosis in youth is that females with ADHD are more likely to present with predominantly inattentive symptoms, and often greater levels of internalising symptoms such as anxiety and depression, rather than the hyperactive and impulsive symptoms (Arnold, 1996; Quinn, 2008). In contrast, males with ADHD are often characterised as presenting with externalising disruptive behaviours, with more hyperactivity, impulsivity, and co-occurring behavioural problems such as oppositional defiant and conduct disorder (Arnold, 1996; Quinn, 2008). If females present with less overt disruptive behaviour they may be less likely to be referred due to their behaviour having less of a negative impact on parents and teachers. Additionally, their internalising symptoms may lead to alternative diagnoses, such as an anxiety disorder or depression. However, the literature provides inconsistent findings regarding sex differences in the phenotypic presentation of ADHD. Findings also appear to be affected by a range of factors, including the diagnostic measures used, the informants, and the sample type - namely if it is a clinically ascertained or population-based sample (Gaub & Carlson, 1997; Gershon, 2002; Ramtekkar et al., 2010).

Studies in clinical samples of males and females have found the combined presentation is the most prevalent, followed by the inattentive and hyperactive/impulsive presentations (Biederman et al., 1999, 2005, 2002; Ghanizadeh, 2009; Novik et al., 2006). Some studies have found that females are more likely than males to be diagnosed with the inattentive presentation (Biederman et al., 2002; Rucklidge, 2010), whilst others have shown no difference (Ghanizadeh, 2009). Population-based studies tend to show that males are more likely than females to meet criteria for all of the subtypes of ADHD (Ford et al., 2003; Graetz, Sawyer, & Baghurst, 2005; Levy, Hay, Bennett, & Mcstephen, 2005; Ramtekkar et al., 2010; Willcutt, 2012), and that the inattentive presentation is most common in both sexes (Ramtekkar et al., 2010; Willcutt, 2012). However, a meta-analytic review found that among children meeting criteria for ADHD from the population, a significantly larger proportion of females had the inattentive presentation compared to males, with the opposite pattern for the combined presentation (Willcutt, 2012). A study employing interview assessment (rather than rating-scales) found that although a greater percentage of females had the inattentive versus hyperactive/impulsive presentation, there was still a higher percentage of males with the inattentive presentation compared to females (Ford et al., 2003). The use of

structured diagnostic interviews for subject identification when exploring sex differences in ADHD has been highlighted as a necessity (Gaub & Carlson, 1997).

These findings suggest that females with ADHD are more prone to having difficulties with attention, although findings are not consistent or definitive. Primarily inattentive symptoms tend to be rated as less impairing than the externalising hyperactive and impulsive symptoms (Coles, Slavec, Bernstein, & Baroni, 2012; Willcutt, 2012), and research indicates that individuals with the combined presentation are more likely to be referred (Willcutt, 2012). This means an individual with primarily inattentive symptoms of ADHD may be less frequently referred for services (Nussbaum, 2012), which has implications for females if it is the case that they have a more inattentive presentation.

Regarding co-existing symptoms, when comparing females and males in clinical samples, some studies show that females with ADHD demonstrate less risk for depression (Biederman et al., 2002), whilst others find that females score greater for depression and males for anxiety (Mitchison & Njardvik, 2015), and others find that females and males are equally as likely to be impaired by anxiety and/or depression, but females have greater parent-rated emotional symptoms (Novik et al., 2006). Further, some studies have shown males to have greater conduct disorder compared to females (Jensen & Steinhausen, 2015), whilst others find an absence of differences in externalising symptoms (Mitchison & Njardvik, 2015). A number of other studies also detail a lack of sex differences for co-occurring problems (Arcia & Conners, 1998; Novik et al., 2006; Sharp et al., 1999). Population-based samples show the percentage of males and females with ADHD meeting symptom criteria for depressive disorders to be similar (Graetz et al., 2005), as well as the absence of sex differences for externalising disorders (Graetz et al., 2005; Levy et al., 2005).

Research has also demonstrated that females with ADHD are less likely to have learning difficulties or manifest problems at school compared to males (Biederman et al., 2002; Graetz et al., 2005), which could lead to lower identification of ADHD in females (Biederman et al., 2002; Graetz et al., 2005). In addition to greater prosocial behaviour in females compared to males with ADHD (Novik et al., 2006), this could mask impairment to key informants.

In relation to symptom severity, studies tend to show that males and females in clinical samples have similar severity, but in population-based sample males tend to have higher ratings compared to females. In one of the first meta-analyses of sex differences in ADHD, Gaub and Carlson (1997) found lower rates of inattention, internalising behaviour, peer aggression and peer disliking among females versus males with ADHD identified from non-referred populations. However, in clinic-referred samples these differences between males and females with ADHD were not observed. Findings also demonstrated within-sex differences; clinic-referred and non-referred males with ADHD presented with similar levels of internalising behaviour relative to non-ADHD males. In contrast, clinic-referred females with ADHD had higher levels of internalising behaviours than females without ADHD, but this was not shown in non-referred females with ADHD versus females without ADHD. This highlighted that clinic-referred females may not be representative of non-referred females in the same way that males are. In the most recent meta-analytic review, Gershon (2002) found that in non-referred populations, females with ADHD had lower ratings for hyperactivity and inattention than males, but in clinic samples parent ratings of inattentiveness were greater for ADHD females than ADHD males. Of note, conclusions from both meta-analyses were based on extremely small female samples.

Findings from more recent studies investigating sex differences in ADHD symptom severity in diagnosed cases are inconsistent: some studies have demonstrated that ADHD symptom severity is greater in females (Fedele, Lefler, Hartung, & Canu, 2012), lower in females (Arnett et al., 2015), or a there is a lack of differences between male and female symptom severity (Elkins, Malone, Keyes, Iacono, & McGue, 2011). In contrast, most population-based screens for ADHD tend to find higher mean ADHD symptom scores in males relative to females (Larsson et al., 2012; Levy et al., 2005; Martin et al., 2014), although there are exceptions (Graetz et al., 2005).

Sex differences in adult ADHD have received much less attention in the literature in comparison to childhood (Corbisiero, Hartmann-schorro, Riecher-Rössler, & Stieglitz, 2017; Fedele et al., 2012) and have often been neglected as a potential moderator of the nature of adult ADHD (Solberg et al., 2018; Williamson & Johnston, 2015). The few studies that do exist also demonstrate mixed results regarding whether males and females are affected differently by ADHD in adulthood. Some studies find that females with ADHD have higher symptom levels and impairment than males with ADHD (Fedele et al., 2012; Fredriksen et al., 2014; Nussbaum, 2012), some show only higher

current inattention symptoms (Biederman et al., 2004), and others show a similar phenotypic presentation (Rasmussen & Levander, 2009; Wilens et al., 2009). A lack of differences could be due to the fluidity of the subtypes and the reduction of hyperactive/impulsive symptoms with age (Larsson et al., 2011). Regarding sex differences in co-morbidity, studies are lacking and again the existing findings are mixed. A recent study using Norwegian national registry data found that the association between ADHD and psychiatric comorbidities differed significantly amongst males and females (Solberg et al., 2018). Specifically, prevalence differences between ADHD and non-ADHD adults were significantly larger amongst females than males for anxiety disorders, bipolar disorder, major depressive disorder, and personality disorder. The opposite pattern was observed for schizophrenia and substance use disorder, with greater prevalence differences amongst males.

1.3.4.2   Mechanisms underlying sex differences in ADHD

The reason for the substantial sex difference in ADHD diagnosis observed in youth is unclear (Martin, Taylor, et al., 2018; Martin, Walters, et al., 2018) and is likely to be complex due to the extreme heterogeneity of ADHD. One hypothesis is that the observed sex differences may reflect true etiological differences due to a 'female protective effect'. This theory proposes that females require greater genetic and environmental 'load' or exposure to risk factors associated with ADHD to manifest the same degree of impairment as males with ADHD and warrant diagnosis (Eriksson, Lundström, Lichtenstein, Bejerot, & Eriksson, 2016; Rhee & Waldman, 2004; Taylor et al., 2016). Partial support for this hypothesis has been demonstrated: for example, siblings of females with ADHD have been found to display greater risk of ADHD compared to siblings of males with ADHD (Martin, Walters, et al., 2018; Rhee & Waldman, 2004; Taylor et al., 2016). This suggests that when ADHD exists in females it reflects a greater exposure to genetic and environmental factors associated with ADHD compared to ADHD in males. An alternative explanation is that parents may have a higher threshold for recognising ADHD symptoms in daughters, or clinicians may have a higher threshold for diagnosing ADHD in females (Martin, Walters, et al., 2018). Furthermore, clinicians may be more likely to diagnose ADHD in females if their ADHD symptoms are accompanied by additional behavioural problems which make their ADHD symptoms more prominent (Martin, Walters, et al., 2018).

Another set of hypotheses put forward are the Mean Difference and the Variance Difference Models. The Mean Difference Model proposes that, relative to males, the female liability distribution for ADHD symptoms is shifted in the less-affected direction. Given the absolute cut-off for diagnostic status, fewer females will fall into this category and so more males will be diagnosed (Arnett et al., 2015). When controlling variances across sexes, it has been shown that more males are present in the top affected percentile and more females are present in the least affected percentile (Arnett et al., 2015). The Variance Difference Model proposes that greater variance in males symptom scores leads to more males falling into the extreme tails of the distribution (this also has the expectation that more males fall into the non-symptomatic extreme) (Arnett et al., 2015). Arnett et al. (2015) found this was the case, but the sample was over-selected for ADHD symptoms which, as detailed next, may mean that more males were selected. Thus, the findings require replication.

Speaking to the view that observed sex differences do not reflect 'true' differences, it may also be that the lower prevalence of ADHD in females in clinical samples is due to systematic referral or identification biases, or that diagnostic criteria are biased or poorly defined for females compared to males (Williamson & Johnston, 2015). Despite it now being widely recognized that a large number of females suffer from ADHD (Nussbaum, 2012; Rucklidge, 2010), diagnostic criteria may be geared towards the identification of ADHD in males (Martin, Taylor, et al., 2018; Nussbaum, 2012). Indeed, the DSM-IV criteria for ADHD were based primarily on observations of behaviour in male children (Lahey et al., 1994) and the DSM-5 field studies included a greater percentage of males (Clarke et al., 2013). It has also been shown that parents perceived the DSM-IV ADHD criteria as being descriptive of males (Ohan & Johnston, 2005). If diagnostic criteria are based on male presentation of the disorder, then females may be less likely to meet full diagnostic criteria and instead classify as subthreshold (Hong et al., 2014), particularly if ADHD in females is expressed as greater internalising symptoms, rather than externalising symptoms that are not as directly observable.

As there is currently no existing biomarker for diagnosis, behavioural diagnoses such as ADHD can bring issues of interpretation and perception. The tendency to view ADHD as a predominantly male disorder can affect how behaviour in males and females is perceived by individuals key to the diagnostic process (such as parents and teachers). If a male stereotype of ADHD is the norm, then

it is possible that parents and teachers may not as readily recognise manifestations of ADHD in females compared to males. Thus, potentially only the most severe females or those whose symptoms manifest as disruptive behaviours will be identified. A recent study found that parent ratings of females with ADHD were not consistent with levels of directly observed behaviours (Meyer, Stevenson, & Sonuga-Barke, 2017). In males and females with directly comparable levels of ADHD symptoms in the classroom (based on blind assessment from researchers using a validated ADHD observation measure), parents and teachers rated the ADHD behaviours lower in females. This led the authors to conclude that parents and teachers may be less sensitive to ADHD-type behaviours in females (Meyer et al., 2017).

Another factor which may suggest a clinical referral bias in childhood is that the sex disparity appears to balance out in adulthood (Ginsberg et al., 2014; Solberg et al., 2018). However, the reasons for this remain unclear. It could indicate that in youth females with ADHD tend to be misdiagnosed or underdiagnosed, but this changes in the adult years due to greater awareness of ADHD and/or greater ability of adult women to self-report on ADHD symptoms. Further, females are more likely to present to adult mental health services compared to males, initiating referral themselves as opposed to parents and teachers in childhood (Arcia & Conners, 1998; Kessler et al., 2006). Alternative explanations are that the age of onset tends to occur later in females (Agnew-Blais et al., 2016), or it may reflect a buffering effect of earlier developmental maturity and increased sociability which masks impairment in females.

Thus, the high sex ratio in diagnostic rates of ADHD could partly reflect sex-specific stereotypes operating in the referral process and/or bias in the current diagnostic criteria, or the way they are applied to males and females in clinical settings. Clearly, referral and diagnostic biases are potentially important contributing factors to the observed sex differences in the prevalence of ADHD and it is imperative to clarify these possible sources of bias as potentially females with ADHD are being missed and not gaining access to services they would benefit from. However, they are unlikely to be the sole explanation. As discussed, in the population mean scores are generally higher for males suggesting the contribution of other factors (Martin, Taylor, et al., 2018).

1.3.4.3   Methodological limitations of research into sex differences in ADHD

Given that historically ADHD was thought of as primarily a male disorder, our current understanding of ADHD is mainly based on findings from studies of how the disorder manifests in young males. Knowledge regarding the impact and expression of ADHD in females in childhood and especially adulthood remains relatively sparse (Holthe & Langvik, 2017).

Further, much of the knowledge we have about sex effects in ADHD comes from clinical samples. Given the male preponderance observed in clinical samples of children with ADHD, such studies may not provide the full picture regarding sex differences in ADHD or generalise to the overall ADHD population. This potential problem is suggested by the difference in ratio of males to females with ADHD in population-based samples compared to in clinical samples (with greater sex ratios found in clinical samples). Previous meta-analyses have also highlighted that clinic-referred females may not be representative of non-referred females in the same way that males are (Gaub & Carlson, 1997; Gershon, 2002). Clearly information is needed about those individuals whose ADHD is not diagnosed, especially females. The two meta-analyses of sex differences in ADHD called for more research to better understand sex differences in ADHD and highlighted a particular need for population-based studies to avoid potential biases inherent to clinical samples (Gaub & Carlson, 1997; Gershon, 2002). It is therefore of interest to consider in more detail the differences between females and males in non-referred or population-based samples to identify sex differences in the presentation of ADHD which might contribute to the systematic sex bias in diagnostic practice.

However, despite many studies highlighting the issue of sex differences in ADHD and the lack of clear understanding regarding them, there is still a lack of research in this area. Many studies fail to acknowledge sex differences as a core moderator in their analysis and very few actually test for sex effects. In those studies that do, most look at sex differences post hoc rather than a priori (Davies, 2014). Additionally, many studies often do not include an equal balance of males and females in their studies to allow for powered analysis of sex differences in relation to their chosen outcome, with many studies of ADHD still recruiting predominantly male samples. Regarding adulthood, in their review of sex differences in adults with ADHD, Williamson and Johnston commented that "gender has been neglected as a potential moderator of the nature of ADHD in

adulthood", and findings on sex differences in adults with ADHD seem to be lacking (Corbisiero et al., 2017; Fedele et al., 2012).

1.3.4.4   The importance of understanding sex differences in ADHD

If we are to significantly progress in our understanding of ADHD then it is imperative that a clearer understanding of the impact of sex in the disorder is achieved, including how the disorder manifests in females. Sex effects can influence all aspects of ADHD, from referral and diagnosis, to intervention and outcomes. When ADHD remains unrecognised, leading to late or missed diagnosis, this means that adequate treatment options are lost, and long-term outcomes may be more adverse (Holthe & Langvik, 2017; Quinn, 2005). For this reason, it is of great importance that both sexes are equally included in research studies of ADHD, at least until differences and similarities in males and females with ADHD have been firmly established. Studying sex differences in ADHD can also increase our understanding of the underlying aetiology, and will benefit the academic community, clinicians, teachers, females with ADHD and their families, as well as society.

Understanding sex differences in ADHD also has the potential to inform diagnostic practices. For example, if it is the case that females with ADHD have a more internalising manifestation of the disorder then it could be of value to develop measures that are better able to assess these aspects of ADHD. Current measures are validated in male samples and are very much based on male manifestations of ADHD, reflecting predominantly externalising behavioural symptoms. As it is possible that the manifestation of ADHD in females differs from males, it is important to examine if alternative assessments may aid diagnosis.

1.3.5   Summary

ADHD is one of the most common psychiatric disorders of youth that frequently persists into adulthood, although research in this age group is relatively limited in comparison to childhood ADHD. A high incidence of co-occurring traits and disorders are found in those with ADHD and the evidence suggests that 'pure' ADHD without comorbidity is a rarity. In youth, more males than females are diagnosed with ADHD, whilst in adulthood females constitute a more equal proportion of the ADHD population. Reasons for the shift in the ratio of diagnosed males-to-females between

childhood and adulthood remain to be clarified. Further, the ratio of males-to-females with ADHD in childhood differs in clinical versus population-based samples, potentially meaning that females are being 'missed' or misdiagnosed. This has led to questions regarding the manifestation of ADHD in females. It also highlights – along with the current view of ADHD as a dimensional trait - the value of studying the ADHD phenotype in population-based samples.

1.4   Aetiology of ADHD

Consistent with its heterogeneity, ADHD is a multifactorial disorder that presents a complex aetiological architecture arising from the interplay between genetic and environmental factors (Thapar & Cooper, 2016). A key focus in the investigation of ADHD has been on understanding how the combined effect of genetic and environmental influences contribute to risk for ADHD and its associated impairments.

1.4.1   Genetics

Family, twin, and adoption studies consistently indicate that ADHD is highly heritable (Faraone et al., 2005). For example, twin studies of liability for ADHD among children and adolescents have found strong genetic influences, with heritability estimates around 60-90% (Burt, 2009; Faraone et al., 2005; Larsson, Chang, D'Onofrio, & Lichtenstein, 2014; Nikolas & Burt, 2010). Similar heritability estimates for the two symptom dimensions of ADHD have been shown, with substantial genetic overlap found between inattention and hyperactivity/impulsivity as well as independent genetic effects (Greven, Rijsdijk, & Plomin, 2011; Larsson, Lichtenstein, & Larsson, 2006; McLoughlin, Ronald, Kuntsi, Asherson, & Plomin, 2007; Nikolas & Burt, 2010). Studies also suggest persistent ADHD is more familial than non-persistent ADHD (Biederman et al., 1995; Faraone, 2004). Regarding sex differences, twin studies have not demonstrated quantitative or qualitative sex differences (Larsson et al., 2012, 2014; McLoughlin et al., 2007; Polderman et al., 2015). Thus, the influence of genetic and environmental risk factors in the development ADHD appears to be of similar magnitude in males and females.

Lower heritability estimates in the order of 30% have been reported in late adolescence and adulthood (Boomsma et al., 2010; Saviouk et al., 2011). However, these lower estimates may

reflect the use of self-ratings in adult population samples giving rise to measurement error, rather than a lower genetic contribution to ADHD in adults. This was indicated by a review of studies that found the heritability of adult ADHD could be as high as 70-80% when employing cross-informant-rated ADHD (Brikell, Kuja-Halkola, & Larsson, 2015), including a study of clinically diagnosed adults which estimated the heritability at 88% (Larsson et al., 2014).

Most twin studies of ADHD have examined continuous symptoms in population-based samples, due to the assumption that risk for ADHD is normally distributed along a continuum throughout the population. Similar estimates of the genetic and environmental contributions have been found in studies using a categorical definition (Larsson et al., 2012, 2014).

A more recent approach to examining the genetic architecture of ADHD involves genome-wide scans of a large number of unrelated individuals with ADHD compared to controls. Genome-Wide Association Studies (GWAS) have identified multiple common genetic variants associated with ADHD, each of very small effect. The most recent ADHD GWAS used a substantially larger dataset than previous studies and identified 12 genome-wide significant loci associated with ADHD (Demontis et al., 2017). Investigating sex differences in ADHD at the genetic level using the recent ADHD GWAS, no differences in polygenic burden between male and female ADHD cases were found, suggesting that in both sexes it is largely similar common genetic risk variants that contribute to ADHD (Martin, Taylor, et al., 2018; Martin, Walters, et al., 2018).

1.4.2 Environmental risk factors

Despite evidence for a large genetic component, the aetiology of ADHD is unlikely to be explained by genetic factors alone (Lifford, Harold, & Thapar, 2009; Thapar, Cooper, Eyre, & Langley, 2013; Thapar, Cooper, Jefferies, & Stergiakouli, 2012). Several environmental measures have been associated with risk for ADHD, such as premature birth, low birth weight, dietary factors, environmental toxins, psychosocial factors (e.g., adverse social and family environments), and in-utero exposure to maternal stress, smoking, alcohol, prescribed drugs, and illicit substances (Thapar & Cooper, 2016; Thapar et al., 2012). However, associations between these environmental factors with ADHD cannot be seen to infer causation as exposure to environmental risks is not random. For example, exposure can arise from confounding familial factors that characterise

families with ADHD (i.e., parents provide both genetic and environmental influences) (Langley, Heron, Smith, & Thapar, 2012; Thapar & Cooper, 2016; Thapar et al., 2012). In addition, some environmental risk factors associated with ADHD may not be involved in the causal pathway, but influence the course and outcome (Thapar et al., 2012). For example, psychosocial risks associated with ADHD, such as low income and family adversity, may shape the developmental trajectory, severity and outcomes of ADHD rather than causing ADHD (Thapar et al., 2013).

1.4.3   Gene-environment interplay

Genetic and environmental factors do not act in isolation, and there is likely to be interplay between the two. Certain genotypes may increase the likelihood of exposure to certain environmental influences (gene-environment correlation) and so environmental risks can be brought about as a consequence of genetic propensities (Plomin, 2014). The most important environmental risk factors for ADHD and its secondary impairments are likely to be affected by genetically influenced parent and child dispositions that demonstrate gene-environment correlation (Thapar et al., 2013). The interplay can also take the form of gene-environment interaction, whereby certain genotypes can make an individual more susceptible to environmental risk or protective factors (Nigg, Nikolas, & Burt, 2011; Purcell, 2002). That is, the effect of environmental factors may depend on genetic liability, with the environment likely to play a role in modifying genetic factors. With each risk gene likely to have low penetrance, environmental risks are more likely to play an important role in the likelihood of individuals developing ADHD (Gizer, Ficks, & Waldman, 2009). Understanding environmental risk and protective factors along with their interaction with genetic risk can enable an extension of the findings from genetic studies, exploring the pathways to varying outcomes in individuals with ADHD (Deault, 2010). Even with a model that assumes a strong heritable component to ADHD, the environment remains an important factor to be considered in relation to the disorder's development, manifestation, and outcome (Johnston & Mash, 2001).

1.4.4   Summary

Findings from quantitative and molecular genetics studies suggest that ADHD is highly heritable and of complex polygenic inheritance. Multiple environmental risk measures have also been

identified but their role in the aetiology of ADHD remains uncertain. The current view is that it is multiple common genetic variants of small to moderate effects in combination with certain environmental factors that contribute to risk for ADHD, but in isolation none are necessary or sufficient (Faraone et al., 2015). Due to the complex nature and heterogeneity of ADHD, as well as its shared genetics with other disorders, uncovering its genetic basis and the interplay of genes and environmental factors remains challenging.

1.5 Clinical Assessment of ADHD

1.5.1 Diagnostic considerations

Psychiatric diagnoses are based on operational criteria and rely on descriptive accounts of symptoms. Currently, there are no biomarkers to determine ADHD and the diagnosis is made when a set of defined behavioural symptoms and criteria for onset, course and impact have been met. Thus, diagnosis of ADHD is dependent on subjective ratings of symptom clusters as opposed to more objective measures of aetiological processes or biomarkers.

Methods to evaluate ADHD vary across the lifespan, although the principle approach remains the same. In childhood and adolescence, the primary informants in the diagnostic process are usually parents and teachers who rate symptoms based on observed behaviours. It is partly for this reason that the diagnostic criteria reflect observed behaviours as opposed to reports of internal mental states (Asherson et al., 2016). However, there is only low-to-moderate cross-informant agreement for reports of ADHD symptoms; an observation that is one of the most robust findings in clinical child research (De Los Reyes & Kazdin, 2005). Correlations between parent and teacher ratings for ADHD symptoms range from 0.09 - 0.66, with a tendency towards higher rated symptoms from parents than teachers (Achenbach & Rescorla, 2001; Antrop, Roeyers, Oosterlaan, & Oost, 2002; Goodman, 2001; Murray et al., 2007; Narad et al., 2015; Papageorgiou, Kalyva, Dafoulis, & Vostanis, 2008; Sibley, Pelham Jr, Molina, et al., 2012; Sollie et al., 2012; Wolraich et al., 2004) and greater agreement for hyperactivity/impulsivity than symptoms of inattention (Murray et al., 2007; Narad et al., 2015).

Explanations for these discrepancies include parents being better placed to assess their child's overall functioning compared to teachers, as they observe and interact with them across a wider range of settings and situations, as well as receiving feedback from teachers regarding their child's school behaviour (Shemmassian & Lee, 2012). However, teachers are likely to be more familiar with age-appropriate behaviour compared to parents and may be more tolerant of problem behaviour (Antrop et al., 2002). That said, ADHD symptoms are to some extent situation specific, and so this may not necessarily reflect differences in the way symptoms are interpreted by different informants (Valo & Tannock, 2010).

Additionally, self-report is sometimes used among youth, which can be helpful with regard to general adjustment and comorbidity (especially in children aged 6 and above), but less so for reporting the presence or absence of ADHD symptoms (Taylor et al., 2004). Low agreement is also found between youths and parents (correlations range from 0.41 – 0.48) and youths and teachers (0.29 – 0.32) (Achenbach & Rescorla, 2001; Goodman, 2001).

In late adolescence and adulthood, symptom presence is more often established with self-report (Asherson, 2005) and it is not always possible to obtain information from parents or employers. As with youth, agreement between adult self-report and friends, spouses, and parents are modest (Kooij et al., 2008; Magnússon et al., 2006; Van Voorhees, Hardy, & Kollins, 2011). Diagnosis of ADHD can be further complicated by difficulties establishing the presence of symptoms in childhood, and individuals may underestimate their difficulties (Du Rietz et al., 2016; Faraone & Biederman, 2016; Knouse, Bagwell, Barkley, & Murphy, 2005). However, there are also some studies showing that adults are able to provide accurate accounts of their current behaviour (Murphy & Schachar, 2000) and may provide more accurate information than informants (Kooij et al., 2008).

Since the ADHD diagnosis requires the presence of symptoms in multiple settings, multiple-informant reports are valuable and, where possible, should be incorporated into the diagnostic assessment in both clinical and research settings (Taylor et al., 2004). In youth, guidelines recommend that the views of children are taken into account when determining the clinical significance of impairment as a result of diagnostic symptoms (NICE, 2018). Further, self-report is optimal for obtaining information about internal mental states, such as emotions, thoughts,

moods and feelings. In adulthood, it is possible that greater emphasis should be placed on internal mental states as opposed to observable behaviours, which might enable more accurate self-report of ADHD symptoms such as inattention and restlessness (see section 1.5.2.2).

Rating scales are often used in the assessment of ADHD due to their efficient nature, good psychometric properties, and because they can be used with multiple informants (Shemmassian & Lee, 2012). One disadvantage when used with informants is uncertainty about how the questions are interpreted, ratings applied, and halo and adaptation effects (Taylor et al., 2004). Thus, rating scale questionnaires are useful as an initial screening tool and for an indication of symptom severity, but potential biases in perceptions should be taken into consideration. For example, sex-specific stereotypes may influence interpretations of behaviours by informants (Meyer et al., 2017). Thus, as outlined in the NICE guidelines, a diagnosis of ADHD should not be made solely on the basis of rating scale or observational data, despite their value as an adjunct (NICE, 2018). Structured diagnostic interviews that address all relevant diagnostic criteria (e.g., age of onset, persistence, impairment) are considered the gold standard based on their superior psychometric properties (Shemmassian & Lee, 2012). The advantage of such interviews is that examples of specific symptoms and impairment can be elicited, and decisions based on the views of a trained clinical or research investigator.

1.5.2   Additional symptoms

Currently, ADHD is defined almost entirely at the behavioural level by reports of inattentive, hyperactive and impulsive behaviours. However, people with ADHD also present with other symptoms, including some that may form part of the core symptomatology. These include more subjective and internal experiences of their mental state such as emotional lability and excessive mind wandering (Asherson et al., 2016). Enhanced understanding of the broader range of symptoms or problems associated with ADHD and the phenomenology that underlies ADHD symptomatology may aid diagnosis and provide insight into specific impairments in the disorder.

1.5.2.1   Emotional Lability

Research has demonstrated that emotional lability (EL) or emotional instability/dysregulation - characterised by volatile and fluctuating emotions and irritable mood - is a common co-occurring feature in ADHD (Reimherr et al., 2010; Skirrow et al., 2014). As many as 47 - 76% of children and adolescents and 72 - 90% of adults with ADHD report symptoms of EL (Anastopoulos et al., 2012; Mick, Spencer, Wozniak, & Biederman, 2005; Sobanski et al., 2010). Research also shows EL to be associated with persistence of ADHD into adulthood (Barkley & Fischer, 2010) and to contribute to impairments in major life domains, frequently showing independent effects beyond core ADHD symptomatology on schooling, family life, and social problems (Anastopoulos et al., 2012; Barkley & Fischer, 2010; Barkley & Murphy, 2010; Skirrow & Asherson, 2013). EL symptoms may also be more prominent in females (or viewed as less acceptable in females) (Reimherr et al., 2010; Sobanski et al., 2010), and linked specifically with hyperactivity/impulsivity (Skirrow & Asherson, 2013; Skirrow, McLoughlin, Kuntsi, & Asherson, 2009; Sobanski et al., 2010). These findings have implications for clinical practice, suggesting that clinicians should also screen for ADHD in individuals who present with severe emotional instability (Skirrow et al., 2014, 2009).

In both the DSM-IV and DSM-5, symptoms of emotional lability (i.e., mood volatility, irritability) are outlined as associated features of ADHD that may be used to support the diagnosis (American Psychiatric Association, 2000, 2013). It has also been suggested that EL may be best conceptualised as one of the core components of the disorder (Barkley, 2010; Reimherr et al., 2010). Evidence demonstrates that ADHD pharmacological treatments have a similar effect on reducing EL as on the core symptoms of inattention and hyperactivity/impulsivity (Moukhtarian, Cooper, Vassos, Moran, & Asherson, 2017; Reimherr et al., 2010; Rösler et al., 2010; Skirrow et al., 2009). In addition, EL is present at an increased rate in family members of individuals with ADHD (Epstein et al., 2000; Surman et al., 2011), and shares genetic influences with ADHD (Merwood et al., 2014). However, EL lacks specificity to ADHD since it is also seen to occur across a wide range of psychiatric disorders, such as borderline personality disorder and bipolar disorder (American Psychiatric Association, 2013; Skirrow et al., 2009).

1.5.2.2 Mind wandering

Adults with ADHD also report frequently experiencing excessive and uncontrolled mind wandering (Asherson, 2005). Descriptions include having a 'mind like a hamster wheel', 'mind like a whirlwind', and 'thoughts jumping or flitting between different ideas'. In contrast to the core ADHD symptomatology (inattention and hyperactivity/impulsivity), mind wandering is very much a descriptive term of internal processes as opposed to a directly observable behaviour.

Mind wandering is a universal human experience, conceptualised as periods in time when attention and the contents of thoughts shift away from external sources and/or ongoing tasks, to unrelated internal thoughts or feelings (Smallwood & Schooler, 2015) (known as stimulus-independent or task-unrelated thought [Smallwood, 2013]). This is a ubiquitous and universal human experience, with individuals spending between 24 – 50% of their waking hours focusing on self-generated mental content (Kane et al., 2007; Killingsworth & Gilbert, 2010; Smallwood & Schooler, 2015; Song & Wang, 2012). The contents of a wandering mind are believed to be associated with affective processes (Jonkman, Markus, Franklin, & Van Dalfsen, 2017), regulated by executive control, and are most often of a personal nature (Smallwood & Schooler, 2015).

Most mind wandering experiences occur without explicit awareness and individuals often fail to realise their mind has wandered (i.e., the individual lacks meta-awareness of their mind wandering state) (Christoff, Gordon, Smallwood, Smith, & Schooler, 2009; Schooler, 2002). The occurrence of mind wandering without meta-awareness has been referred to as 'zoning out', in contrast to 'tuning out' which occurs when one is aware their mind has wandered (Smallwood & Schooler, 2015). Zoning out episodes have shown association with heightened behavioural cost, such as failure to inhibit responses (Smallwood, McSpadden, & Schooler, 2007). The type of mind wandering the individual is engaging in is also of relevance and may indicate differing neural processes. Self-generated thoughts can occur both intentionally/deliberately (e.g., when planning the menu for a dinner party whilst driving to work) or unintentionally/spontaneously (e.g., when our mind drifts off during a lecture). Spontaneous mind wandering could reflect executive control failure, as opposed to deliberate mind wandering that could be engaging executive processes for internal information processing (Seli et al., 2015). Although mind wandering is often thought to represent a cognitive failure with negative implications, in some cases it may confer functional

value, such as for creativity or future planning, and so a complex balance of benefits and costs is involved.

Despite the ubiquitous nature of mind wandering, not all minds wander to the same degree. Excessive mind wandering has been linked to impairment and implicated in disorders such as ADHD (Biederman et al., 2017; Franklin et al., 2014; Jonkman et al., 2017; Seli et al., 2015; Shaw & Giambra, 1993). Furthermore, both mind wandering and ADHD are related to inattention and distraction from external sources due to internal thoughts; and mental restlessness, a descriptive term encompassing mind wandering, has been reported to be common in ADHD (Downey, Stelson, Pomerleau, & Giordani, 1997; Weyandt et al., 2003). Given that individuals with ADHD report the experience of their mental state in descriptive terms that are closely related to mind wandering, there is strong premise to link the phenomenon of mind wandering to ADHD. Specifically, it may be closely linked to the inattention and characterise the subjective experience of this symptom (Biederman et al., 2017). However, relatively few studies exist in this area, with research on mind wandering and ADHD being largely independent.

In an early study of mind wandering and ADHD, Shaw and Giambra (1993) looked at the number of task-unrelated thoughts in college students with a childhood history of ADHD, relative to those with no prior diagnosis of ADHD but who scored highly on self-report measures of ADHD symptoms (sub-clinical group), and to those who had low symptom scores (control group). Participants were asked to engage in a simple vigilance task where they were intermittently asked to indicate if they were experiencing thoughts unrelated to the task. If so, they were asked to specify if these task-unrelated thoughts were deliberate or spontaneous. Those with a childhood history of ADHD experienced significantly more spontaneous, but not deliberate, task-unrelated thoughts compared to the sub-clinical and control groups. The sub-clinical group also demonstrated more task-unrelated thoughts compared to controls. These preliminary findings suggested that a core difficulty for adults with ADHD is controlling thoughts unrelated to the current task or the external environment.

Mind wandering was also associated with ADHD symptomatology in an adult community sample in both the laboratory and everyday life (Franklin et al., 2014). Franklin et al. (2014) found a composite ADHD score to positively correlate with both the frequency of mind wandering and the

lack of awareness of engaging in mind wandering. Furthermore, those with high ADHD symptom scores were more likely to experience mind wandering episodes that were detrimental to performance of the task at hand and that interfered with daily life. This is perhaps because they were more likely to lack meta-awareness of their mind wandering, since meta-awareness was found to mediate the relationship between ADHD symptomatology and detrimental mind wandering. Namely, the association between ADHD symptoms and detrimental mind wandering was reduced when accounting for awareness of mind wandering. Those with low ADHD scores tended to have detrimental mind wandering episodes that were also useful. In other words, they were willing to incur the cost to the current task if they believed the mind wandering episode conferred some benefit.

More recently, Seli et al. (2015) showed that spontaneous rather than deliberate mind wandering is associated with ADHD symptoms, which is consistent with Shaw and Giambra's (1993) earlier findings. The authors examined this in both clinical and non-clinical samples, and these findings were similar across groups. Regression analysis also revealed spontaneous mind wandering to show a strong independent association with ADHD symptoms, whereas deliberate mind wandering was only weakly associated.

Some authors suggest that mind wandering in ADHD may be closely linked to the inattentive symptoms (Biederman et al., 2017; Jonkman et al., 2017). However, questions remain regarding whether excessive spontaneous mind wandering in ADHD is an epiphenomenon of the processes that lead to ADHD symptoms or has a more direct causal role in generating the symptoms and impairments of ADHD. For example, both mind wandering and ADHD have been linked to dysregulated deactivation of the Default Mode Network (DMN), a specific network of interacting brain regions that demonstrates a task-related dichotomy, with activation at rest and task-induced deactivation (Andrews-Hanna, Smallwood, & Spreng, 2014; Bozhilova, Michelini, Kuntsi, & Asherson, 2018; Castellanos et al., 2008; Christoff et al., 2009; Fassbender et al., 2009; Liddle et al., 2011; Mason et al., 2007; Peterson et al., 2009; Tian et al., 2008, 2006; Uddin et al., 2008; Zang et al., 2007).

Collectively, these findings suggest that adults with ADHD frequently experience excessive and uncontrolled mind wandering, which could be a major source of the difficulties they experience

day-to-day. The DSM-5 diagnostic criteria reflects this, with mention of being distracted by unrelated thoughts or the mind seeming elsewhere even in the absence of any obvious distraction. As with emotional lability, mind wandering may represent a core deficit in ADHD, but it is also seen in other conditions such as anxiety and depression (worrying or ruminations) or obsessive compulsive disorder (Seli, Risko, Purdon, & Smilek, 2017). Further research is needed to clarify the nature of the relationship between mind wandering and ADHD, and Chapters 4 and 5 of this thesis explore this.

1.5.3   Treatment and intervention

Given the high prevalence rates and the impairing nature of ADHD, there is a continued need for efficient and effective management of ADHD across the lifespan to improve prognosis for individuals affected by the disorder. The proportion of the population receiving treatment for ADHD in the UK and other Western countries is much lower than the estimated prevalence (Bolea-Alamañac et al., 2014). The NICE guidelines recommend that when planning the management of ADHD, individuals have a comprehensive, holistic treatment plan that addresses psychological, behavioural, and educational/occupational needs (NICE, 2018). Treatment and intervention for ADHD will depend on symptom severity, impairments, and individual preference, but generally involves pharmacological treatment and/or behavioural interventions.

The NICE guidelines recommend that in children under 5 years first-line treatment should be an ADHD-focused group parent-training programme. If ADHD symptoms remain pervasive and impairing, then further specialist opinion should be sought before the offer of medication. In children over 5 years, NICE recommend environmental modifications as first-line treatment (e.g., parental-education and classroom strategies), and medication should only be offered if symptoms are still causing significant impairment. In the most severe cases (i.e., individuals who are still experiencing significant impairment whilst on medication), it is advised that cognitive behavioural therapy (CBT) is offered as an adjunct to medication. In line with the persistence of ADHD into adolescence and adulthood, NICE recommends that healthcare providers ensure the continuity of care for people with ADHD (NICE, 2018).

In adults with ADHD, if symptoms are still causing impairment after environmental modification, then medication should be offered. Non-pharmacological treatment for adults with ADHD should be offered to those who do not wish to take medication, have difficulty adhering to medication, or who have found medication to be ineffective or intolerable. At a minimum, NICE recommend that non-pharmacological treatment should include the option of a structured and supporting psychological intervention focused on ADHD, regular follow-up, and may include a full course of CBT. However, it is important to note that across countries there is variation in the recommended first-line treatment for ADHD, for example in the USA the first-line treatment for adolescents tends to be medication, preferably in combination with behavioural therapy (Subcommittee on Attention-Deficit/Hyperactivity Disorder, 2011).

When pharmacological treatment is offered, the first-line medication often involves stimulants such as methylphenidate and lisdexamfetamine (NICE, 2018), which affect the dopaminergic and noradrenergic systems (Engert & Pruessner, 2008). In those who have not responded to, or are unable to tolerate stimulant medications, non-stimulant alternatives can be offered, such as atomoxetine, a noradrenaline reuptake inhibitor (NICE, 2018). There is a large body of research demonstrating moderate to large effects of these medications on ADHD symptoms and outcomes in children and adolescents (Abikoff et al., 2004; Brown et al., 2005; Chan, Fogler, & Hammerness, 2016; Cheng, Chen, Ko, & Ng, 2007; Findling et al., 2011; Garnock-Jones & Keating, 2009; Gayleard & Mychailyszyn, 2017; Prasad et al., 2013; Ruiz-Goikoetxea et al., 2018; Tanaka, Rohde, Jin, Feldman, & Upadhyaya, 2013; Van der Oord, Prins, Oosterlaan, & Emmelkamp, 2008) and adults (Castells et al., 2011; Faraone & Glatt, 2010; Koesters, Becker, Kilian, Fegert, & Weinmann, 2009; Mészáros et al., 2009; Moriyama, Polanczyk, Terzi, Faria, & Rohde, 2013; Sobanski et al., 2012; Surman, Hammerness, Pion, & Faraone, 2013), although the literature base is much smaller in this group and is limited beyond the fifth decade of life (Solanto, Surman, & Alvir, 2018). A recent systematic review and network meta-analysis comparing the efficacy and tolerability of ADHD medications across the life-span supports methylphenidate in children and adolescents and amphetamines in adults, as the preferential first-choice medications for the short-term treatment of ADHD (Cortese et al., 2018). However, pharmacological treatments have limitations, such as side effects (most commonly including reduced appetite and insomnia) (Cheng et al., 2007; Schachter, Pham, King, Langford, & Moher, 2001) and non-response, and complete normalisation

of symptoms is rare (Banaschewski et al., 2006). Additionally, the long-term effectiveness and safety of pharmacological treatments is not fully known (Cortese et al., 2018; van de Loo-Neus, Rommelse, & Buitelaar, 2011).

Regarding non-pharmacological interventions, behavioural interventions including psychoeducation, CBT, support groups, skills training, and coaching are thought to provide benefits in the management of ADHD (Asherson et al., 2016). A recent meta-analysis, with blinded ratings of outcomes, found that behavioural interventions to treat children and adolescents with ADHD (including behavioural training, social skills training, CBT, and organisational skills training) had beneficial effects on important aspects of child and parent functioning, such as reducing conduct problems and increasing positive parenting, but non-significant effects on core ADHD symptoms (Daley et al., 2017, 2014). A variety of other non-pharmacological interventions for ADHD are also receiving increasing empirical interest, such as mindfulness (Hoxhaj et al., 2018; Mitchell et al., 2017; Mitchell, Zylowska, & Kollins, 2015), neurofeedback (Cortese et al., 2016), and cognitive training (Cortese et al., 2015).

Overall, evidence for the efficacy of behavioural interventions in reducing core ADHD symptoms is not established and limited by the fact that many of those assessing the behavioural outcomes are not blinded to the intervention allocation (Cortese et al., 2015, 2016, Daley et al., 2017, 2014; Sonuga-Barke et al., 2013). Taken together, these findings highlight the need for increasing the number of studies assessing the efficacy of behavioural interventions for ADHD and enhancing their methodology, for example through blinded randomised-controlled designs and the inclusion of a range of outcome measures (Daley et al., 2017; Sonuga-Barke et al., 2013).

Dietary interventions, such as omega-3 fatty acid supplementation (Bloch & Qawasmi, 2011; Cooper, Tye, Kuntsi, Vassos, & Asherson, 2015), restriction diets and food colour/additive exclusion (Nigg, Lewis, Edinger, & Falk, 2012) have also received much empirical interest, with some evidence to support their beneficial effects (Sonuga-Barke et al., 2013). However, the evidence is too weak to recommend such dietary interventions as standalone treatments for ADHD, but they could be useful in managing ADHD in certain cases (Nigg et al., 2012; Pelsser, Frankena, Toorman, & Pereira, 2017).

Multimodal treatment plans including both medication and psychological interventions which are based on the specific needs of the presenting individual should be considered for managing ADHD (NICE, 2018). The large Multimodal Treatment Study of Children with ADHD (MTA) suggests superiority in combination treatment for composite outcomes and domains of functional impairment (such as academic achievement, social skills, and parenting behaviour) in the short term; however, evidence for the long-term effectiveness is not substantiated (Hinshaw & Arnold, 2015). Furthermore, other studies tend not to support a significant advantage of medication combined with non-pharmacological intervention (Abikoff et al., 2004; Daley et al., 2017; Van der Oord et al., 2008).

Interest in developing additional interventions is growing and will increase the choice for those with ADHD and the likelihood of finding a suitable management plan that works for them. Recently, studies have looked at cannabinoids and exercise as interventions which could hold promise in reducing the impact of ADHD (Cooper et al., 2017; Den Heijer et al., 2017; Rommel et al., 2015).

1.5.3.1   Sex differences in treatment

Generally, the ADHD treatment literature has not focused on sex differences, and there is no clear answer regarding sex-by-treatment effects or the moderating role of sex (Rucklidge, 2010). Some studies have shown that males are more likely to receive ADHD medication than females (Angold, Erkanli, Egger, & Costello, 2000; Derks, Hudziak, & Boomsma, 2007), which could be due to different manifestation of the disorder. The possibility that females with ADHD are undertreated is an important public health concern (Rucklidge, 2010). The current thesis includes investigation of whether the predictive association of ADHD symptoms on receiving pharmacological treatment differs in males and females.

1.6   Prognosis: Functional Impairment and Long-term Outcomes of ADHD

In both childhood and adulthood, ADHD is often a severe and impairing disorder, with functional impairment necessary for diagnosis and tending to be the primary reason for referral. ADHD is associated with functional impairments that span multiple settings and affect a realm of major life

domains, such as home/family life (Chutko, Anisimova, Surushkina, & Aïtbekov, 2011; Deault, 2010; Eakin et al., 2004; Harold et al., 2013; Johnston & Mash, 2001; Lange et al., 2005), at school/work (Biederman, Faraone, et al., 2006; Biederman et al., 2008; Frazier, Youngstrom, Glutting, & Watkins, 2007; Gjervan, Torgersen, Nordahl, & Rasmussen, 2012; Kuriyan et al., 2013; Loe & Feldman, 2007; Mannuzza, Klein, Bessler, Malloy, & LaPadula, 1993; Murphy & Barkley, 1996), and social contexts (DuPaul, McGoey, Eckert, & VanBrakle, 2001; Gardner & Gerdes, 2015; Harpin, Mazzone, Raynaud, Kahle, & Hodgkins, 2016; Henry, Jones, Henry, & Jones, 2011; Hoza, 2007; Hoza et al., 2005; Kok, Groen, Fuermaier, & Tucha, 2016; Michielsen et al., 2015; Mrug et al., 2012). ADHD is also associated with a greater likelihood of antisocial behaviour in adolescence and adulthood (Asherson, 2005; Langley et al., 2010; Thapar, van den Bree, Fowler, Langley, & Whittinger, 2006), criminality (Asherson et al., 2012; Cahill et al., 2012; Fletcher & Wolfe, 2009; Ginsberg, Hirvikoski, & Lindefors, 2010; Langley et al., 2010; Young, Moss, Sedgwick, Fridman, & Hodgkins, 2015), driving-risk and traffic accidents (Barkley & Cox, 2007; Jerome, Segal, & Habinski, 2006), problematic substance use (Charach, Yeung, Climans, & Lillie, 2011; Harstad, Levy, & Committee on Substance Abuse, 2014; Huntley & Young, 2014; Langley et al., 2010; Lee, Humphreys, Flory, Liu, & Glass, 2011), and risky sexual behaviour (Flory et al., 2006; Hosain, Berenson, Tennen, Bauer, & Wu, 2012). While the symptoms of ADHD may attenuate in severity as individuals move across the developmental trajectory into adulthood, their impact on various aspects of daily functioning is still significant. Further, poorer outcomes tend to be seen when ADHD is untreated (Shaw et al., 2012). However, not everyone will experience the same impairments, again demonstrating the heterogeneity of the disorder. Some individuals may actually take advantage of their ADHD symptoms and so their impairing nature is reduced (Becker, Chorpita, & Daleiden, 2011).

The impact of impairments linked with ADHD goes beyond the individual, affecting society as a whole, with large economic costs to the public (Bernfort, Nordfeldt, & Persson, 2008; Birnbaum et al., 2005; Doshi et al., 2012; Parsonage, 2014; Pelham, Foster, & Robb, 2007; Snell et al., 2013). Beyond the direct expenditures from assessment and treatment, there are long-term indirect costs linked to special education provisions, the criminal justice system, and problematic substance use treatment (Bernfort et al., 2008; Ford, Fowler, Langley, Whittinger, & Thapar, 2008; Hinshaw, 2018). From a societal perspective, education costs have been shown to account for the

largest proportion of total costs for ADHD (Parsonage, 2014; Snell et al., 2013; Telford et al., 2013). If individuals with certain presentations of ADHD, and specifically females, are being missed this will have important public health implications. The NICE guidelines (2018) specifically raise the issue of under-recognition of ADHD in females and encourages awareness of this amongst practitioners.

1.6.1 The relationship between symptoms and impairment: undiagnosed and subthreshold ADHD

The literature also demonstrates associations between subthreshold levels of ADHD and negative outcomes (Balazs & Kereszteny, 2014; Bussing et al., 2010; Faraone, Kunwar, Adamson, & Biederman, 2009; Hong et al., 2014; Malmberg, Edbom, Wargelius, & Larsson, 2011; Noren Selinus et al., 2016; Shankman et al., 2009). Access to a range of support services is limited in those with subthreshold ADHD, such as educational provisions, despite the association of subthreshold ADHD with real world impairment (Angold et al., 1999; Balazs & Kereszteny, 2014; Bussing et al., 2010; Faraone, Biederman, Spencer, et al., 2006; Hong et al., 2014; Noren Selinus et al., 2016). Also, many individuals with subthreshold symptoms go on to meet criteria for the full syndrome in adolescence and adulthood (Bussing et al., 2010; Lecendreux, Konofal, Cortese, & Faraone, 2015; Noren Selinus et al., 2016). This has public health implications given the associated negative long-term outcomes.

Further, ADHD symptoms and impairment are not isomorphic (Becker et al., 2011; Gathje, Lewandowski, & Gordon, 2008; Gordon et al., 2006). Thus, some individuals may be subthreshold and experience significant impairment, whilst others can meet threshold symptomatically but not experience significant impairment (Gathje et al., 2008; Gordon et al., 2006). Additionally, beyond adaptive functioning on the continuum is positive functioning, and it is not a foregone conclusion that symptom severity and functional impairment are always positively associated. For example, those with relatively severe symptoms may function well as a result of personal resilience, compensatory behaviours, and/or environmental supports (Becker et al., 2011), including more suited environmental contexts.

1.7   Thesis aims and outline

This overarching aim of this thesis is to provide further understanding of sex differences in ADHD. The first part of this thesis (Chapters 2 and 3) investigates sex differences in ADHD in youth and the second part investigates ADHD in adulthood (Chapters 4 and 5). Analyses are based on data from five different projects:

1) The Pathways to Hyperactivity and Attention Deficit Study (PHAD), a spin-off study of children from the Twins Early Development Study (TEDS) (Trouton, Spinath, & Plomin, 2002) which is a large population-based study of over 15,000 twins born in the United Kingdom between 1994 and 1996;

2) The Child and Adolescent Twin Study in Sweden (CATSS) (Anckarsater et al., 2011), an ongoing prospective longitudinal cohort study that targets all twins born in Sweden since 1992, which can be linked to Swedish National Population-based Registers containing information on psychiatric care and drug prescriptions;

3) The Mood Instability Research in ADHD study (MIRIAD) (Skirrow & Asherson, 2013), a case-control study of adult men with and without ADHD;

4) The Oils and Cognitive Effects in Adult ADHD Neurodevelopment study (OCEAN), a case-control study of adults with and without ADHD;

5) The Creativity, Occupation, Mind Wandering and Education Study (COME-ON! – What does a wandering mind lead to?), a large online survey study of adults from the population with and without ADHD.

Two of the results chapters are published articles and have been presented in published format, and two of the results chapters are currently under peer-review. References from the published results chapters are shown in the articles only and are not repeated in the main reference list at the end of the thesis. Supplementary materials for each study are presented in the appendices. An outline of the subsequent chapters is provided below.

The first empirical study (Chapter 2) uses a population-based sample to investigate sex differences in traits relevant to the pathology of ADHD in relation to diagnosis. Specifically, it examines whether, amongst males and females with comparably elevated levels of ADHD symptoms, different characteristics impact whether males and females meet diagnostic criteria based on a comprehensive diagnostic interview. Thus, the diagnosed group are not clinically ascertained. Measures of core ADHD symptom dimensions, co-occurring behavioural and emotional problems, and impairment are examined. This study also investigates sex-dependent biases in parental perceptions of ADHD symptoms through examining whether, despite children meeting diagnostic criteria through detailed interview, parents under or over-rate their children's behaviour relative to the objective interview measure, and if a different pattern is observed in males and females.

The second empirical study (Chapter 3) uses a population-based sample linked to data from national registries to investigate whether the predictors of ADHD clinical diagnosis and pharmacological treatment differ in males and females. Specifically, it examines sex differences in the severity and presentation of ADHD symptoms, conduct problems, and learning problems in males and females with and without clinically diagnosed ADHD, and then examines if there are sex differences in the predictive associations of these symptom domains on being diagnosed and treated for ADHD. This study has been published in *European Child & Adolescent Psychiatry* (Mowlem et al., 2018).

My investigation of sex differences in ADHD led me to ask more about the expression of ADHD and the basic phenomenon of the disorder, and if females do present differently to males with ADHD, this could suggest that a new perspective and way of looking at the psychopathology of ADHD may be needed. It became clear that further research was needed to identify the best screening methods for ADHD, which may differ for males and females and be more sensitive to the differential manifestation of the disorder across sex. Thus, the second part of the thesis takes a phenomenological approach to ADHD and investigates a new measure of the subjective experience of excessive mind wandering, and if there are sex differences in mind wandering in adults with ADHD.

The third empirical study (Chapter 4) investigates the 'symptom' of mind wandering in ADHD through evaluation of the psychometric properties of a newly developed measure of this internal,

subjective experience of ADHD in adults: The Mind Excessively Wandering Scale (MEWS). Specifically, it examines the validity and reliability of the MEWS as an instrument to assess adult ADHD, including how it relates to core symptom dimensions currently used for clinical diagnosis. In addition, it examines if the MEWS is sensitive to treatment effects and if it accounts for unique variance in function impairment in adults with ADHD. This study has been published in the *Journal of Attention Disorders*, and is the first paper to be published on this scale (Mowlem et al., 2016).

The fourth empirical study (Chapter 5) further validates the MEWS in a large population sample and examines sex differences in the manifestation of adult ADHD. Specifically, it evaluates the factor structure of the MEWS, assesses measurement invariance across sex, age, and ADHD diagnostic status, examines reliability and validity, and investigates sex differences in mind wandering, inattention, hyperactivity/impulsivity, emotional lability, impairment and wellbeing.

The thesis concludes (Chapter 6) with a summary of the main findings from each of the results chapters before drawing them together to discuss the wider implications of this body of work. The limitations of the studies in this thesis are also addressed, and areas for future research are explored.

Chapter 2. Do different factors influence whether girls versus boys meet ADHD diagnostic criteria? Sex differences among children with high ADHD symptoms

This chapter is adapted from a manuscript currently under review.

Mowlem, F.D., Agnew-Blais, J., Taylor, E., & Asherson, P. (*under review*). Do different factors influence whether girls versus boys meet ADHD diagnostic criteria? Sex differences among children with high ADHD symptoms.

Supplementary materials for this chapter, as detailed in the text, are attached in Appendix A.

2.1   Abstract

We investigate if different factors influence whether girls versus boys meet diagnostic criteria for attention-deficit/hyperactivity disorder (ADHD) among children with high ADHD symptoms. Participants were 283 children aged 7-12 from a population-based study. Girls and boys meeting diagnostic criteria for ADHD, based on an objective investigator-based interview, were compared to children who did not meet criteria despite high symptoms on a rating-scale measure of ADHD. We assessed factors that could differentially relate to diagnosis across girls and boys including ADHD symptoms, co-occurring behavioural/emotional problems and impairment, and sex-effects in rater perceptions of ADHD symptoms. While overall similar factors distinguished girls and boys who met diagnostic criteria from high-symptom peers, effect sizes were larger in girls. Emotional problems were particularly salient to distinguishing diagnosed versus high-symptom girls but not boys. Parents rated boys meeting diagnostic criteria as more impaired than high-symptom boys but did not do so for girls, and under-rated diagnosed girls' hyperactive/impulsive symptoms compared to more objective interview assessment, with the opposite observed in boys. Results suggest girls' ADHD may need to be made more prominent by additional behavioural/emotional problems for them to meet full diagnostic criteria and that sex differences in parental perceptions of ADHD behaviours and impairment exist.

2.2 Introduction

A well-established feature of attention-deficit/hyperactivity disorder (ADHD) is the large sex difference in referral and diagnostic rates. The ratio of boys to girls diagnosed with ADHD in childhood falls in the range of 2:1 to 10:1 (Arnett et al., 2015; Biederman et al., 2002; Novik et al., 2006; Ramtekkar et al., 2010; Willcutt, 2012), with higher ratios seen in clinical compared to population samples. This difference highlights the possibility that ADHD may be underdiagnosed in girls in clinical practice (Ramtekkar et al., 2010). Further, it suggests that investigating sex differences in population-based samples could extend and enrich our understanding of the ADHD construct beyond that of clinical samples.

A common explanation for the observed sex differences in referral and diagnosis is that girls with ADHD are more likely to present with predominantly inattentive symptoms, rather than the more potentially disruptive hyperactive/impulsive symptoms, as well as greater levels of internalising symptoms such as anxiety and depression which might lead to alternative diagnoses (Arnold, 1996; Quinn, 2008). In contrast, boys with ADHD are often characterised as presenting with more hyperactivity/impulsivity, and co-occurring behavioural problems such as oppositional defiant and conduct disorder (Arnold, 1996; Quinn, 2008). It has also been shown that proportionally more boys than girls with ADHD annoy or upset their teachers, and that parents see the 'feminine' ADHD diagnostic items as less problematic than the 'masculine' ones (Graetz et al., 2005; Ohan & Johnston, 2005). It is highly likely that these explanations, along with the greater rate of diagnosis in boys, has led to an ADHD stereotype of a 'disruptive boy', which may influence how behaviour in boys and girls is perceived by individuals key to the referral and diagnostic process (e.g., parents and teachers). Consistent with this view, it has been shown that parents perceived the DSM-IV ADHD criteria as being descriptive of boys (Ohan & Johnston, 2005).

If sex-specific stereotypes of ADHD exist, then it is possible that parents and teachers may not as readily recognise manifestations of ADHD in girls compared to boys. Furthermore, sex differences in recognition of ADHD may in part reflect bias in the diagnostic criteria, or the way they are applied. For example, if diagnostic criteria are based on a male presentation of the disorder then females may be less likely to meet full diagnostic criteria (Hong et al., 2014).

The male preponderance could also be due to underlying aetiology of ADHD in relation to a 'female protective effect'. This model proposes that females require greater genetic and environmental 'load' or exposure to factors associated with ADHD to manifest the same degree of impairment and warrant diagnosis as males with ADHD (Eriksson et al., 2016; Rhee & Waldman, 2004; Taylor et al., 2016). Partial support for this hypothesis has been demonstrated, for example siblings of females with ADHD have been shown to display greater familial risk of ADHD compared to siblings of males with ADHD (Martin, Walters, et al., 2018; Rhee & Waldman, 2004; Taylor et al., 2016). Of note, such findings could result from parents having a higher threshold for recognising ADHD symptoms in daughters or clinicians having a higher threshold for diagnosing ADHD in females, and/or greater likelihood of diagnosing ADHD in females if their ADHD symptoms are accompanied by additional behavioural problems which make their ADHD symptoms more prominent (Martin, Walters, et al., 2018).

Several methodological limitations exist in the study of sex differences in ADHD. First, many studies of ADHD are comprised of predominantly (or exclusively) male participants, limiting our understanding of ADHD in females; although efforts to investigate ADHD in females are increasing (e.g., Biederman et al., 1999; Hinshaw, Owens, Sami, & Fargeon, 2006). Further, the DSM-IV criteria for ADHD are based primarily on observations of males (Lahey et al., 1994), and DSM-5 field studies included a greater percentage of males (Clarke et al., 2013). Second, much of our knowledge about sex effects in ADHD comes from clinical samples, yet referral bias related to sex suggests that studies in clinical samples may not provide the full picture regarding sex differences in ADHD, or generalise to the overall ADHD population. In addition, individuals whose ADHD is not diagnosed are absent from clinical samples and so findings may not be wholly applicable to females if they are more often 'missed'. Moreover, previous meta-analyses highlight that clinic-referred girls may not be representative of non-referred girls in the same way that boys are (Gaub & Carlson, 1997; Gershon, 2002). Third, an additional obstacle in assessing sex differences in ADHD is that to date, nearly all studies of population or non-referred samples have relied on parent or teacher rating scales. If a male stereotype of ADHD is the norm, potentially only the most severe girls or those whose symptoms manifest as disruptive behaviours will be identified.

It is important, especially for clinical practice, to understand more about phenotypic differences in boys and girls with ADHD (Taylor et al., 2016), including sex differences beyond that of ADHD

symptoms. One way to do this is to examine girls and boys from the general population with comparable numbers of ADHD symptoms and investigate which children meet diagnostic criteria, to help understand whether different factors impact if boys and girls meet diagnostic threshold. One hypothesis is that if current diagnostic criteria and perceptions of ADHD characterise a male stereotype, and/or if there is a female protective effect, then girls may be less likely to meet diagnostic criteria or receive an ADHD diagnoses unless their symptoms are made more prominent by additional problems, for example greater emotional problems or school impairment.

To address the methodological issues detailed above, the current study examined data from a population-based twin sample, overcoming issues of referral and clinic bias. Separate trait and diagnostic measures of ADHD were available which extends methodology typically used in population-based samples. We examined what characteristics distinguish girls meeting diagnostic criteria (based on the Parental Account of Childhood Symptoms [PACS]) from girls who do not despite high ADHD symptom levels on a rating-scale measure of ADHD, and if the same distinguishing characteristics operate in boys. We examined core ADHD symptom dimensions, co-occurring behavioural and emotional problems, and impairment. We also assessed sex-dependent biases in parental perceptions of ADHD symptoms by examining whether, despite their offspring meeting diagnostic criteria, parents systematically under- or over-rate relative to the PACS, and if this differs for boys and girls.

2.3   Method

2.3.1   Sample

Participants were 283 children: 153 (121 boys, 32 girls) who met DSM-5 research diagnostic criteria for ADHD based on the Parental Account of Childhood Symptoms (PACS) investigator-rated parental interview (M=9.33 years, SD=0.77), and 130 (81 boys, 49 girls) who showed a high level of ADHD symptoms based on parental report using DSM-5 symptom criteria but did not meet full diagnostic criteria (M=9.52 years, SD=0.88). We refer to the groups as the 'diagnosed ADHD' group and the 'high-symptom' group. Further details of the PACS is given in the measures section and details on how the diagnosis is made can be found in the supplementary material (Appendix A). We defined a high level of ADHD symptoms as the presence of 5 or more symptoms (out of 18),

based on definitions used in previous studies (Biederman et al., 1996; Faraone, Kunwar, Adamson, & Biederman, 2009; Faraone et al., 2006; Shankman et al., 2009). Of note, three children were missing their ADHD symptom score (2 boys, 1 girl) but met PACS diagnostic criteria, and 16 (14 boys, 2 girls) met PACS diagnostic criteria but had less than 5 symptoms present on the DSM-5 ADHD rating-scale; these children were included in the diagnosed group (see Fig. 2.1 for a flow chart of how the groups were derived).

Participants were part of the Developmental Pathways to Hyperactivity and Attention Deficit Study (PHAD), a sub-study of children at risk for ADHD identified from the Twins Early Development Study (TEDS), which is a population-based study of over 15,000 twin pairs born in the United Kingdom between 1994 and 1996, followed up prospectively from the age of 18 months. Details of TEDS is described elsewhere (Trouton et al., 2002), and details of the PHAD sample ascertainment can be found in the supplementary material (Appendix A). Briefly, children were screened for ADHD symptoms at age 7 years. Twins at risk were identified by at least one twin in each twin-pair scoring in the top 15% of the TEDS population for ADHD symptoms. 196 families with children identified as being at risk for ADHD (comprising 276 boys and 116 girls) completed the PACS ADHD diagnostic interview at the family home when the children were aged between 7–12 years (*M*=9.42 years, *SD*=0.84 years) (data was collected for both children in the twin pair regardless of whether one or both had been identified as being at risk for ADHD). Exclusion criteria were: autism spectrum disorder, learning disability, and neurological disability.

2.3.2   Measures

2.3.2.1   ADHD symptom measure

Parents completed a checklist assessing the 18 DSM-IV items for inattention (9 items) and hyperactivity/impulsivity (9 items) (American Psychiatric Association, 1994). Each item is rated on a four-point likert scale from 0 (not at all true) to 3 (very much true), with the highest possible score being 54. Of note, DSM-IV items for ADHD are the same in the most recent edition (DSM-5), and so we refer to DSM-5 for clarity.

2.3.2.2 ADHD diagnostic measure

The Parental Account of Childhood Symptoms (PACS) was used to identify children who met diagnostic criteria for ADHD. The PACS is an investigator-rated semi-structured interview developed as a standardised measure for use in assessing and recording accurately the behaviours of children. Parents are asked to describe the behaviour of their child across a range of situations in relation to its frequency and severity, which is then scored according to a standardised operational scale (Chen & Taylor, 2006). As such, PACS can be considered a gold-standard tool for the research assessment of children with ADHD (Chen et al., 2008; Müller et al., 2011), and shows high inter-rater reliability (Chen et al., 2008). Details on the PACS diagnosis have been described elsewhere (Chen et al., 2008; Müller et al., 2011) and are included in the supplementary material (Appendix A).
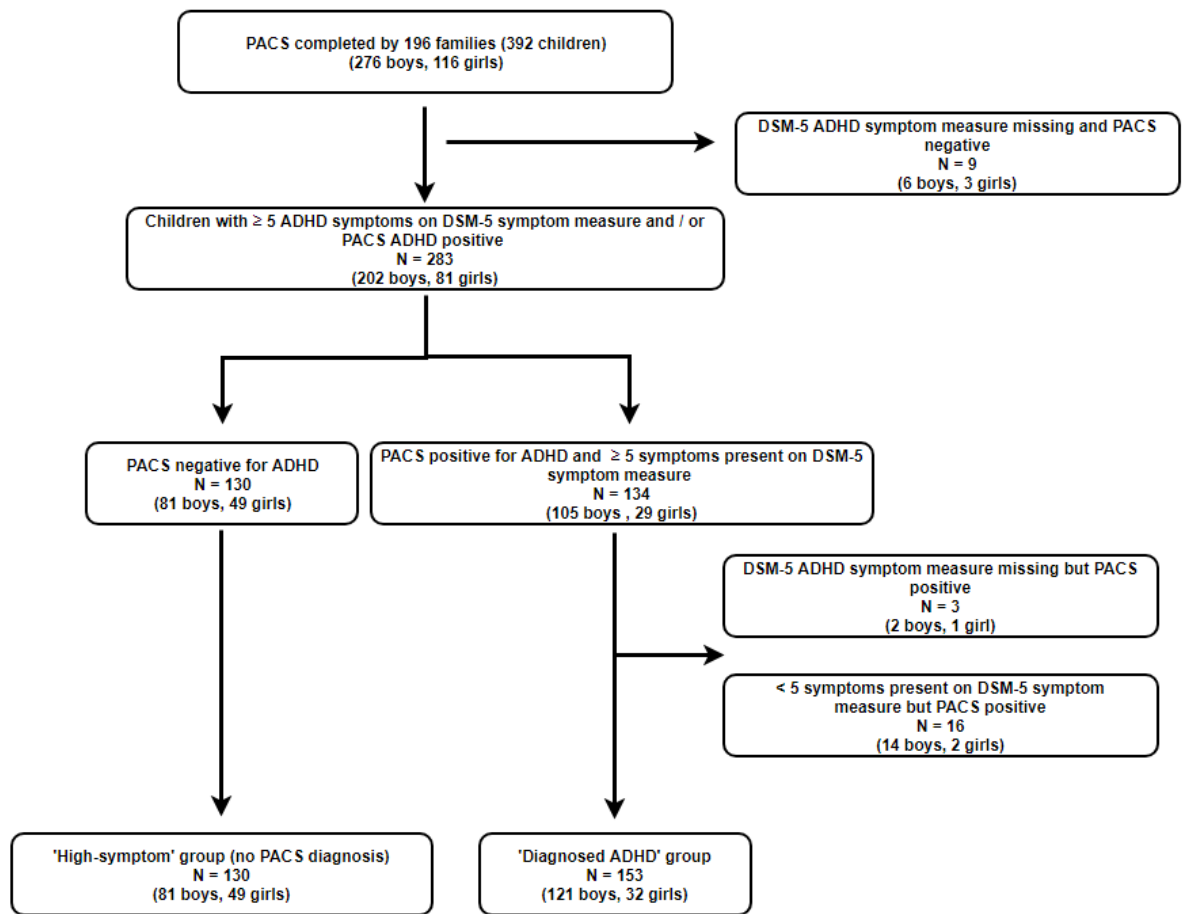
Figure 2.1. Flow diagram of how the 'diagnosed ADHD' and 'high-symptom ADHD' groups were derived for the current study

2.3.2.3 Co-occurring behavioural and emotional problems

The Strengths and Difficulties Questionnaire (SDQ) was used to assess behavioural and emotional problems using mothers ratings (Goodman, 1997). The SDQ comprises 5 subscales: emotional problems, conduct problems, hyperactivity, peer problems, and prosocial behaviour. The SDQ subscales can also be used to generate a 'total problem' score. The hyperactivity items were not used in this study as this behaviour is already measured.

2.3.2.4 Impairment

The SDQ impact supplement comprises items related to overall distress and impairment which can be used to generate an impact score ranging from 0-10 (see supplementary material, Appendix A, for further information). The PACS includes questions on both impairment and school behaviour, as related to the child's inattention and/or hyperactivity/impulsivity problems. The impairment items include: 'problem is cause for concern', 'serious problem perceived/much concern', 'no control over behaviour', 'serious impairment/social impact of problem', and 'interviewer rates problem as markedly or severely abnormal'. Items are scored on likert scales which were used to create dichotomous variables for 'yes' or 'no' categories; we then calculated a total impairment score for each participant ranging from 0-5. School behaviour items were scored as 'yes' or 'no' and included: 'child shows distress', 'problems getting on with others', 'difficulty concentrating', 'change of school due to problems', 'suspended or excluded', 'special educational provision', 'complaints about hyperactivity', and 'complaints about aggression'. We did not to include the 'difficulty concentrating' item in analysis due to it being so closely linked with the definition of ADHD. 'Change of school due to problems' and 'suspended or excluded' were also omitted from analysis due to so few participants endorsing these items. A total school impairment score was derived for each participant ranging from 0-5.

2.3.3 Statistical analysis

We compared girls and boys meeting PACS DSM-5 diagnostic criteria to girls and boys with a high level of ADHD symptoms who did not meet diagnostic criteria on a-priori selected variables: parent-rated levels of inattention and hyperactivity/impulsivity, co-occurring behavioural and emotional problems, and impairment. We used linear regression models for continuous outcomes and logistic regression for binary outcomes. Age was controlled for in all analyses and we adjusted for familial clustering using the *cluster(variable)* function in Stata 14 (StataCorp, 2015). Effect sizes were established using Cohen's d for continuous variables (where: d≥0.20 is a small effect, d≥0.50 a medium effect, and d≥0.80 a large effect) and odds ratios for categorical variables.

To describe sex differences in the diagnosed and high-symptom groups, we compared girls versus boys meeting diagnostic criteria on the PACS, and high-symptom girls to high-symptom boys. To

investigate which characteristics distinguish girls above and below the diagnostic threshold, and if the same distinguishing features operate in boys, we compared PACS diagnosed girls to high-symptom girls and PACS diagnosed boys to high-symptom boys by testing for an interaction between diagnostic group (diagnosed versus high-symptom) and sex (male versus female). A significant sex-by-diagnostic group interaction would indicate that certain characteristics are greater in diagnosed versus high-symptom individuals and in one sex compared to the other.

To elucidate potential sex biases in parent report of ADHD symptoms we examined whether, despite both sexes meeting diagnostic criteria, parents systematically under- or over-rate ADHD symptoms compared to the PACS interview assessment, and if this differs by sex. We tested for an interaction between sex and measure (parent-rating scale versus PACS) separately for total scores on the inattention and hyperactivity/impulsivity scale in the diagnosed group of children using linear regression. A significant interaction would suggest ADHD symptom score differs as a function of the type of measure and that this difference is greater in one sex compared to the other, or that the direction of the difference differs in girls and boys.

2.4   Results

Of the 153 children meeting PACS diagnostic criteria for ADHD, 121 were boys (79%) and 32 were girls (21%), giving a male-to-female ratio of 3.8:1. Of the 130 children in the high-symptom group, 81 were boys (62%) and 49 were girls (38%), a male-to-female ratio of 1.7:1. The ratio of diagnosed to high-symptom girls was 0.65:1 compared to 1.5:1 for boys. The diagnosed and high-symptom groups did not differ significantly in the total number of symptoms present based on the DSM-5 parent-rated scale ($p=.10$, $d=0.20$), fulfilling a critical assumption on which the study design lies (i.e., that the diagnosed and high-symptom groups had comparable numbers of ADHD symptoms, therefore we can identify other factors that distinguish these groups).

Among the children meeting PACS diagnostic criteria, girls had higher rated emotional problems ($p=.04$, $d=0.47$) and were more prosocial (this difference showed a trend towards significance: $p=.06$, $d=0.42$), compared with equivalent boys (Table 2.1). Girls meeting diagnostic criteria also had lower parent-rated impact scores ($p=.03$, $d=-0.47$), relating to overall distress and impairment, compared to boys meeting diagnostic criteria. Few characteristics distinguished girls and boys in

the high-symptom group, except that girls were significantly more prosocial (*p*<.001, *d*=0.78), had lower levels of conduct problems (*p*=.03, *d*=-0.45), and were less likely to have complaints about hyperactivity at school (*p*=.02, OR: 0.36 [95% CI: 0.15, 0.86]) compared to boys (Table 2.1).

Table 2.1. Characteristics of PACS diagnosed and high-symptom girls and boys. Mean (SD) unless otherwise stated

Characteristic[a]	PACS diagnosed				High-symptom			
	Girls (n=32)	Boys (n=121)	*p*	Cohen's d	Girls (n=49)	Boys (n=81)	*p*	Cohen's d
ADHD (parent-rated)								
Inattention	17.62 (5.37)	16.47 (5.87)	.32	0.20	15.78 (4.58)	14.75 (4.94)	.25	0.22
Hyperactivity/ Impulsivity	15.39 (5.66)	15.37 (6.44)	.89	0.003	13.96 (5.63)	14.49 (4.85)	.65	-0.10
Co-occurring difficulties								
Emotional	**4.55 (2.75)**	**3.39 (2.37)**	**.04**	**0.47**	2.95 (2.10)	3.19 (2.47)	.63	-0.10
Conduct	3.24 (2.23)	3.72 (2.06)	.35	-0.23	**2.00 (1.69)**	**2.87 (2.13)**	**.03**	**-0.45**
Peer	3.34 (2.29)	3.58 (2.56)	.61	0.37	1.73 (1.87)	2.15 (2.18)	.33	-0.21
Prosocial	7.28 (2.39)	6.33 (2.22)	.06	0.42	**8.48 (1.97)**	**6.77 (2.40)**	**<.001**	**0.78**
Total Problem Score	11.14 (5.56)	10.69 (5.23)	.71	0.09	6.68 (3.61)	8.22 (5.08)	.11	-0.35
Impairment								
Total Impact Score (SDQ)	**1.79 (2.28)**	**2.93 (2.44)**	**.03**	**-0.47**	1.15 (1.46)	1.51 (2.18)	.31	-0.19
PACS total impairment	2.16 (1.69)	2.07 (1.84)	.83	0.05	0.73 (0.93)	0.89 (1.16)	.41	-0.15
School Impairment (PACS)								
Child shows distress (%)	43.8	49.6	.55	OR: 0.80 (0.38, 1.66)	42.9	29.6	.14	OR:1.78 (0.84, 3.78)
Problems getting on with others (%)	40.6	47.1	.52	OR: 0.78 (0.37, 1.66)	22.5	27.2	.53	OR:0.74 (0.29, 1.88)
Special educational provision (%)	40.6	42.2	.91	OR: 0.95 (0.40, 2.29)	16.3	12.4	.57	OR:1.38 (0.45, 4.26)
Complaints about hyperactivity (%)	59.4	58.7	.96	OR: 1.02 (0.47, 2.24)	**18.4**	**38.3**	**.02**	**OR:0.36 (0.15, 0.86)**
Complaints about aggression (%)	21.9	33.9	.72	OR: 0.54 (0.18, 1.62)	8.2	17.3	.16	OR:0.41 (0.12, 1.42)
Total school impairment	2.06 (1.37)	2.31 (1.46)	.37	-0.17	1.08 (1.17)	1.25 (1.33)	.44	-0.14

Bold data signify statistical significance of the tests

PACS = The Parental Account of Childhood Symptoms; ADHD = Attention-deficit/hyperactivity disorder; OR = Odds ratio (with 95% Confidence Intervals)

[a] Data were missing on some variables; all available data were used in analysis

All models were adjusted for familial clustering and age

2.4.1 Distinguishing characteristics of PACS diagnosed versus high-symptom girls, compared to boys

2.4.1.1 PACS diagnosed versus high-symptom girls

Compared to high-symptom girls, girls meeting PACS diagnostic criteria had significantly higher reported levels of emotional (p=.02, d=0.65), conduct (p=.04, d=0.63), and peer problems (p=.002, d=1.20), as well as higher total problem scores (p=.001, d=0.95) (Table 2.2). The PACS diagnosed girls were also more impaired based on the PACS impairment measure (p<.001, d=1.05) than the high-symptom girls, but the SDQ parent-rated impairment measure did not distinguish the two groups. At school, diagnosed girls received more complaints about hyperactive behaviour (p<.001, OR: 3.07 [95%CI: 2.42, 16.73]) and had higher overall school impairment scores (p=.001, d=0.77). Girls meeting diagnostic criteria were also 3.89 times (95%CI: 1.19, 12.76) more likely to receive special educational provision (p=.03) than those with high ADHD symptom scores.

2.4.1.2 PACS diagnosed versus high-symptom boys

Compared to the high-symptom boys, boys meeting PACS diagnostic criteria had greater parent-rated inattention (p=.03, d=0.32) (Table 2.2), higher reported levels of conduct (p=.01, d=0.41) and peer problems (p<.001, d=0.60), and higher total problem scores (p=.004, d=0.48). Greater impairment was demonstrated in boys meeting diagnostic criteria compared to high-symptom boys on all the impairment measures (see Table 2.2).

2.4.1.3 Do the same distinguishing characteristics operate in girls and boys?

Overall there were no significant sex by diagnosis interactions, suggesting that many of the same factors distinguished high-symptom children from those who met diagnostic criteria in both boys and girls (Table 2.2). There were, however, some interactions nearing statistical significance in which certain characteristics played a larger role in distinguishing high-symptom girls from girls meeting diagnostic criteria, as compared to the equivalent groups of boys (Table 2.2, Supplementary Fig S1, Appendix A). Regarding co-occurring problems, girls who met PACS diagnostic criteria had more emotional problems compared with high-symptom girls (d=0.65,

p=.02), while this characteristic did not distinguish diagnosed and high-symptom boys (*d*=0.08, *p*=.57; OR for interaction: 1.40 [95%CI: -0.05, 2.86], *p*=.058). Both girls and boys meeting PACS diagnostic criteria were distinguished from their high-symptom peers by greater total problem scores on the SDQ, and specifically conduct and peer problems, but the magnitude of the effect was greater in girls (total problems score: *d*=0.95 vs 0.48; conduct problems: *d*=0.63 vs 0.41; peer problems: *d*=1.20 vs 0.60). In addition, a factor that showed a trend towards significance in distinguishing diagnosed girls versus high-symptom girls but not boys, was prosocial behaviour (girls: *d*=-0.55*, p*=.08 vs boys: *d*=-0.19*, p*=.34).

The SDQ total impact score (parent-rated measure of impairment) only distinguished between the PACS diagnosed and high-symptom boys, with almost double the effect size (boys: *d*=0.61 vs girls: *d*=0.33). Whereas the more objective PACS measure of impairment distinguished children meeting full diagnostic criteria from the children with high-symptoms who did not meet full diagnostic criteria in both girls and boys; however, the magnitude of this difference was greater in girls (*d*=1.05 vs 0.78).

The total school impairment score distinguished PACS diagnosed from high-symptom children in both girls and boys, with similar effect sizes. PACS diagnosed boys were 2.38 times (95%CI: 1.31, 4.30) more likely to show distress at school than high-symptom boys, but PACS diagnosed and high-symptom girls were equally as likely to (OR: 1.09, 95%CI: 0.46, 2.56). In both girls and boys, the likelihood of children meeting diagnostic criteria having complaints about their hyperactivity at school was greater than in high-symptom children, but the odds were greater for girls (OR: 3.07 [95%CI: 2.42, 16.73] vs 2.27 [1.24, 4.17]; OR for interaction: 2.82 [0.91, 8.72], *p* = .07). Problems getting on with others and complaints about aggression similarly distinguished diagnosed boys and girls from their high-symptom peers, but the difference was only significant for diagnosed versus high-symptom boys.

Table 2.2. Results of statistical analyses for within sex differences between diagnosed vs high symptom children, and sex-by-diagnostic status interaction analyses

Characteristic[a]	PACS diagnosed vs high-symptom girls		PACS diagnosed vs high-symptom boys		Interaction (sex-by-diagnostic status)[b]	
	p	Cohen's d	*p*	Cohen's d	b/OR (95% CI)	*p*
ADHD (parent-rated)						
Inattention	.16	0.37	**.03**	**0.32**	0.10 (-2.77, 2.97)	.95
Hyperactivity/ Impulsivity	.45	0.25	.39	0.15	0.42 (-2.71, 3.54)	.79
Co-occurring difficulties						
Emotional	**.02**	**0.65**	.57	0.08	1.40 (-0.05, 2.86)	.06
Conduct	**.04**	**0.63**	**.01**	**0.41**	0.39 (-0.82, 1.61)	.53
Peer	**.002**	**1.20**	**<.001**	**0.60**	0.20 (-1.02, 1.41)	.75
Prosocial	.08	-0.55	.34	-0.19	-0.73 (-2.03, 0.56)	.27
Total Problem Score	**.001**	**0.95**	**.004**	**0.48**	1.99 (-0.96, 4.95)	.19
Impairment						
Total Impact Score (SDQ)	.20	0.33	**<.001**	**0.61**	-0.78 (-2.04, 0.47)	.22
PACS total impairment	**<.001**	**1.05**	**<.001**	**0.78**	0.24 (-0.59, 1.06)	.57
School Impairment (PACS)						
Child shows distress	.84	OR: 1.09 (0.46, 2.56)	**.004**	**OR: 2.38 (1.31, 4.30)**	0.45 (0.16, 1.25)	.12
Problems getting on with others	.05[c]	OR: 2.65 (0.98, 7.15)	**.003**	**OR: 2.72 (1.42, 5.21)**	1.04 (0.31, 3.44)	.95
Special educational provision	**.03**	**OR: 3.89 (1.19, 12.76)**	**<.001**	**OR: 5.23 (2.38, 11.50)**	0.69 (0.17, 2.74)	.60
Complaints about hyperactivity	**<.001**	**OR: 3.07 (2.42, 16.73)**	**.008**	**OR: 2.27 (1.24, 4.17)**	2.82 (0.91, 8.72)	.07
Complaints about aggression	.14	OR: 3.07 (0.70, 13.54)	**.02**	**OR: 2.58 (1.20, 5.55)**	1.31 (0.24, 6.99)	.76
Total school impairment	**.001**	**0.77**	**<.001**	**0.76**	-0.07 (-0.77, 0.63)	.85

Bold data signify statistical significance of the tests

PACS = The Parental Account of Childhood Symptoms; ADHD = Attention-deficit/hyperactivity disorder; OR = Odds ratio (with 95% Confidence Intervals)

[a] Data were missing on some variables; all available data were used in analysis

All models were adjusted for familial clustering and age

[b] Results for interaction analyses are presented as odds ratios (for School impairment measures, except total school impairment score) or unstandardised regression coefficients (for ADHD, co-occurring difficulties, and impairment) with 95% CIs.

[c] *p* = .054

1.1.1.1 Sensitivity analyses

To further ensure that the findings were not a function of differences in the number of ADHD symptoms between the groups being compared, analyses were re-run adjusted for this. This revealed the same pattern of results in terms of significance.

2.4.2   DSM-5 parent-rated ADHD symptoms compared to the PACS-reported symptoms in the diagnostic group

A comparison of the frequency of parent rated DSM-5 ADHD symptoms compared to the same items on the PACS is illustrated in Fig. 2.2. In both boys and girls meeting diagnostic criteria, frequencies of inattentive symptoms were greater in the parent-rated scale compared to the PACS interview, apart from 'attention to details' (12.5% lower in the parent-rated scale in girls and 7.5% in boys), 'organizing tasks' (28.1% lower in girls and 22.3% in boys), 'loses things' in girls only (3.1% lower), and 'listening' and 'forgetful' in boys only (0.8% and 2.5% lower respectively).

Sex differences in the two measures were more noticeable for hyperactive/impulsive symptoms. In girls meeting diagnostic criteria, hyperactive/impulsive symptom frequencies were higher in the PACS compared to the parent-rated scale, except for 'difficulty playing quietly in leisure activities' (34.4% lower in the PACS) and 'exhibits a consistent pattern of restlessness' (50.1% lower). In diagnosed boys hyperactive/impulsive symptom frequencies were higher in the parent-rated scale than the PACS, except for leaves seat (1.7% lower on the parent-rated measure), runs about (20.6% lower), and interrupts or intrudes (26.5% lower). This pattern was reflected in the total score, and analyses found a significant sex-by-scale interaction for hyperactivity/impulsivity ($p<.02$, 95%CI: -2.48 - -0.32) indicating that parents tend to under-rate girls and over-rate boys for the presence of hyperactive/impulsive symptoms compared to the PACS (Fig. 2.2).

Total score (out of 9)	Inattention (SD)			Hyperactivity/Impulsivity (SD)		
	Parent-rated	PACS	Mean difference	Parent-rated	PACS	Mean difference
Girls	5.78 (2.85)	5.19 (1.86)	0.59	4.96 (2.83)	5.56 (1.88)	-0.60
Boys	5.42 (2.87)	4.82 (2.11)	0.60	4.96 (2.89)	4.38 (2.34)	0.58

Figure 2.2. Frequencies of ADHD symptoms on the PACS interview compared to the parent-rating scale in children meeting full diagnostic criteria

2.5   Discussion

In this study, we compared girls and boys who met full ADHD diagnostic criteria using an objective interview assessment to those who did not despite elevated levels of ADHD symptoms. When examining the factors that distinguished girls and boys who met full diagnostic criteria from their high-symptom peers, we found diagnosed girls had more additional problems than high-symptom girls, while this effect was less strong for boys. This could suggest girls with ADHD require a higher burden of other behavioural/emotional problems before they meet criteria for the disorder. We also found sex-dependent parental perceptions of ADHD behaviours and impairment.

We found that girls meeting diagnostic criteria had higher rated emotional, conduct, and peer problems, total problem scores, and complaints about hyperactivity at school compared to the girls with high symptoms that did not pass the diagnostic threshold. Although similar differences were observed in boys (except for emotional problems) effect sizes were greater in girls, and were not due to the diagnosed and high-symptoms girls having a greater difference in ADHD symptoms compared to the equivalents groups of boys. The prominence of emotional symptoms to girls meeting diagnostic criteria suggests that this characteristic may be more important to the female phenotype and that girls may express their difficulties differently to boys. Higher rated emotional problems in girls than boys with ADHD has been shown previously (Novik et al., 2006). It is possible that emotional problems are not perceived to be as problematic compared to disruptive behaviours by individuals key in the diagnostic process, such as parents and teachers, reducing the likelihood of referral compared to children displaying disruptive behaviours. Further, perhaps emotional problems experienced by girls with ADHD are how they express or manifest their impairment, which could overshadow their ADHD symptoms in clinical assessment and lead to receiving alternative diagnoses more closely associated with the internal manifestation of symptoms (e.g., anxiety or depression), or delay time to diagnosis. Indeed, there is evidence to suggest that girls are diagnosed later (Agnew-Blais et al., 2016). This is problematic given the long-term outcomes associated with ADHD and may be a particular issue if these symptoms result from the strain of compensating for their symptoms. It is important that the presence of emotional problems does not rule out an ADHD diagnoses (Quinn, 2008).

Parent-rated impairment using the SDQ did not distinguish between diagnosed versus high-symptom girls; yet it did in the equivalent groups of boys. This is an important finding with regard to sex differences in ADHD as referral based on parent concern requires recognition of impairment, yet parents appear to be less able to spot impairment among girls. One interpretation of these findings is that parents may not be as good at judging impairment in girls, highlighting that objective measures of impairment are especially important in the assessment of girls' ADHD symptoms (Gaub & Carlson, 1997). Some diagnostic tools, such as rating-scale measures of ADHD or standardised parent interview assessments, may lead to underestimating girls' impairment and contribute to their under-diagnosis, and parents may be less likely to take girls for assessment if they perceive them to be less impaired by symptoms compared to boys. Furthermore, this has implications for whether girls with ADHD receive appropriate treatments.

One characteristic that may influence the perception of impairment is prosocial behaviour. Not only is it clear that social functioning is likely to be linked with perceptions of impairment and coping, socially adaptive behaviour may mask symptoms and impairment to informants (Livingston & Happé, 2017). It appears that prosocial behaviour may have an influence on diagnostic status in girls but not boys. One interpretation of these findings it that in the presence of positive social behaviour, girls' symptoms may be 'masked' making them appear less impaired, which could reduce the likelihood of girls with ADHD symptoms being referred and subsequently fewer girls compared to boys being diagnosed with ADHD. This hypothesis requires more research, along with the question of whether prosocial behaviour acts as a form of compensatory mechanism in girls with ADHD.

Finally, we also found sex-dependent biases among parental perceptions of ADHD symptoms in children meeting diagnostic criteria. Parents under-rated diagnosed girls hyperactive/impulsive symptoms compared to the more objective accounts from the PACS, with the opposite pattern observed in boys. These findings suggest that sex-specific biases in perceptions of child behaviour may exist. As with the parental under-report of impairment in girls discussed previously, this also has clinical implications for the referral and subsequent diagnosis of girls with ADHD symptoms. Parents may be less likely to take girls for assessment if they perceive them to display less stereotypical ADHD behaviours (as well as being less impaired). It may also contribute to a

systematic bias in diagnostic practice, as it may influence the identification and interpretation of symptoms by clinicians if they are relying on parental reports.

The present study has several strengths. We extended the methodology typically used in population-based studies by incorporating a comprehensive diagnostic interview and were therefore able to investigate sex differences in the factors that may affect whether children with high ADHD symptoms meet diagnostic criteria in a population-based sample. In addition, the use of an objective, investigator-rated interview enabled investigation of potential sex-specific biases in parental report of ADHD symptoms. We have begun to tackle some of the possible contributing factors to the sex differences that could impact the referral and diagnostic process, but replication is needed.

However, some limitations should be noted. While sizeable for a study of its kind, there was a mismatch in the number of girls to boys, which is a common issue for studies of sex differences in ADHD. This reduces the power in interaction analyses to detect group differences and if these interactions were small they may have been missed; analyses should be repeated in a larger sample. We also acknowledge that the exclusion of children with autistic spectrum disorder and learning problems (applied during the original selection process for deriving the PHAD sample) may somewhat limit the generalisability of our study, particularly if females with ADHD are more likely to have such co-occurring conditions. However, the literature currently does not provide evidence that this is necessarily the case (Biederman et al., 2002; Green et al., 2015; Mulligan et al., 2009; Novik et al., 2006), and such exclusions are not unusual in studies of childhood ADHD (Cheung et al., 2015; Cooper, Martin, Langley, Hamshere, & Thapar, 2014), Finally, in the current study we were not looking at who gets diagnosed in clinical settings, but rather investigating sex differences associated with meeting diagnostic criteria in a unique sample with less selection than studies of children who present to clinics. Unfortunately, as with many population-based studies, we do not have information on which individuals were actually referred, and so it is not possible to infer directly what the implications of the findings are on the referral and diagnostic process in clinical practice.

It is clear that research is needed to identify the best screening methods, most accurate informants, and most appropriate thresholds for the diagnosis of ADHD, which may differ for boys

and girls (Rucklidge, 2010). It is likely that the same instruments should be used for boys and girls, but possibly with the addition of items that are more sensitive to the manifestation of ADHD in girls (Arnold, 1996). For example, items that relate better to social functioning and emotionality, and that are better placed to assess more internalising symptoms (Skogli, Teicher, Andersen, Hovik, & Øie, 2013). Perhaps this is timely given the ADHD diagnostic criteria are primarily based on studies in males (Clarke et al., 2013; Lahey et al., 1994).

In summary, these data suggest that factors which distinguish girls who meet full ADHD diagnostic criteria from high-symptom peers who do not may be somewhat sex specific, with additional behavioural and emotional problems playing a larger role in distinguishing diagnosed from high-symptom girls than the equivalent male comparison. Additionally, we found different parental perceptions of ADHD behaviours as shown by our comparison of parent report to a more objective measure of ADHD symptoms. Such differences may explain why girls are less likely to be referred for their ADHD behaviours. This may also contribute to the relatively low recognition rate of ADHD in girls in clinical practice if girls with ADHD are perceived to display less stereotypical disruptive ADHD behaviours and perceived as less impaired by symptoms than boys, especially in the presence of socially adaptive behaviour and more internalising emotional symptoms. From a clinical perspective, our findings highlight the importance of detailed interview assessments in the diagnostic process, especially for girls who may not be identified with rating-scale measures which are more subject to sex biased perceptions of behaviour, and that emotional problems should not be used to rule out an ADHD diagnoses.

Chapter 3. Sex differences in predicting ADHD clinical diagnosis and pharmacological treatment

This chapter is presented as a published paper. It is an exact copy of this publication:

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Supplementary materials for this chapter, as detailed in the text, are attached in Appendix B.

ORIGINAL CONTRIBUTION

CrossMark

Sex differences in predicting ADHD clinical diagnosis and pharmacological treatment

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Abstract

In youth, ADHD is more commonly diagnosed in males than females, but higher male-to-female ratios are found in clinical versus population-based samples, suggesting a sex bias in the process of receiving a clinical diagnosis of ADHD. This study investigated sex differences in the severity and presentation of ADHD symptoms, conduct problems, and learning problems in males and females with and without clinically diagnosed ADHD. We then investigated whether the predictive associations of these symptom domains on being diagnosed and treated for ADHD differed in males and females. Parents of 19,804 twins (50.64% male) from the Swedish population completed dimensional assessments of ADHD symptoms and co-occurring traits (conduct and learning problems) when children were aged 9 years. Children from this population sample were linked to Patient Register data on clinical ADHD diagnosis and medication prescriptions. At the population level, males had higher scores for all symptom domains (inattention, hyperactivity/impulsivity, conduct, and learning problems) compared to females, but similar severity was seen in clinically diagnosed males and females. Symptom severity for all domains increased the likelihood of receiving an ADHD diagnosis in both males and females. Prediction analyses revealed significant sex-by-symptom interactions on diagnostic and treatment status for hyperactivity/impulsivity and conduct problems. In females, these behaviours were stronger predictors of clinical diagnosis (hyperactivity/impulsivity: OR 1.08, 95% CI 1.01, 1.15; conduct: OR 1.43, 95% CI 1.09, 1.87), and prescription of pharmacological treatment (hyperactivity/impulsivity: OR 1.24, 95% CI 1.02, 1.50; conduct: OR 2.20, 95% CI 1.05, 4.63). Females with ADHD may be more easily missed in the ADHD diagnostic process and less likely to be prescribed medication unless they have prominent externalising problems.

Keywords Attention-deficit/hyperactivity disorder/ADHD · Sex differences · Clinical diagnosis · Population-based study

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Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterised by age-inappropriate and maladaptive levels of inattention and/or hyperactivity/impulsivity. In children and adolescents, ADHD is more commonly diagnosed in males, with the sex ratio ranging from 2:1 to 10:1 [1–5]. However, sex ratios appear to be dependent on the type of sample, with higher male-to-female ratios found in clinical versus population-based samples. Furthermore, the male-to-female ratio is smaller in adult clinic samples than in childhood and adolescent samples [6]. This suggests that, in youth, ADHD affects a greater proportion of females than reflected in clinical practice and that differences exist in the diagnostic process for males and females with ADHD symptoms [7, 8].

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The findings relating to sex differences in ADHD are variable and sometimes contradictory, partly due to differences in sample characteristics. Meta-analyses tend to show less severe symptoms in females versus males with ADHD identified from non-referred, community populations, but similar levels in clinically ascertained samples—with the exception of inattention for which females had higher ratings in the more recent meta-analysis [5, 9]. Several other studies have also not found support for sex differences for ADHD symptoms and co-occurring problems in clinical and referred samples [1, 10]. While important information has been gained from both population-based and clinical samples of children with ADHD, the approach of investigating sex differences in either a population-based or clinical sample means that it is not clear what factors are specifically leading to the clinical diagnosis of children with ADHD from the population, and if these differ as a function of sex.

Sex differences in the phenotypic expression of ADHD are often proposed as an explanation for the greater rates of ADHD diagnosis in males. A common hypothesis is that females with ADHD are more likely to present with predominantly inattentive symptoms, and less hyperactive/impulsive or conduct problems than boys, and are thus perceived as less problematic [4, 7, 11]. Therefore, females with ADHD problems that manifest as predominantly inattentive symptoms and lower levels of disruptive behaviours may be less likely to receive a diagnosis of ADHD [5].

Studies also show sex differences in the pattern of ADHD treatment, with males being more likely to receive ADHD medication than females [12, 13]. However, the underlying reasons for the observed sex differences in treatment remain to be investigated. Different pharmacological treatment rates in males and females could also be due to a different manifestation of the disorder. It is important to understand whether certain symptom manifestations have greater influence on being prescribed pharmacological treatment, and the possibility that females with ADHD are undertreated is an important public health concern [8].

Another consideration in the diagnostic and treatment process of individuals with ADHD is the presence of co-occurring learning problems, since learning problems represent another leading reason for identification of children with ADHD. Research has demonstrated that females with ADHD are less likely to have learning difficulties or manifest problems at school compared to males [14, 15], which could also lead to lower identification of ADHD in females. Sex differences in learning problems related to ADHD, and their impact on the diagnostic and treatment process, are not well investigated.

This study investigated sex differences in ADHD using a large population-based sample [The Child and Adolescent Twin Study in Sweden (CATSS)] linked to Swedish National Patient Register data on clinical ADHD diagnoses and prescribed ADHD medications. Thus, enabling investigation of a population-based and clinical sample for which there is not an ascertainment bias and overcoming important limitations of studies reliant on one type of sample alone. We first described the severity of ADHD symptoms, conduct, and learning problems in males and females with and without clinically diagnosed ADHD, followed by examination of the ADHD symptom presentation. We then investigated whether the predictive associations of inattention, hyperactivity/impulsivity, conduct problems, and learning problems on being diagnosed and treated for ADHD differed in males and females. It was hypothesised that (1) at the population level, males would show greater symptom severity than females, but at the clinical level similar severity would be observed, with the exception of inattention for which levels may be higher in females as suggested by meta-analysis, (2) hyperactivity/impulsivity and conduct problems would be a stronger predictor of diagnosis in females than in males and inattention a weaker predictor, and (3) in children with a clinical diagnosis of ADHD, hyperactivity/impulsivity and conduct problems would be a stronger predictor of medication status in females than males.

It is important to increase our understanding of sex effects in ADHD and whether certain symptoms are more predictive of clinical diagnosis and pharmacological treatment (including whether sex differences in such predictors exist), as it can lead to improved identification of females with the disorder. Furthermore, it may point towards certain biases in the diagnostic and treatment process which has implications for clinical practice and can inform our understanding of the way that clinicians recognise ADHD symptoms, and potentially apply the diagnostic criteria.

Methods

Sample

Participants were from The Child and Adolescent Twin Study in Sweden (CATSS) [16], an ongoing prospective longitudinal cohort twin study that targets all twins in Sweden born since 1992. A telephone interview is conducted with parents of all twins, no more than 1 month before or after their 9th or 12th birthdays (CATSS-9/12; baseline). For the present study, data from 19,804 CATSS children assessed at age 9 years were available for analyses (50.64% males). The CATSS-9/12 study has ethical approval from the Karolinska Institute Ethical Review Board and participants are protected by the informed consent process.

Measures

ADHD symptoms and co-occurring behavioural traits The Autism-Tics, AD/HD and other Comorbidities Inventory (A-TAC) was administered to parents of twins over the telephone, and questions were asked from a lifetime perspective. The A-TAC is a broad screening instrument that encompasses multiple neurodevelopmental disorders. Two modules of the A-TAC are used to assess ADHD (one assessing inattention [9 items] and one assessing hyperactivity/impulsivity [10 items]), consisting of a total of 19 items that correspond closely to DSM-5 diagnostic criteria for ADHD [17]. Questions are answered on a 3-point scale: 'no' (scored as 0), 'yes, to some extent' (scored as 0.5), and 'yes' (scored as 1). Thus, the maximum score that can be obtained is 19. These questions were identified to achieve the optimal sensitivity, specificity, and predictive value for clinical ADHD diagnoses in validation studies, with high internal consistency [18–21].

Using the A-TAC ADHD items, it is possible to categorise individuals based on DSM-5 symptom criteria for the three ADHD presentations: the predominately inattentive presentation, based on the presence of six or more symptoms of inattention; the predominantly hyperactive/impulsive presentation, based on the presence of six or more symptoms of hyperactivity/impulsivity (using nine of the ten A-TAC items); and the combined presentation, based on six or more symptoms of both inattention and hyperactivity/impulsivity. From the three-point scale described above, we dichotomised responses for each item into 'symptom present' ('yes' and 'yes to some extent' were collapsed into one category) and 'symptom absent' to enable categorisation of participants into one of the three ADHD presentations.

The A-TAC also includes questions that target other well-described clinical features of psychiatric disorders, such as conduct problems (five items relating to lying, cheating, stealing, being cruel, or starting fights) and learning difficulties (three items relating to reading and maths skills and slow learning), also scored on a three-point scale as above. Thus, whilst looking specifically at one disorder, co-occurring problems can also be examined. Of note, although the A-TAC also includes questions on anxiety and mood, we were unable to examine these variables due to a reduced number of CATSS participants completing these questions.

Socio-Economic Status (SES) Maternal education from the Swedish Register of Education was used as an indicator of socio-economic status. A categorical variable was created (low = primary and secondary education, ≤ 9 years; medium = upper secondary education, 10–12 years; high = post-secondary education, > 12 years).

Population-based registers

Unique personal identifier numbers enable data from participants in the CATSS sample to be accurately linked with information from National population-based registers up until December 2013. Thus, it was possible to determine whether participants in CATSS had been referred to a specialist clinic and diagnosed with ADHD, and if they were prescribed ADHD medication. Registry data were also used to identify 273 participants in CATSS who had emigrated (obtained from The Migration Register) or died (obtained from The Cause of Death Register) after their participation in the study; these individuals were excluded from analyses.

The National Patient Register (NPR) The NPR contains information about all psychiatric inpatient (from 1987) and outpatient (from 2001) care in Sweden, from both private and public caregivers (primary care is not currently included). Clinical ADHD diagnoses are based on the International Classification of Diseases (ICD), code F90 [22], but most clinicians base their clinical assessment on DSM criteria for ADHD and recode to ICD. Participants were identified as having a diagnosis of ADHD from the NPR if they had at least one record of inpatient or outpatient care for ADHD from 2001 to 2013.

Prescribed Drug Register (PDR) The PDR contains data for all dispensed drug prescriptions to the entire Swedish population since July 2005. Information on the indication for the prescription is not recorded; however, ADHD is a group that can be identified as treatment is characterised by a few drugs exclusively used for this disorder (methylphenidate hydrochloride, atomoxetine, amphetamine sulfate, or dextroamphetamine sulfate). Participants treated with ADHD medication were identified if they had at least one prescription from 2005 to 2013.

Statistical analysis

Descriptive statistics are presented to describe the severity and presentation of ADHD symptoms and co-occurring behaviours in males and females with and without clinically diagnosed ADHD. Sex differences in parent-rated ADHD symptom scores (inattention and hyperactivity/impulsivity) and co-occurring conduct and learning problems scores were tested using linear regression models (hypotheses 1), and sex differences in ADHD medication status was tested using logistic regression.

To assess whether the predictive associations of inattention, hyperactivity/impulsivity, conduct problems, and learning problems with clinical diagnoses differed in males and females, we used a series of logistic regression models (hypotheses 2). The models were conducted separately for each symptom domain (inattention, hyperactivity/impulsivity, conduct problems, and learning problems) using

the continuous score, and stratified by sex. We also applied logistic regression models with males and females included in one model to investigate sex-by-symptom interactions on diagnostic status (again, separate models were run for each symptom domain using the continuous score).

Next, we used a series of logistic regression models to examine sex differences in the associations between these symptom domains and ADHD medication status in children with clinically diagnosed ADHD (hypotheses 3). The models were conducted separately for each symptom domain using the continuous score and stratified by sex. We also investigated sex-by-symptom interactions on treatment status.

All regression models were adjusted for the effects of year of birth and family SES. Furthermore, as the data were used as population data and not analysed in a twin analysis model, we controlled for the clustered data structure (to correct for the inclusion of two study children in each family) using a cluster-robust sandwich estimator (the *cluster(vce)* command in Stata [23]).

Results

Prevalence

In the CATSS sample, 3.28% ($n = 650$) of the children had a clinical diagnosis of ADHD recorded in the National Patient Register (NPR). Clinically diagnosed ADHD was more common in males (4.65%, $n = 466$) than in females (1.88%, $n = 184$), which corresponds to a prevalence ratio of ~2.5:1.

Based on DSM-5 ADHD symptom criteria using the parent-reported A-TAC questionnaire, 2556 individuals (12.9%) from the CATSS sample met criteria for ADHD. More males (16.3%, $n = 1635$) than females (9.43%, $n = 921$) met the symptom criteria, corresponding to a prevalence ratio of ~1.8:1. Among these children, 303 (18.5%) of the males with elevated symptoms, and 111 (12.1%) of the females with elevated symptoms had an ADHD diagnosis recorded in the NPR.

Symptom severity

Table 1 shows mean symptom scores for children with and without a clinical diagnosis of ADHD in the NPR. Among non-diagnosed children, females had significantly lower scores compared to males for total ADHD, inattention, hyperactivity/impulsivity, conduct problems, and learning problems (p values < 0.001). In contrast, among children with clinically diagnosed ADHD, males and females showed similar severity across the symptom domains, except for significantly higher inattention scores in males ($p = 0.03$,

Table 1 Characteristics of the non-diagnosed and clinically diagnosed children (means and SD unless otherwise stated)

Characteristic[a]	Non-diagnosed[b]					Diagnosed in the NPR				
	Overall (n=19,154)	Males (n=9563)	Females (n=9591)	P	Cohen's d	Overall (n=650)	Males (n=466)	Females (n=184)	P	Cohen's d
Total ADHD	1.85 (2.77)	**2.19 (3.02)**	**1.50 (2.45)**	**<.001**	0.25	8.44 (5.53)	8.72 (5.46)	7.75 (5.64)	.08	0.18
Inattention	0.94 (1.58)	**1.13 (1.72)**	**0.74 (1.41)**	**<.001**	0.25	4.43 (2.86)	**4.60 (2.80)**	**4.01 (2.97)**	**.03**	0.21
Hyperactivity/impulsivity	0.91 (1.53)	**1.06 (1.67)**	**0.76 (1.37)**	**<.001**	0.20	4.02 (3.17)	4.12 (3.17)	3.76 (3.18)	.25	0.11
Conduct	0.08 (0.31)	**0.10 (0.35)**	**0.07 (0.27)**	**<.001**	0.10	0.60 (0.99)	0.58 (0.97)	0.63 (1.03)	.50	−0.05
Learning	0.25 (0.57)	**0.27 (0.59)**	**0.23 (0.55)**	**<.001**	0.07	1.01 (1.05)	0.98 (1.02)	1.11 (1.13)	.17	−0.12
Medication % (n)	–	–	–	–	–	552	84.98% (396)	84.78% (156)	.93	–

Bold data signify statistical significance of the tests

All models were adjusted for familial clustering, year of birth, and SES

ADHD attention-deficit/hyperactivity disorder, *NPR* National Patient Register

[a] Data were missing on some variables; all available data were used in analysis

[b] Scores for the entire population can be found in the Supplementary Table 1

$d = 0.21$). Females and males with a clinical diagnosis were equally likely to be prescribed ADHD medication.

ADHD presentations

Among all children from the CATSS sample meeting DSM-5 symptom criteria for ADHD as identified with the parent-reported A-TAC questionnaire, the inattentive presentation was most common (53.7%), followed by the combined (26.8%) and hyperactive/impulsive (19.5%) presentations (Table 2). A significantly greater percentage of females met symptom criteria for the inattentive presentation category compared to males ($\chi^2(1) = 11.27$, $p = 0.002$, $d = 0.11$), and a significantly greater percentage of males met symptom criteria for the combined presentation category compared to females ($\chi^2(1) = 17.39$, $p < 0.001$, $d = 0.15$). There was a similar percentage of males and females meeting symptom criteria for the hyperactive/impulsive presentation ($\chi^2(1) = 0.19$, $p = 1.0$, $d = 0.08$).

Looking exclusively among the children clinically diagnosed with ADHD in the NPR, the combined presentation was most common (55.3%), followed by the inattentive (36.7%) and hyperactive/impulsive (8.0%) presentations (Table 2). Among these cases, there were no statistically significant differences between males and females in the ADHD presentations (Table 2).

Does the predictive value of ADHD symptoms, conduct problems, and learning problems on ADHD diagnosis and treatment differ by sex?

Using the A-TAC continuous scores, in both males and females, symptom severity with respect to inattention and hyperactivity/impulsivity increased the likelihood of receiving a clinical ADHD diagnosis (Table 3) (for example, for males, with each unit increase on the inattention scale the odds of having a clinical diagnosis of ADHD increased by 1.67, whereas in females the odds increased by 1.73). Co-occurring conduct and learning problems were also associated with an increased likelihood of ADHD diagnosis in both males and females. Odds ratios were higher across all predictors in females than males, although these differences were small and non-significant for inattention and learning problems. Interaction analyses revealed sex-by-symptom interactions for hyperactivity/impulsivity (OR 1.08, 95% CI 1.01, 1.15, $p = 0.03$) and conduct problems (OR 1.43, 95% CI 1.09, 1.87, $p = 0.01$), suggesting that externalising symptoms of hyperactivity/impulsivity and conduct problems are more strongly associated with the prediction of clinically diagnosed ADHD in females than in males.

Symptom severity with respect to hyperactivity/impulsivity increased the likelihood of being prescribed ADHD medication in both sexes (Table 4). Inattention and conduct

Table 2 ADHD presentations based on DSM-5 criteria symptom counts measured with parent-rated A-TAC, in the entire CATSS population and diagnosed children

Presentation; n (%)	Entire population[a]						Diagnosed in the NPR[b]					
	Overall	Males	Females	χ^2 [c]	P	Cohen's d	Overall	Males	Females	χ^2 [c]	P	Cohen's d
Inattentive	1372 (53.7)	837 (51.2)	535 (58.1)	11.27	**.002**	0.11	151 (36.7)	107 (35.6)	44 (39.6)	0.56	1.0	−0.02
Hyperactive/impulsive	499 (19.5)	315 (19.3)	184 (20.0)	0.19	1.0	0.08	33 (8.0)	25 (8.3)	8 (7.2)	0.13	1.0	0.05
Combined	685 (26.8)	483 (29.5)	202 (21.9)	17.39	**<.001**	0.15	228 (55.3)	169 (56.1)	59 (53.2)	0.29	1.0	0.09

Bold data signify statistical significance of the tests

NPR National Patient Register

[a]Inclusive of children with a clinical diagnosis

[b]236 children (163 males) did not meet symptom criteria for any of the presentations based on the A-TAC

[c]Chi square tests are adjusted for multiple testing using Bonferroni correction

Table 3 Predictive value of core ADHD symptoms and co-occurring problems on clinical ADHD diagnosis (based on the National Patient Register) in males and females

Characteristic[a]	Males		Females		Interaction (sex-by-symptom)	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Inattention	**1.67 (1.61, 1.74)**	**<.001**	**1.73 (1.63, 1.84)**	**<.001**	1.02 (0.96, 1.10)	.43
Hyperactivity/impulsivity	**1.55 (1.49, 1.61)**	**<.001**	**1.68 (1.58, 1.77)**	**<.001**	**1.08 (1.01, 1.15)**	**.03**
Conduct problems	**2.79 (2.41, 3.25)**	**<.001**	**4.09 (3.20, 5.23)**	**<.001**	**1.43 (1.09, 1.87)**	**.01**
Learning problems	**2.53 (2.28, 2.81)**	**<.001**	**2.87 (2.45, 3.35)**	**<.001**	1.11 (0.93, 1.33)	.25

Bold data signify statistical significance of the tests

All models were adjusted for familial clustering, year of birth, and SES

OR Odds Ratio (95% confidence interval)

[a]Data were missing on some variables; all available data were used in analysis

Table 4 Influence of core ADHD symptoms and co-occurring problems on prescription of ADHD medication (in the Prescribed Drug Register) in males and females with a clinical diagnosis of ADHD (in the National Patient Register)

Characteristic[a]	Males		Females		Interaction (sex-by-symptom)	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Inattention	1.08 (.98, 1.20)	.12	**1.22 (1.05, 1.42)**	**.01**	1.13 (0.95, 1.34)	.16
Hyperactivity/impulsivity	**1.12 (1.02, 1.23)**	**.01**	**1.37 (1.15, 1.64)**	**.001**	**1.24 (1.02, 1.50)**	**.03**
Conduct problems	1.04 (.78, 1.36)	.76	**2.29 (1.09, 4.82)**	**.03**	**2.20 (1.05, 4.63)**	**.04**
Learning problems	1.05 (.79, 1.39)	.75	0.83 (.56, 1.23)	.36	0.84 (0.53, 1.31)	.44

Bold data signify statistical significance of the tests

All models were adjusted for familial clustering, year of birth, and SES

OR Odds Ratio (95% confidence interval)

[a] Data were missing on some variables; all available data were used in analysis

For mean scores of clinically diagnosed males and females stratified by medication prescription, see Supplementary Table 2

problems were associated with an increased likelihood of being prescribed medication in females, but not in males. Interaction analyses revealed sex-by-symptom interactions for hyperactivity/impulsivity (OR 1.24, 95% CI 1.02, 1.50, $p = 0.03$) and conduct problems (OR 2.20, 95% CI 1.05, 4.63, $p = 0.04$), suggesting that externalising symptoms of hyperactivity/impulsivity and conduct problems influence being prescribed pharmacological treatment for ADHD to a greater extent in females than males. Learning problems did not predict medication treatment in the sample overall, or for either males or females (Table 4).

Discussion

This large population-based study investigated the role of sex differences in ADHD symptoms and co-occurring conduct and learning problems on clinical diagnosis and pharmacological treatment of ADHD. The main finding was that the predictive association of hyperactive/impulsive and conduct symptoms on ADHD diagnosis and treatment status was stronger in females than in males. We also found, consistent with previous findings, greater ADHD symptoms

and co-occurring conduct and learning problems in males than females at the population level [2, 14], more males than females received a clinical diagnosis of ADHD, and that clinically diagnosed males and females showed similar symptom severity [5, 15, 24, 25], except for higher inattention scores in males (which is not in line with the most recent meta-analysis showing greater inattention in females, but the effect size was modest: $d = 0.21$).

Severity of all the symptom domains assessed increased the likelihood of having a clinical diagnosis of ADHD in both males and females. Across all domains, odds ratios were slightly higher for females, suggesting greater deviation from their typical behaviour, and may indicate a greater symptom threshold requirement for referral and diagnosis in females. Significant sex differences were found for the predictive value of hyperactivity/impulsivity and conduct problems, with these externalising behaviours being stronger predictors of diagnosis in females than males. This finding is consistent with a previous study showing that girls with externalising symptoms were referred at a younger age than boys with similar behavioural problems [24]. One explanation for this finding is that externalising symptoms are in greater contrast to what is perceived as normative behaviour

in females [7, 24, 26]. Indeed, we found lower levels of hyperactivity/impulsivity and conduct problems in females versus males without a diagnosis of ADHD (i.e., lower baseline levels). These results may also suggest that externalising behaviours drive referral for ADHD [7], speaking to the view that externalising behaviours are more likely to get females clinical recognition for their symptoms. Finally, our finding that externalising behaviours are stronger predictors of diagnosis in females than males suggests that females with ADHD may be more easily missed in the ADHD diagnostic process unless they have prominent externalising problems. This may suggest that the current diagnostic criteria and/or clinical practice are somewhat biased towards the male presentation of ADHD, and has implications for clinical training related to sex role socialisation.

Both hyperactivity/impulsivity and conduct problems were also stronger predictors of ADHD medication status in females compared to males, despite clinically diagnosed males and females being equally as likely to be prescribed ADHD medication. This suggests that if females display less prominent externalising behavioural problems they are less likely to be prescribed medication, whereas males may be prescribed medication based on ADHD diagnostic status alone.

We found no difference in learning problem scores by sex in those with ADHD, which is in contrast to previous research showing more pronounced learning and school-related problems in males with ADHD than in females [14, 15]. Furthermore, the predictive association between learning problems and ADHD diagnosis was similar in males and females. However, learning problems were not associated with being prescribed medication, suggesting that learning problems may not be pertinent to pharmacological treatment decisions for children with ADHD, and in cases where learning problems are particularly prominent in the presentation, alternative interventions may be adopted. The relevance of learning problems to referral, diagnosis, and treatment of ADHD may also differ across countries, where differing importance may be placed on these difficulties in the diagnostic process. It would be interesting to see if findings regarding the impact of learning problems on diagnosis and treatment are replicated in other countries.

Our study found that the combined presentation was the most common ADHD presentation in children with a clinical diagnosis. In contrast, among the children meeting ADHD criteria based on parent-rated symptoms, the inattentive presentation was the most common, which is consistent with some previous research [3, 7, 14, 27, 28], but not all studies [1, 29]. This suggests that some children with primarily inattentive symptoms may not get diagnosed with ADHD. It is possible that: (1) children with predominantly inattentive symptoms are referred but may receive alternative diagnoses in the absence of externalising behaviours [7,

11]; (2) children with the inattentive presentation may be perceived as less impaired and their behaviour as less problematic in comparison to disruptive behavioural problems [30, 31]. These possibilities may be of particular relevance to females, since we found a greater percentage of females than the percentage of males presented with predominately inattentive symptoms at the population level. This could partially explain the greater number of males than females in clinical samples of children with ADHD compared to non-referred samples [14].

This study represents one of the largest samples used to investigate sex differences in ADHD. In addition, previous studies have investigated sex differences in either clinical *or* population samples; here, we uniquely bring the two together. This enabled investigation of a population-based and clinical sample for which there is not an ascertainment bias, overcoming limitations of studies using one type of sample alone. Prevalence rates in this cohort are in line with expectations and suggest an overall reasonable detection of ADHD in Sweden. The administrative prevalence of ADHD was 3.28%, and the symptomatic prevalence based on the A-TAC was substantially higher at 12.9% as impairment criteria and symptom pervasiveness across settings were not applied, consistent with previous estimates of ADHD classification based on symptom counts alone [3]. However, this rate is similar to estimates from other community studies that apply impairment criteria [2]. Of note, another potential explanation for the prevalence difference between clinically diagnosed ADHD and symptomatic ADHD is that males and females who have less pronounced levels of externalising behaviours and a predominantly inattentive presentation are less often clinically diagnosed. Among children clinically diagnosed with ADHD, the ratio of males to females was 2.5:1, which is somewhat lower than previously reported [5, 9]. Of the entire CATSS sample, the ratio of males to females meeting symptomatic threshold was 1.8:1, which is consistent with previous findings [3]. Thus, the difference in ratios of males to females in the clinical and population sample was small, and findings of this study may not generalise to countries with lower (or higher) administrative prevalence rates.

Our findings should be considered in the context of some limitations. Our findings are telling us about diagnosis patterns and do not provide information about referral patterns. It is possible that a number of children are referred but receive alternative diagnoses or are not considered sufficiently impaired by symptoms to obtain a diagnosis. Future studies should investigate such hypotheses. We were also unable to confirm whether additional children from CATSS should have a clinical diagnosis of ADHD (i.e., children who are potentially 'missed' in the community); as an epidemiologic cohort, our study did not have objective clinician or research interviews. Furthermore, we relied on

parent-ratings of ADHD symptoms and co-occurring problems, which may be influenced by sex-specific biases and expectations [26, 32]. For example, there is some evidence that parents may underrate females' ADHD symptoms compared to males [32]. A further limitation is that, unfortunately, our main analyses did not examine co-occurring internalising problems due to a reduced number of CATSS participants completing these measures. Sex differences in internalising problems have been reported [9] and further research is needed to explore the predictive associations with diagnosis and treatment of ADHD. We were also unable to explore potential sex differences in referral to non-pharmacological interventions for ADHD. Finally, the study was carried out in a twin sample and findings may not generalise to singletons; for example, twins are more likely to have lower birth weight compared to singletons which is a risk factor for ADHD [33, 34]. Findings require replication in a non-twin sample.

These limitations notwithstanding, overall the current findings highlight the importance of the clinical presentation of ADHD as it can influence diagnosis and treatment decisions differentially in males and females, and the prominence of different symptoms clearly matters. Externalising behavioural problems were more predictive of diagnosis and pharmacological treatment in females than males, perhaps because they contrast more with perceptions of normative behaviour in females. One interpretation of these findings is that females with ADHD may be under-identified in the absence of prominent externalising problems.

We hope that our findings encourage more research in this area to foster greater understanding of sex-specific diagnostic patterns and more effective recognition, diagnosis, and treatment of ADHD in females in clinical, educational, and other settings.

Disclosures

Paul Lichtenstein has served as a speaker for Medice. King's College London received funds for consultancy and other work by Philip Asherson, which has been used to support departmental research on ADHD: consultancy to Shire, Eli-Lilly, and Novartis, regarding the diagnosis and treatment of ADHD; educational/research awards from Shire, Eli-Lilly, Novartis, Vifor Pharma, GW Pharma, and QbTech; speaker at sponsored events for Shire, Eli-Lilly, and Novartis—all outside the submitted work. Henrik Larsson has served as a speaker for Eli-Lilly and Shire and has received a research grant from Shire; all outside the submitted work. Florence Mowlem, Mina Rosenqvist, and Joanna Martin report no potential conflicts of interest.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict for interest.

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Chapter 4. Validation of the Mind Excessively Wandering Scale and the relationship of mind wandering to impairment in adult ADHD

This chapter is presented as a published paper. It is an exact copy of this publication:

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Supplementary materials for this chapter, as detailed in the text, are attached in Appendix C.

Validation of the Mind Excessively Wandering Scale and the Relationship of Mind Wandering to Impairment in Adult ADHD

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Abstract

Objective: This study investigates excessive mind wandering (MW) in adult ADHD using a new scale: the Mind Excessively Wandering Scale (MEWS). **Method:** Data from two studies of adult ADHD was used in assessing the psychometric properties of the MEWS. Case-control differences in MW, the association with ADHD symptoms, and the contribution to functional impairment were investigated. **Results:** The MEWS functioned well as a brief measure of excessive MW in adult ADHD, showing good internal consistency ($\alpha > .9$), and high sensitivity (.9) and specificity (.9) for the ADHD diagnosis, comparable with that of existing ADHD symptom rating scales. Elevated levels of MW were found in adults with ADHD, which contributed to impairment independently of core ADHD symptom dimensions. **Conclusion:** Findings suggest excessive MW is a common co-occurring feature of adult ADHD that has specific implications for the functional impairments experienced. The MEWS has potential utility as a screening tool in clinical practice to assist diagnostic assessment. *(J. of Att. Dis. XXXX; XX(X))*

Introduction

The diagnosis of ADHD is based mainly on descriptions of behaviors that reflect inattention, hyperactivity, and impulsivity. Yet older children, adolescents, and adults frequently report phenomenological descriptions of internal subjective experiences that may underlie the behavioral changes seen in ADHD. Characteristic descriptions of the mental state in ADHD include reports of ceaseless mental activity, thoughts that are constantly on the go, or a mind constantly full of thoughts. Thoughts are experienced as uncontrolled, with multiple occurring at the same time. Another common description is of short-lived thoughts that flit from one thing to another, jumping between different ideas (Asherson, 2005; Downey, Stelson, Pomerleau, & Giordani, 1997; Weyandt et al., 2003). Here, we propose that such excessive mind wandering (MW) may reflect a core difficulty in ADHD that underlies some of the experienced impairments.

MW is conceptualized as periods in time when attention and the contents of thoughts shift away from external sources and/or ongoing tasks to unrelated internal thoughts or feelings (Smallwood & Schooler, 2015). It is a universal human experience; individuals in the general population are estimated to spend between 24% and 50% of their waking hours engaging in self-generated thoughts unrelated to their external environment (Kane et al., 2007; Killingsworth & Gilbert, 2010; Smallwood & Schooler, 2015; Song & Wang, 2012). Two main types of MW have been identified; first, self-generated internal thoughts that occur intentionally/deliberately, such as planning the menu for a party while driving to work. Second, unintentional/spontaneous MW when the mind drifts off, for example, during a lecture or

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Item:
1. I have difficulty controlling my thoughts
2. I find it hard to switch my thoughts off
3. I have two or more different thoughts going on at the same time
4. My thoughts are disorganised and 'all over the place'
5. My thoughts are 'on the go' all the time
6. [a] Because my mind is 'on the go' at bedtime, I have difficulty falling off to sleep
7. I experience ceaseless mental activity
8. I find it difficult to think about one thing without another thought entering my mind
9. I find my thoughts are distracting and prevent me from focusing on what I am doing
10. [a] I try to distract myself from my thoughts by doing something else or listening to music
11. I have difficulty slowing my thoughts down and focusing on one thing at a time
12. I find it difficult to think clearly, as if my mind is in a fog
13. I find myself flitting back and forth between different thoughts
14. [a] I use alcohol or other drugs to slow down my thoughts and stop constant 'mental chatter'
15 I can only focus my thoughts on one thing at a time with considerable effort

Figure 1. Items from the Mind Excessively Wandering Scale (MEWS).

Note. Items are scored on a 4-point Likert-type scale (0 = *not at all* or *rarely*, 1 = *some of the time*, 2 = *most of the time*, 3 = *nearly all of the time* or *constantly*). The MEWS scale is copyrighted and available without charge from the corresponding author, and we welcome use of this scale in research.

[a]Items we recommend excluding from the scale in future research, based on analysis conducted here.

conversation. Despite its ubiquitous nature, individuals differ in the frequency and intentionality of their MW.

Excessive spontaneous MW has been associated with functional impairment and implicated in psychopathologies such as ADHD (Franklin et al., 2014). Mental restlessness, a descriptive term encompassing excessive MW, has been reported as more common in ADHD than non-ADHD individuals (Downey et al., 1997; Weyandt et al., 2003). Previous work suggests that ADHD is associated with spontaneous MW, rather than deliberate MW, and detrimental episodes of MW (Franklin et al., 2014; Seli, Smallwood, Cheyne, & Smilek, 2015; Shaw & Giambra, 1993). Detrimental MW has been defined as instances when task-unrelated thoughts (TUTs) interfere with task performance. In contrast, strategic MW occurs at times when TUTs are less likely to interfere with performance (whether intentional or not) or when the benefits outweigh the costs, and can be an economic use of neuronal resources (Franklin et al., 2014; Smallwood & Schooler, 2015).

Using an experience sampling technique to measure on- and off-task thoughts during an attention task, Shaw and Giambra (1993) found the frequency of spontaneous (but not deliberate) TUTs was increased in college students with a childhood history of ADHD compared with controls. Furthermore, a sub-clinical group with high levels of ADHD symptoms demonstrated more TUTs compared with those with low ADHD scores. This finding was subsequently replicated using a rating scale measure of deliberate and spontaneous MW in both clinical and non-clinical ADHD samples (Seli et al., 2015). In addition, regression analyses revealed spontaneous MW to be independently related to ADHD symptomatology, whereas deliberate MW was unrelated, further suggesting that spontaneous MW is a feature of ADHD.

ADHD symptomatology has also been shown to positively correlate with both the frequency of MW and the lack of awareness of engaging in MW (Franklin et al., 2014). A sub-clinical group with high ADHD symptom scores had disruptive MW episodes even when they were detrimental and interfered with function in daily life. In this study, lacking awareness of MW was shown to mediate between ADHD symptoms and impairment, suggesting that increasing awareness of MW in ADHD might lead to functional improvements.

Collectively, these findings suggest that adults with ADHD are highly susceptible to excessive spontaneous MW and may have a core difficulty controlling spontaneous thoughts unrelated to the current context. Excessive MW could therefore underlie many of the symptoms and impairments that characterize the disorder. To explore the role that MW may play in the pathogenesis of ADHD, as well as its potential role in diagnosis, our research group developed the Mind Excessively Wandering Scale (MEWS; see Figure 1). The MEWS is a 15-item self-report measure designed to reflect MW in ADHD, derived from patient reports of subjective experiences of their thought processes. The scale captures the main characteristics of the mental state described by adults with ADHD: thoughts on the go all the time, thoughts that jump or flit from one topic to another, and multiple lines of thoughts at the same time (Asherson, 2005). The MEWS therefore reflects the form as opposed to the content of the experienced thought processes in ADHD. Uniquely, the MEWS assesses a mental phenomenon as opposed to the behavioral symptoms conventionally assessed with ADHD rating scales.

The aim of the present study was to validate the MEWS as an instrument to assess MW in adult ADHD using two study samples. In Study 1, we conducted a preliminary evaluation of the psychometric properties of the MEWS in a small sample of adult males with ADHD selected for the absence of comorbid psychiatric conditions. In Study 2, we cross-validated the MEWS in a larger independent sample including males and females, less highly selected against comorbidity. We further investigated the relationship of MEWS scores to other measures of ADHD

Table 1. Case-Control Differences for Age, Sex, IQ, MEWS, INN, HI, EL, and IMP.

| | Study 1 | | | | | | | Study 2 | | | | | | |
| | ADHD | | | Control | | | | ADHD | | | Control | | | |
	N	M	SD	N	M	SD	*p*	N	M	SD	N	M	SD	*p*
Age	41	28.54	9.52	47	29.00	10.46	.83	81	33.52	10.26	30	29.51	8.80	.06
Male	41			47			—	44			16			.93
Female	0			0				37			14			
IQ	41	108.95	15.08	47	113.15	13.36	.17	80	109.38	13.68	23	111.59	11.62	.44
Time 1														
MEWS	25	25.00	10.11	24	4.79	6.98	<.0001	79	27.72	9.31	29	7.21	6.26	<.0001
INN	41	19.34	5.03	47	3.87	3.44	<.0001	81	27.16	6.13	30	6.23	3.99	<.0001
HI	40	16.20	6.59	47	3.28	3.30	<.0001	81	20.09	5.80	30	5.33	4.08	<.0001
EL	40	45.93	11.76	46	25.24	9.17	<.0001	80	24.31	12.09	30	4.17	4.86	<.0001
IMP	41	1.23	0.41	47	0.30	0.28	<.0001	80	1.22	0.49	30	0.20	0.20	<.0001

Note. See Online Supplementary Table 1 for Time 2 and Time 3. MEWS = Mind Excessively Wandering Scale; INN = inattention; HI = hyperactivity/impulsivity; EL = emotional lability; IMP = impairment.

symptomatology, and investigated the relationship between MW and functional impairment.

Method

Study 1 Sample

Participants were a small subset of adults from the MIRIAD (Mood Instability Research in ADHD) project, a longitudinal case-control study of emotional lability (EL) and neuropsychological functioning in adult men with ADHD with no co-occurring comorbidities (Skirrow & Asherson, 2013). Forty-one adults with ADHD and 47 controls aged between 18 and 65 years (ADHD: *M* = 28.54 years, *SD* = 9.52 years; control: *M* = 29.00 years, *SD* = 10.46 years) participated in the MIRIAD project. There were no significant differences between groups for age or IQ (see Table 1). ADHD participants were recruited from the waiting list of the National Adult ADHD Clinic at the South London and Maudsley Hospital (SLaM) and were medication free at the time of the research assessment. Further detail on the recruitment process is provided elsewhere (Skirrow & Asherson, 2013).

As the MEWS was developed after the MIRIAD project began, only a subset of the ADHD cases and controls provided MEWS data. At study entry (baseline), 25 cases and 24 controls completed the MEWS. Follow-up assessments completed approximately 9 months after baseline provided data on 18 cases and 18 controls at both time points. In addition, six cases and 18 controls provided MEWS data at follow-up assessment alone. Of the 18 ADHD cases with data at both time points, 16 were treated with methylphenidate and one with atomoxetine at follow-up, initiated by local services and not following a specific protocol. Ethical approval for this study was obtained from the Joint Research Ethics Committee of the Institute of Psychiatry and SLaM.

Study 2 Sample

Participants were from the OCEAN (Oils and Cognitive Effects in Adult ADHD Neurodevelopment) project, a study investigating the relationship of omega-3 dietary supplementation (not analyzed in this study) to cognitive and electrophysiological measures in adults with ADHD. Participants were aged between 18 and 65 years. The sample consisted of 81 adults with ADHD (37 female, 44 male; *M* age = 33.52 years, *SD* = 10.26 years) and 30 healthy controls (14 female, 16 male; *M* age = 29.51 years, *SD* = 8.8 years). Groups did not significantly differ on age, sex, or IQ (see Table 1). ADHD participants were recruited through SLaM Adult ADHD Service, advertisements on ADHD support websites, and previous study databases. See online supplementary material for further information on recruitment.

At baseline (Time 1), 79 cases and 29 controls provided MEWS data. Two separate follow-up assessments of the ADHD cases took place, 3 months (Time 2) and 6 months (Time 3) after baseline. At Time 2 and Time 3, 79 and 55 ADHD cases provided MEWS data, respectively. Ethical approval for the study was granted by the National Research Ethics Service (NRES) Committee London.

Measures

ADHD symptoms. ADHD symptoms were assessed using the self-rated Barkley Adult ADHD Rating Scale (BRS; Barkley, 1998) in Study 1, and the Conners' Adult ADHD Rating Scales (CAARS; Conners, Erhardt, & Sparrow, 1999) in Study 2. Both scales cover the same list of 18 DSM-IV/DSM-5 items for inattention and hyperactivity (*Diagnostic and Statistical Manual of Mental Disorders* (4th ed. and 5th ed.; American Psychiatric Association [APA], 1994 and 2013).

Emotional dysregulation. Emotional Lability (EL) was measured using the Affective Lability Scale–Short Form (ALS-SF; Oliver & Simons, 2004), which measures rapid changes in emotional states.

Impairment. Functional impairment across major life domains (family, work, school, life-skills, self-concept, social, and risk) was measured using the Weiss Functional Impairment Rating Scale–Self-Report (WFIRS-S; Sadek, 2014).

Mind wandering. MW was measured using the newly created MEWS (see Figure 1). This publication is the first report of this scale. The MEWS is a 15-item self-report measure reflecting MW in ADHD. Items were based on patient descriptions of MW in ADHD as previously described by Asherson (2005). P.A., C.S., and P.R. drew up the list of questions based heavily on their combined experience of patient's reports of MW, and questions were refined during several consensus meetings. The final item checklist was agreed by all three authors and implemented initially in the MIRIAD study before further testing in the OCEAN study (reported here). The MEWS scale is copyrighted and available without charge from the corresponding author.

Statistical Analyses

Mean values for each rating scale and subscale were used as summary measures. The raw data and square-root transformations were used in analysis, and parametric and nonparametric tests were used as appropriate.

Principal components analysis (PCA) with varimax rotation was conducted to examine the factor structure of the MEWS. Cronbach's alpha was used as a measure of reliability to assess internal consistency and Pearson's correlation coefficient was used to analyze test–retest reliability of the scale. Construct validity was assessed with independent *t* tests and Mann–Whitney U tests to investigate case-control differences. Receiver operating characteristic (ROC) analysis was used to examine diagnostic accuracy and the optimal cut-off point of the measure.

Convergent validity of the MEWS in relation to ADHD symptom scales was assessed using polyserial correlations to provide unbiased estimates of cross-variable correlations in case-control samples (Olsson, 1979). For these analyses, we fixed the *z* value threshold for affection status corresponding to 3.4% prevalence of ADHD in adults (Fayyad et al., 2007). In Study 1, polyserial correlations were also conducted on change scores (Time 1-Time 2). For change scores in Study 2, we used partial correlations to control for potential influences of the study intervention (placebo or essential fatty acid). Hierarchical multiple regression was used to investigate whether MEWS scores were independent predictors of impairment; inattention and hyperactivity/ impulsivity were entered in the first step and MW in the second.

Results

Study 1

Psychometric evaluation. The scree plot and eigenvalues indicated a unidimensional structure to the MEWS with one factor accounting for 69.16% of the variance (eigenvalue = 10.37; see online supplementary material). Factor loadings were greater than .7, with the exception of Item 14 (.51). Table 2 shows Cronbach's alpha coefficients for the full 15-item MEWS in comparison with the other rating scales. At baseline, internal consistency was high for all scales for both cases and controls ($\alpha > .78$). Examination of item total correlations showed each item to correlate well with the full 15-item scale (correlations > .75, with the exception of Items 6 [.66], 10 [.70], and 14 [.47]), suggesting items are measuring the same underlying construct. Inter-item correlations ranged from .27 to .88, with an average inter-item correlation of .66, reflecting the internal consistency of the scale items.

There was a mean interval of 9.7 months ($SD = 3.3$ months) for cases and 9.5 months ($SD = 4.0$ months) for controls between baseline and follow-up. Test–retest reliability was significant for the whole sample ($r = .84$, 95% confidence interval [CI] = [.74, .92], $p < .001$), and for both cases ($r = .63$, 95% CI = [.06, .88], $p = .005$) and controls ($r = .82$, 95% CI = [.40, .93], $p < .001$).

Construct validity. Case-control comparisons at baseline revealed significantly elevated ratings of MW in individuals with ADHD, $t(47) = -7.83$, $p < .0001$, comparable with that found for the other rating scales of ADHD symptom domains: inattention, $t(73.07) = -14.58$, $p < .0001$; hyperactivity/impulsivity, $t(85) = -11.40$, $p < .0001$; emotional lability, $U = 168.5$, $z = -6.53$, $p < .0001$ (Table 1). Participants with ADHD also demonstrated significantly greater overall impairment on the WFIRS-S, $t(86) = -13.08$, $p < .0001$, as well as for each domain of impairment, t range = -5.78-11.40, $p < .0001$, for impairment in family life, work, school, life-skills, self-concept, social problems, and risk taking. Similar results were found at follow-up (see online supplementary material).

ROC analysis was used to examine the capacity of the scale to discriminate between cases and controls. Area under the curve (AUC) was .92 (95% CI = [.85, 1.00], $p < .0001$) which, being close to 1, indicates excellent discriminant capacity of the MEWS. This was comparable with the AUC value of existing rating scales of ADHD symptom domains (inattention: AUC = .99, 95% CI = [.97, 1.00]; hyperactivity/impulsivity: AUC = .95, 95% CI = [.91, .99]; emotional lability: AUC = .91, 95% CI = [.84, .97]). A score

Table 2. Reliability Coefficients (α) for the MEWS as Compared With the INN, HI, EL, and IMP Rating Scales.

Study 1	Time 1			Time 2		
	Whole sample	Cases	Controls	Whole sample	Cases	Controls
MEWS	.97	.93	.95	.96	.94	.93
INN	.96	.83	.80	.96	.92	.82
HI	.95	.88	.78	.92	.88	.76
EL	.96	.91	.95	.96	.91	.96
IMP	.98	.96	.96	.97	.88	.98

Study 2	Time 1			Time 2	Time 3
	Whole sample	Cases	Controls	Cases	Cases
MEWS	.96	.91	.90	.94	.95
INN	.96	.85	.82	.91	.98
HI	.93	.83	.75	.87	.99
EL	.95	.92	.87	.91	.93
IMP	.98	.98	.86	.98	.97

Note. MEWS = Mind Excessively Wandering Scale; INN = inattention; HI = hyperactivity/impulsivity; EL = emotional lability; IMP = impairment.

Table 3. Polyserial Correlations (95% Confidence Intervals), Corrected for Selection (Affection Threshold = 3.4%), Between the MEWS, INN, HI, EL, and IMP Rating Scales, and AFF.

Time 1	MEWS	INN	HI	EL	IMP
Study 1					
MEWS	—	—	—	—	—
INN	.81 [.72, .87]	—	—	—	—
HI	.77 [.66, .84]	.85 [.79, .89]	—	—	—
EL	.81 [.72, .88]	.74 [.65, .81]	.75 [.64, .81]	—	—
IMP	.82 [.71, .89]	.83 [.76, .88]	.82 [.75, .87]	.77 [.68, .83]	—
AFF	.70 [.57, .79]	.83 [.75, .89]	.71 [.60, .79]	.65 [.51, .75]	.75 [.64, .83]
Study 2					
MEWS	—	—	—	—	—
INN	.77 [.69, .83]	—	—	—	—
HI	.69 [.58, .76]	.76 [.68, .82]	—	—	—
EL	.74 [.66, .81]	.62 [.50, .71]	.53 [.40, .65]	—	—
IMP	.81 [.74, .086]	.74 [.65, .80]	.65 [.54, .73]	.78 [.70, .83]	—
AFF	.67 [.55, .77]	.83 [.76, .88]	.74 [.64, .81]	.59 [.46, .70]	.68 [.57, .78]

Note. MEWS = Mind Excessively Wandering Scale; INN = inattention; HI = hyperactivity/impulsivity; EL = emotional lability; IMP = impairment; AFF = affection status.

of 15 or above provides the optimal balance of sensitivity (.88) and specificity (.88), suggesting a cut-off for disorder threshold (see online supplementary material).

Convergent validity. Polyserial correlations in the combined case-control data set showed strong positive correlations between MW and the other rating scales of ADHD and impairment: inattention (r = .81, 95% CI = [.72, .87]), hyperactivity/impulsivity (r = .77, 95% CI = [.66, .84]), emotional lability (r = .81, 95% CI = [.72, .88]), and impairment (r = .82, 95% CI = [.71, .89]), as well as ADHD

affection status (r = .70, 95% CI = [.57, .79]). The strongest correlation was between MW and impairment (Table 3). In addition, moderate to large positive correlations were seen between MW and ADHD symptom dimensions and impairment in both cases and controls analyzed separately (see online supplementary material), indicating severity of symptoms and impairment in both cases and controls.

For the sub-sample with both baseline and follow-up data, the correlation of baseline to follow-up change scores for MW with change scores for the rating scale measures of ADHD symptoms and impairments revealed temporal

Table 4. Correlations (95% Confidence Intervals) Between Change Scores for the MEWS, INN, HI, EL, and IMP Rating Scales.

Change scores	MEWS	INN	HI	EL
Study 1				
MEWS	—	—	—	—
INN	.72 [.54, .83]	—	—	—
HI	.55 [.33, .70]	.73 [.59, .82]	—	—
EL	.70 [.44, .84]	.55 [.35, .70]	.58 [.39, .72]	—
IMP	.51 [.23, .72]	.62 [.45, .74]	.62 [.45, .74]	.55 [.35, .70]
Study 2				
MEWS	—	—	—	—
INN	.53 [.25, .71]****	—	—	—
HI	.31 [.01, .52]*	.74 [.53, .86]****	—	—
EL	.43 [.19, .62]***	.48 [.16, .71]****	.31 [−.03, .59]*	—
IMP	.62 [.37, .78]****	.50 [.31, .66]****	.41 [.18, .59]**	.44 [.18, .65]***

Note. Polyserial correlations corrected for selection (affection threshold = 3.4%) were used in Study 1, and partial correlations to correct for study intervention in Study 2 (with significance levels). MEWS = Mind Excessively Wandering Scale; INN = inattention; HI = hyperactivity/impulsivity; EL = emotional lability; IMP = impairment.
*$p < .03$. **$p < .01$. ***$p = .001$. ****$p < .0001$.

covariance between the measures: positive correlations were found between change in MW and change in inattention ($r = .72$, 95% CI = [.54, .83]), hyperactivity/impulsivity ($r = .55$, 95% CI = [.33, .70]), emotional lability ($r = .70$, 95% CI = [.44, .84]), and impairment ($r = .51$, 95% CI = [.23, .72]; see Table 4). In the 16 cases treated with methylphenidate at follow-up, there was a significant reduction in MEWS scores, $t(15) = 2.28$, $p = .04$, between the baseline medication-free period ($M = 23.38$, $SD = 10.93$) and follow-up ($M = 17.25$, $SD = 10.58$).

Impairment. Data from 49 participants were used in regression analyses with the WFIRS-S total impairment score. Inattention and hyperactivity/impulsivity accounted for 82.4% of the variability in functional impairment ($R^2 = .824$). The addition of MW as a predictor led to a significant increase in predictive power of the model ($R^2\Delta = .024$), with the variability accounted for by the model increasing to 84.9%, $F\Delta(1, 45) = 7.17$, $p = .01$. This indicates that MW is having a small but significant effect beyond that accounted for by inattention and hyperactivity/impulsivity. Inattention carried the most importance in the model ($\beta = .45$), followed by MW ($\beta = .31$) and hyperactivity/impulsivity ($\beta = .21$). Only inattention and MW significantly contributed to the model ($p = .001$ and .01, respectively).

Within the ADHD group, MW had an independent effect on impairment in the domains of self-concept, $R^2\Delta = .145$, $F\Delta(1, 21) = 6.57$, $p < .02$, and social problems, $R^2\Delta = .137$, $F\Delta(1, 21) = 4.50$, $p < .05$. For the social problems domain, MW carried more importance in the model ($\beta = .44$) than inattention ($\beta = -.42$), but not hyperactivity/impulsivity ($\beta = .50$). Only MW and hyperactivity/impulsivity significantly contributed to the model ($p = .05$ and .03, respectively). Interpretation of work and life-skills dimensions was not possible due to heteroskedasticity in the data.

Study 2

Psychometric evaluation. The scree plot and eigenvalues suggested a one-factor solution with an eigenvalue of 9.44, accounting for 62.92% of the variance (see online supplementary material). All items loaded highly onto this factor (>.76, with the exception of Items 6 [.60], 10 [.68], and 14 [.40]). Internal consistency was high for all scales for both cases and controls ($\alpha > .78$; see Table 2). Examination of item total correlations showed each item to correlate well with the full 15-item scale (correlations > .72, with the exception of Items 6 [.56], 10 [.63], and 14 [.37]). Inter-item correlations ranged from .24 to .82, with an average inter-item correlation of .59, reflecting the internal consistency of the scale items.

The mean interval between Time 1 and Time 3 was 6.4 months ($SD = 0.58$ months), and MEWS scores showed satisfactory retest reliability across this time period ($r = .63$, 95% CI = [.42, .80], $p < .0001$).

Construct validity. Case-control comparisons revealed significantly elevated ratings of MW in individuals with ADHD ($U = 87.00$, $z = -7.34$, $p < .0001$). This difference was comparable with that found for the other rating scales of ADHD symptom domains (inattention: $U = 20.00$, $z = -7.94$, $p < .0001$; hyperactivity/impulsivity: $U = 64.50$, $z = -7.65$, $p < .0001$; emotional lability: $U = 140.50$, $z = -7.12$, $p < .0001$; see Table 1). ADHD cases also demonstrated significantly greater overall impairment on the WFIRS-S ($U = 53.50$, $z = -7.70$, $p < .0001$), as well as for each domain of impairment (z range = -4.87 to -7.57, $p < .0001$ for impairment in family life, work, school, self-concept, social problems, life-skills, and risk taking; see online supplementary material).

ROC curve analysis indicated that the MEWS successfully discriminated between cases and controls (AUC = .96,

95% CI = [.93, .99], p < .0001). This was comparable with the AUC value of existing rating scales of ADHD symptom domains (inattention: AUC = .99, 95% CI = [.98, 1.00]; hyperactivity/impulsivity: AUC = .97, 95% CI = [.95, 1.00]; emotional lability: AUC = .94, 95% CI= [.90, .98]). A score of 15 on the MEWS provides the optimal balance of sensitivity (.90) and specificity (.90; see online supplementary material).

Convergent validity. Using polyserial correlations in the combined case-control data set, we found a positive correlation between MW and the other rating scales of ADHD and impairment: inattention (r = .77, 95% CI = [.69, .83]), hyperactivity/impulsivity (r = .69, 95% CI = [.58, .76]), emotional lability (r = .74, 95% CI = [.66, .81]), impairment (r = .81, 95% CI = [.74, .86]), and ADHD affection status (r = .67, 95% CI = [.55, .77]). The strongest correlation was between MW and impairment (see Table 3). Moderate to large positive correlations were also seen between MW and ADHD symptom dimensions and impairment in both cases and controls analyzed separately (see online supplementary material).

Investigation of change scores also revealed a temporal relationship. Analyses indicated significant covariation of change in MW with change in inattention (r = .53, 95% CI = [.25, .71], p < .0001), hyperactivity/impulsivity (r = .31, 95% CI = [.01, .52], p = .02), emotional lability (r = .43, 95% CI = [.19, .62], p = .001), and impairment (r = .62, 95% CI = [.37, .78], p < .0001). MW and impairment showed the strongest relationship (see Table 4).

Impairment. Data from 108 participants were used in regression analysis with the WFIRS-S total impairment score. Inattention and hyperactivity/impulsivity accounted for 71.3% of the variability in functional impairment (R^2 = .713). The addition of MW as a predictor led to a significant increase in predictive power of the model ($R^2\Delta$ = .076), with the variability accounted for by the model increasing to 78.9%, $F\Delta(1, 104)$ = 37.17, p < .0001. MW carried the most importance in the model (β = .49), followed by inattention (β = .29) and hyperactivity/impulsivity (β = .17). Only MW (p < .0001) and inattention (p = .002) significantly contributed to the model.

Within the ADHD group, MW had an independent effect on impairment in life-skills, $R^2\Delta$ = .18, $F\Delta(1, 75)$ = 24.79, p < .0001; self-concept, $R^2\Delta$ = .10, $F\Delta(1, 75)$ = 9.72, p = .003; social problems, $R^2\Delta$ = .10, $F\Delta(1, 75)$ = 9.92, p = .002; and risk taking, $R^2\Delta$ = .09, $F\Delta(1, 75)$ = 9.37, p = .003. MW carried the most importance in the model for life-skills (β = .52), self-concept (β = .39), and social problems (β = .39), and was the only significant contributor to the model for the self-concept (p = .003) and social problems (p = .002) domains. Interpretation of the family and work domains was not possible due to heteroskedasticity in the data.

Discussion

We report the psychometric properties and initial validation findings for a new self-report scale of excessive MW in adults with ADHD. Using two independent samples, we found that MEWS scores functioned extremely well as a measure of the mental phenomenon of MW in ADHD, with good reliability and high sensitivity and specificity for ADHD case-control differences. We found that elevated levels of MW (as indexed by the MEWS) in participants with ADHD were related to self-report measures of functional impairment. Furthermore, the contribution of MW to impairment was independent of the core ADHD symptoms of inattention and hyperactivity/impulsivity. These findings suggest that excessive MW is a characteristic feature of adult ADHD that has specific effects on impairment.

Principal components analysis indicated a unidimensional structure to the scale and other psychometric properties of the MEWS were comparable with existing rating scales of ADHD core symptoms, including good internal consistency and test–retest reliability. The MEWS was able to differentiate between those with and without ADHD with high sensitivity and specificity of the scale, using a threshold score of 15. This is remarkable given that patients were selected for high ADHD symptoms and not specifically for subjective reports of internal thought processes as measured by the MEWS.

In both studies, item total correlations with the full 15-item scale and factor loadings were high apart from Items 6 (Because my mind is "on the go" at bedtime, I have difficulty falling off to sleep), 10 (I try to distract myself from my thoughts by doing something else or listening to music), and 14 (I use alcohol or other drugs to slow down my thoughts and stop constant "mental chatter"). This is likely explained by the nature of these items, which refer to how individuals cope with MW or how it directly affects their functioning, as opposed to a description of the mental phenomenon. To investigate whether the scale could be shortened by dropping Items 6, 10, and 14 without reducing its sensitivity and specificity, we repeated the ROC analysis, finding the shorter 12-item scale had a sensitivity of .89 and specificity of .90 (see online supplementary material). Further analyses in larger data sets could be used to further refine the scale, but based on these data we recommend that future studies use the reduced 12-item scale.

Our findings are in line with previous studies which report elevated levels of MW in ADHD compared with controls, whether measured using clinical rating scales (Franklin et al., 2014; Seli et al., 2015; Weyandt et al., 2003) or experience sampling of TUTs during a sustained attention task (Shaw & Giambra, 1993). Furthermore, the strength of case-control differences for MEWS scores was comparable with that seen for rating scale measures of core ADHD symptoms, for which clinical cases of ADHD are

selected on. MEWS scores were also found to be highly correlated with ADHD symptoms and impairment in the total sample, as well as in cases and controls analyzed separately, replicating previous studies of the association between spontaneous MW and ADHD (Franklin et al., 2014; Seli et al., 2015). These results indicate that the MEWS is a marker of symptom severity in both cases and controls, in line with previous data indicating that ADHD symptoms lie along a continuum in the general population (Chen et al., 2008; Salum et al., 2014).

Change scores for MW also covaried with ADHD symptoms and impairments over time, indicating a close temporal relationship consistent with a potential causal role of MW in ADHD. The finding of significant pre–post treatment effects of methylphenidate in a subset of Study 1 participants raises the possibility that treatment effects on ADHD might be mediated by reductions in MW. However, we were unable to test specifically for treatment effects of methylphenidate because we did not randomize to treatment or include a placebo control arm.

The link between MW and impairment was particularly strong, indicating the clinical importance of MW in adults with ADHD. Of specific interest was the finding that MW showed a main effect on impairment beyond the influence of inattention and hyperactivity/impulsivity and was overall the strongest predictor of impairment in Study 2. Investigating specific domains of impairment, MW was found to be an independent predictor of self-concept and social problems in both studies, and additionally life-skills and risk taking in Study 2. The reasons the MEWS is a particularly good predictor of impairment in ADHD are not well understood, but could be explained by both clinical and theoretical considerations. One possible explanation is that the scale items are rooted in qualitative accounts from adult ADHD patients of experiences of their mental state. When asked to describe the subjective experience of the flow of their thoughts, adults with ADHD repeatedly give descriptions of ceaseless, short-lived, and unfocused thoughts that flit from one topic to another (Asherson, 2005). Such a distractible and poorly regulated mental state could be impairing for several reasons.

First, excessive MW may have a specific effect on functional outcomes due to the failure to deal with distraction and deficient mental processing of "task"relevant events. In social situations, an individual with excessive MW may miss verbal and non-verbal information and effectively *not listen* or *lack awareness* of social cues. MW may make it difficult to follow a single line of thought and interrupting others during conversations could be a strategy to avoid losing their train of thought. Behaviors such as these are likely to have negative effects on an individual's social interactions.

Second, lack of attention paid to events due to one's mind constantly being "on the go" in a non-focused way can also create difficulties with thinking through and planning activities, linked to forgetfulness and disorganization and leading to impairments in basic life-skills. Impaired self-concept may then arise as a bi-product of the effect of excessive MW on other domains of functioning, but could also be due to distress from the constant effort to focus or the experience of having a mind constantly full of unfocused distractible thoughts. Many patients report a sense of calm and relief when the flow of their thoughts becomes more focused and regulated following stimulants or other treatments for ADHD.

Third, the connection between MW and risk-taking behavior is less obvious, but could be due to the impact of highly salient activities, which engage the attention of individuals, leading to a reduction of spontaneous MW and a sense of relief. For the same reasons, some patients with even severe levels of ADHD may excel at activities such as exciting/stimulating sports. Although there is as yet no direct evidence for this hypothesis, studies investigating default mode deactivation (Liddle et al., 2011) and reaction time variability (RTV; Andreou et al., 2007) during tasks requiring sustained attention have shown reduced or absent case-control differences when conducted under highly salient conditions. Reductions in default mode activity under rewarding conditions have been hypothesized to reflect reductions in excessive MW (Liddle et al., 2011). Thus, risky behavior may reflect individuals seeking out activities with salient content, which decreases MW and helps individuals with ADHD to focus their attention.

These accounts of MW leading to impairment in ADHD remain speculative because of the lack of research on MW in ADHD. However, an increase in understanding of MW states in control participants provides a strong theoretical basis for the hypothesis that excessive MW may underlie many of the behavioral symptoms and impairments seen in ADHD. In healthy control samples, MW is associated with performance deficits that overlap with impairments seen in ADHD, including educational performance, driving accidents, and performance on cognitive tasks including errors of commission and RTV during sustained attention and inhibition tasks (Smallwood & Schooler, 2015). Understanding of the neural processes involved in the regulation of internal thought, involving default mode network (DMN) and executive control networks, has advanced in recent years, and overlaps with neural mechanisms implicated in ADHD. TUTs are strongly associated with deficient task-induced deactivation of the DMN (correlation about .9; McKiernan, D'Angelo, Kaufman, & Binder, 2006), and deficient DMN deactivation during task conditions is strongly associated with ADHD (Christakou et al., 2013). Spontaneous MW that is detrimental to performance has, therefore, been proposed as a mechanism that explains many of the symptoms and functional impairments of ADHD (Seli et al., 2015; Weyandt et al., 2003), reflecting

aberrant inter-relationships between default and task positive networks (Fox, Spreng, Ellamil, Andrews-Hanna, & Christoff, 2015; Sripada, Kessler, & Angstadt, 2014).

Interestingly, in one study, meta-awareness of MW (being aware that your mind has wandered) was found to mediate the relationship between ADHD symptoms and detrimental forms of MW, suggesting that psychological treatments aimed at enhancing meta-awareness of MW, such as mindfulness-based interventions (MBIs), might ameliorate the negative consequences of MW in ADHD (Franklin et al., 2014). Recent studies support the beneficial effects of MBIs on ADHD, with the largest study to date showing an effect of $d = .85$ on ADHD symptoms compared with a treatment as usual group (Hepark et al., 2015). Future large-scale controlled experimental designs are therefore indicated to investigate the potential role of MW as a treatment target for the control of ADHD symptoms and impairments using both pharmacological and non-pharmacological interventions.

Current screening tools for adult ADHD consist of rating scales for inattention and hyperactivity/impulsivity. Our findings suggest potential utility of the MEWS as an additional screening tool for adult ADHD in clinical practice, particularly as the MEWS is a strong predictor of impairment. Furthermore, as discussed above MW may also be measured more objectively using experience sampling methods in daily life or during experimental paradigms. Measures of MW may therefore assist in the accurate diagnosis of individuals based on their mental state rather than descriptions of behavior, which may be more subject to bias or influenced by an individual's ability to develop compensatory behavioral strategies.

However, currently we do not know the role that excessive MW, as measured by the MEWS, plays in other clinical disorders. For example, in depression depressive rumination represents another form of MW. Thus, the specificity of the MEWS across common mental health disorders needs to be explored. Therefore, we do not currently recommend the routine use of the MEWS to identify patients with ADHD until the scale has been comprehensively evaluated in other psychiatric disorders with overlapping clinical features, although high MEWS scores could be used to support the diagnosis. Investigation of the role of excessive MW in childhood and early adolescent ADHD is also recommended, including use of the scale in this population. Whether children and young adolescents would be able to conceptualize MW and reliably report on their mental state requires investigation.

Limitations and Future Research

Some participants in Study 2 presented with co-occurring anxiety and depression, raising the possibility that MW might be linked to comorbid conditions. However, in Study 1 participants were free from co-occurring disorders

(Skirrow & Asherson, 2013), yet similar results were found. Nevertheless, TUTs are a common feature of most mental health disorders and future research will need to investigate the distinction of excessive MW in ADHD from depressive ruminations, anxious worrying, and other sources of MW.

In relation to ADHD, a key question is whether MW differs conceptually from the inattentive symptoms currently used to define the disorder or whether the mental phenomenon of MW underlies the behavioral expression of inattention. As discussed above, it is feasible that measures of MW in ADHD are a more direct reflection of the neurobiology, leading to the inattentive symptoms of ADHD. Further work is required to evaluate the plausible hypothesis that aberrant regulation of DMN activity linked to excessive MW leads to ADHD symptoms and impairments. The study of MW has several potential advantages over behavioral inattention for research, because it may be measured using rating scales, as reported here, as well as experience sampling during daily life (Killingsworth & Gilbert, 2010), or during sustained attention tasks (Shaw & Giambra, 1993) and neuroimaging studies (Baird, Smallwood, Lutz, & Schooler, 2014; Christoff, Gordon, Smallwood, Smith, & Schooler, 2009).

A fruitful next step in this research will be to take the MEWS into experimental paradigms. For example, an experimental trial of methylphenidate could be used to formally evaluate whether improvements in MW mediate improvements in ADHD symptoms and impairments, and to investigate the underlying neural mechanisms. Yet, currently, there are very little data that link rating scale measures of MW to experimentally derived measures in ADHD. Validation of MW in ADHD is therefore required across the various levels of measurement (rating scale, experience sampling, and experimental paradigms including neuroimaging studies). We hypothesize that MW is a phenomenon that can be reliably measured, and it will be highly informative to see to what extent MEWS scores reflect TUTs measured during cognitive task performance in ADHD. It will also be advantageous to see how it relates to various cognitive measures such as omission and commission errors (Losier, McGrath, & Klein, 1996), and RTV (Kofler et al., 2013), which may reveal further information about the underlying neurobiology of ADHD.

Conclusion

This research provides further insight into the mental phenomenon of MW in ADHD. We investigate a questionnaire-based measure of excessive MW recently developed in our research group. The MEWS was found to be a valid and reliable measure, with comparable sensitivity and specificity for case-control differences as existing rating scale measures of core ADHD symptoms currently used in clinical practice. The MEWS functioned extremely well for a brief

15-item measure and is potentially a useful measure to incorporate in future clinical and etiological research. MEWS scores were found to be a particularly good predictor of impairment, highlighting the clinical utility of the tool for diagnosis and treatment. Based on these findings, there is strong premise to view MW as a common co-occurring feature of adult ADHD with a specific effect on impairment, potentially explaining a variety of deficits not easily accounted for by the core symptom dimensions.

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Authors' Note

The views expressed in this study are those of the authors.

Declaration of Conflicting Interests

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Supplemental Material

The online supplementary materials are available at http://jad.sagepub.com/supplemental

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Chapter 5.   Evaluating a scale of excessive mind wandering among males and females with and without attention-deficit/hyperactivity disorder from a population sample

This chapter is adapted from a manuscript currently under review.

Mowlem, F.D., Agnew-Blais, J., Pingault, JB., & Asherson, P. (*under review*). Evaluating a scale of excessive mind wandering among males and females with and without attention-deficit/hyperactivity disorder from a population sample

Supplementary materials for this chapter, as detailed in the text, are attached in Appendix D.

5.1 Abstract

Recent studies highlight the role of excessive mind wandering in attention-deficit/hyperactivity disorder (ADHD) and its association with impairment. We believe assessing mind wandering could be especially relevant to individuals, including many females, who present with less externalising manifestations of ADHD. Using a new measure based on ADHD patient reports, the Mind Excessively Wandering Scale (MEWS), we previously found adults with ADHD had elevated levels of mind wandering that contributed to impairment independently of core ADHD symptoms. Using data from an online general population survey, the current study assessed the factor-structure, reliability, validity and measurement invariance of the MEWS. We also investigated sex differences in mind wandering, as well as ADHD symptoms, impairment and wellbeing in those with and without ADHD. The MEWS had a unidimensional structure, was invariant across sex, age and ADHD status, and accounted for unique variance in impairment and wellbeing beyond core ADHD symptoms. Among those with ADHD, we found no evidence for sex differences in mind wandering and among those without ADHD males had higher scores. We also found similar levels of hyperactivity/impulsivity, emotional lability, and impairment in males and females with ADHD, but males reported greater inattention and lower wellbeing. Results suggest the MEWS is a reliable and valid instrument measuring the same construct across sex, age and ADHD status, which could aid diagnosis and monitoring of outcomes. The pattern of sex differences for the behavioural ADHD symptoms in adults also appears to be reflected in the internalised/subjective experience of excessive mind wandering.

5.2   Introduction

Given the extensive evidence that ADHD is not confined to childhood and also occurs in adulthood, identifying measures to aid diagnostic assessment and monitoring of treatment outcomes in this age group is of considerable interest to research and clinical practice (Asherson et al., 2016). Although ADHD diagnosis is made based on the presence of core symptoms of inattention and hyperactivity/impulsivity (American Psychiatric Association, 2013), other characteristic features, such as subjective reports of excessive mind wandering could aid the diagnostic process and/or monitoring of treatment outcomes (Mowlem et al., 2016). Mind wandering is conceptualised as periods in time when attention and the contents of thoughts shift away from external sources and/or ongoing tasks, to unrelated internal thoughts or feelings (Smallwood & Schooler, 2015). Excessive mind wandering has been linked to impairment in ADHD (Biederman et al., 2017; Franklin et al., 2014; Jonkman et al., 2017; Mowlem et al., 2016; Seli et al., 2015; Shaw & Giambra, 1993) and could reflect a core underlying symptom (Bozhilova et al., 2018).

In contrast to the core ADHD symptoms, mind wandering reflects internal thought processes, as opposed to directly observable behaviours. Excessive mind wandering may be particularly relevant to the assessment of ADHD in adolescence and adulthood when self-report plays a larger role in the diagnostic process. It may also be more difficult for individuals to reflect upon the behavioural symptoms that are currently used in the diagnostic criteria, while they may be better able to report on internal thought processes. Furthermore, the traditional symptoms of ADHD may not be obvious in people who have developed good adaptive skills that mask the behavioural symptoms of ADHD. Assessing mind wandering in ADHD could be especially relevant to individuals, including many females, who present with less externalising manifestations of ADHD. Thus, investigation of sex differences in mind wandering is especially pertinent as it does not depend on behavioural adaption to the same degree as traditional ADHD measures.

We recently developed and validated a new rating scale reflecting excessive mind wandering in ADHD: the Mind Excessively Wandering Scale (MEWS) (Mowlem et al., 2016). The scale demonstrated a unidimensional structure with good internal consistency, and high sensitivity and specificity to discriminate between ADHD cases and controls, behaving in a comparable way to

existing ratings scales of ADHD symptoms used in clinical practice. Adult ADHD cases showed elevated levels of mind wandering that contributed to impairment independently of the core ADHD symptom domains. Thus, excessive, uncontrolled mind wandering appears to be a common co-occurring feature of adult ADHD with specific implications for impairment in daily-life (Mowlem et al., 2016).

The current study sought to further validate the MEWS in a large adult population sample, including those who report a diagnosis of ADHD, and assess measurement invariance of the scale across sex, ADHD diagnostic status, and age. Measurement invariance examines whether a scale captures fundamentally the same processes and construct across groups. Comparisons of group means for any scale is based on the assumption that the scale is measurement invariant across groups being compared, and a lack of invariance can render between-group comparisons meaningless and lead to incorrect interpretation of differences (Marsh, Nagengast, & Mori, 2013; Orri et al., 2016). Between-group differences (e.g., ADHD cases vs controls) should not be analysed unless measurement invariance is held across the groups, yet this is rarely tested in empirical studies of psychiatric disorders (Orri et al., 2016).

Given the well documented sex differences in ADHD (Gershon, 2002; Williamson & Johnston, 2015), and persistence of ADHD across the lifespan, it is important that the scale is also measurement invariant across sex and age. Further, as previous studies show mixed results with regard to whether males and females are affected differently by ADHD in adulthood (Biederman et al., 2004; Fedele et al., 2012; Fredriksen et al., 2014; Nussbaum, 2012; Rasmussen & Levander, 2009; Wilens et al., 2009), we examined sex differences within those with and without self-reported ADHD with regard to mind wandering, as well as inattention, hyperactivity/impulsivity, emotional lability, impairment and wellbeing. Given that sex differences in adult ADHD have received much less attention in the literature compared to childhood (Corbisiero et al., 2017; Fedele et al., 2012; Williamson & Johnston, 2015), there is a clear need for additional research. Furthermore, given that mind wandering may account for unique variance in functional impairment beyond core ADHD symptoms, and impairment is the most frequent reason for referral, investigating sex differences in mind wandering is clinically relevant.

5.3 Materials and methods

5.3.1 Sample

This study uses data from a large online survey of individuals from the general population, implemented using Qualitrics. The survey was advertised through King's College London research recruitment page, ADHD user-group and information websites, and social media. The only exclusion criterion was participants could not be below 16 years of age. Data from 1484 participants (425 males, 1059 females) who fully completed the MEWS were used for analysis in the current study.

Participants were aged between 16–83 years (M = 34.80, SD = 13.55) and were categorised into age groups as follows: 1) 16-23 years (n = 382), 2) 24-30 years (n = 360), 3) 31-45 years (n = 365), and 4) 46+ years (n = 372). Those with and without full MEWS data did not differ significantly for sex ($\chi^2(1)$ = 1.05, p = .31) or age group ($\chi^2(3)$ = 5.74, p =.13). Participants who endorsed a childhood or adulthood diagnosis of ADHD based on self-report were included in the ADHD group (n = 198: 76 males, 122 females) and those reporting no diagnosis or 'not sure' (n = 59) were included in the non-diagnosed ADHD group (n = 1181: 319 males, 862 females).

5.3.2 Ethical Approval

Ethical approval was granted by the East of England–Cambridgeshire and Hertfordshire REC (ref:16/EE/0226). The study was carried out in compliance with the Helsinki Declaration of 1975, as revised in 2008. Participants provided informed consent online prior to completing the survey.

5.3.3 Measures

5.3.3.1 Mind wandering

Excessive mind wandering was measured using The Mind Excessively Wandering Scale (MEWS) (Mowlem et al., 2016). While the MEWS was initially developed as a 15-item scale, previous

psychometric evaluation and validation found 3 items had low factor loadings and that shortening the scale to 12-items did not reduce its sensitivity or specificity, so we use the 12-item measure.

To assess validity of the MEWS, unintentional (spontaneous) and intentional (deliberate) mind wandering were also assessed with the Mind Wandering Spontaneous (MW-S) and Mind Wandering Deliberate (MW-D) self-report scales (Carriere, Seli, & Smilek, 2013). Previously it has been shown that spontaneous, but not deliberate mind wandering is associated with ADHD (Seli et al., 2015).

5.3.3.2 ADHD symptoms, functional impairment, emotional lability and positive mental health/wellbeing

ADHD symptoms were assessed using the self-rated Barkley Adult ADHD Rating Scale which consists of 18 items that closely parallel the DSM-5 symptom criteria for ADHD; 9 items pertain to inattention and 9 to hyperactivity/impulsivity (Barkley & Murphy, 2006). The Barkley Current Behaviour Scale Self-report was used to measure the degree to which a participant's inattention and hyperactivity/impulsivity symptoms cause problems for them in major life domains (e.g., family, work, education, social, life-skills, relationships, money, driving, recreation, and daily responsibilities) (Barkley & Murphy, 2006). Emotional lability was assessed with the Affective Reactivity Index self-report measure of irritability (Stringaris et al., 2012), and the Mental Health Continuum-Short Form assessed wellbeing (emotional, psychological, and social) (Keyes, 2009). Further detail on the measures, including Cronbach's alphas, are provided in the Supplementary Content (Supplementary Table S1, Appendix D).

5.3.4 Statistical Analysis

Statistical analyses were carried out using MPlus (Muthén & Muthén, n.d.) and Stata (StataCorp, 2015).

5.3.4.1 Factor Analysis

First, we performed item factor analysis to identify the dimensionality of the MEWS, using exploratory factor analysis (EFA) and confirmatory factor analysis (CFA). We used a random number algorithm to split the sample into two halves, which did not significantly differ for sex ($\chi^2(1) = .95$, $p = .33$) or age group ($\chi^2(3) = 2.64$, $p = .45$); EFA was carried out on the first half ($n = 742$) and CFA on the second half ($n = 742$). EFA (oblimin rotation) and CFA were carried out using a structural equation modelling framework and the Robust Weighted Least Squares (WLSMV) estimator, since this does not make distributional assumptions and is more appropriate for use with categorical variables (Yu, 2002). Goodness of fit was assessed based on the following (Hooper, Coughlan, & Mullen, 2008): standardised mean square residual (SMSR), root mean square error of approximation (RMSEA), Taylor-Lewis Index (TLI), and the comparative fit index (CFI). In line with recommendations, the following values were used as indicators of good-fit: SMSR < .08 (Hooper et al., 2008; Hu & Bentler, 1999; Schmitt, 2011; Yu, 2002), RMSEA < .06 (Hooper et al., 2008; Hu & Bentler, 1999; Schmitt, 2011), TLI values > .9, and CFI close to 1 (Hooper et al., 2008; Hu & Bentler, 1999; Yu, 2002). Of note, although chi-square is the traditional fit index used to evaluate model fit, it is very sensitive to sample size and can be inflated in large samples (Blunch, 2008; Hooper et al., 2008; Schmitt, 2011) and so this was not used as a goodness of fit index for the CFA model.

5.3.4.2 Measurement invariance

The total sample was used to test measurement invariance across sex, age, and ADHD status using multi-group CFA (MGCFA) for categorical variables (sex and ADHD status) and multiple indicators multiple causes (MIMIC) models for continuous variables (age). MGCFA is tested in a sequential/hierarchical manner where constraints are consecutively added to the model. The first step involves running an unconstrained model for all groups combined to test for configural invariance (whether the same factor structure is observed between-groups). This is followed by a series of constrained models where parameters (factor-loadings and thresholds) are constrained to be equal across groups. Metric invariance refers to when factor-loadings are equivalent across groups, and scalar invariance refers to when the factor-loadings and item-thresholds are equivalent across the groups. Certain parameters are fixed for model identification (see

Supplementary Table S2, Appendix D, for more detail). If the difference in fit indices between the model and the preceding, less constrained model, is ≤ -.01 for ΔCFI and ≤ .015 for ΔRMSEA, then we considered the corresponding level of measurement invariance was held (Chen, 2007; Cheung & Rensvold, 2002; Lúcio et al., 2017). If non-invariance was identified, modification indices were used to identify noninvariant items and remove the corresponding equality constraint (i.e., the parameter was freely estimated in each group). Then, if the fit indices were in line with the accepted cut-offs, partial invariance was held and the parameter remained unconstrained in the subsequent models. Of note, the nested chi-square difference test between two models (DIFFTEST) was not used due to its sensitivity to sample size (it has been noted that if sample size is greater than 200, any differences between groups indicated by the DIFFTEST are likely to be trivial and subsequent analyses can proceed (Meade, Johnson, & Braddy, 2008)).

MIMIC models allow covariates in the CFA model (Yu, 2002) and as they do not split the sample by group can accommodate continuous covariates. If the covariate shows a significant direct effect on any of the individual scale items, this provides evidence of measurement non-invariance and the identified items are assumed to be affected by differential item functioning (DIF). However, if the magnitude of any direct effects is very small, then it is likely to have a trivial impact on the model (Brailean, Guerra, Chua, Prince, & Prina, 2015). In the baseline model, associations between the covariate and items are fixed to 0 and then modification indices are consulted, with modification indices >4 of the covariate on an item presenting DIF (Lúcio et al., 2017). If the covariate shows an association with the latent structure (i.e., the factor), this provides evidence of population heterogeneity.

5.3.4.3   Reliability and validity

To assess the reliability of the scale we estimated internal consistency using Cronbach's alpha and examined item-total correlations. Convergent validity was assessed to provide an indication of the degree of relationship between the scale of interest (the MEWS) and other scales measuring similar entities, by calculating Pearson's correlation coefficients between the MEWS and MW-S, ADHD symptom scales, emotional lability, and impairment. To examine discriminant validity, providing an indication of whether two measures that should not be correlated are actually not related, we calculated Pearson's correlation coefficients between the MEWS and MW-D and

wellbeing. We then examined ADHD case-control differences and conducted receiver operating characteristic (ROC) analysis to examine the capacity of the scale to discriminate between those with and without ADHD.

We also carried out regression analysis in the ADHD group to assess whether mind wandering accounts for unique variance in impairment and wellbeing beyond that accounted for by the core ADHD symptoms, which would further emphasise the potential value of the scale. Specifically, a hierarchical regression was conducted with impairment/wellbeing summary scores as the dependent variable and inattention and hyperactivity/impulsivity summary scores entered in Step1, and MEWS summary scores entered in Step2.

5.3.4.4   Sex differences in those with and without self-reported ADHD

Sex differences across ADHD diagnostic status in mind wandering, as well as ADHD symptoms, emotional lability, impairment, and wellbeing, were tested using linear regression models adjusted for age. Cohen's d was used as an indication of effect size where: $d \geq 0.20$ is a small effect, $d \geq 0.50$ a medium effect, and $d \geq 0.80$ a large effect.

5.4   Results

5.4.1   Factor Analysis

All 12-items in the scale were included in the EFA model. The sample correlation matrix produced 1 eigenvalue >1 (8.55), in line with the scree plot (Supplementary Fig S1, Appendix D). The next largest eigenvalue was 0.89. Goodness of fit indices for the 1-factor model were: SMSR = .06, RMSEA = .13 [0.12, 0.14], TLI = .97, CFI = .97. Next, we entered the 12-items into a CFA model specifying a 1-factor solution. Each of the 12-items demonstrated a high loading on to the single hypothesised factor (> 0.75) (Table 5.1). Three out of four fit indices (SMSR = .06, RMSEA = .15 [0.14, 0.16], TLI = .96, CFI = .96) were indicative of good/acceptable model fit; only the RMSEA was higher than the recommended cut-off.

5.4.2 Measurement Invariance

Table 5.1 shows standardised factor loadings for the MEWS items across sex and ADHD status. Table 5.2 summarises the change in goodness of fit indices for measurement invariance (assessed with MGCFA) across sex and ADHD status.

5.4.2.1 Sex

The configural model showed acceptable model fit according to TLI and CFI (TLI = .96, CFI = .97), although RMSEA was higher than the recommended cut-off (RMSEA = .14[0.14, 0.15]). Thus, model fit indices were similar to those for the CFA carried out above, with two out of three fit indices reaching acceptable levels, implying the factor structure is equivalent between males and females. Metric and scalar invariance both held in relation to the ΔCFI and ΔRMSEA.

5.4.2.2 ADHD status

The configural model showed acceptable model fit according to TLI and CFI (TLI = .95, CFI = .96), although RMSEA was higher than the recommended cut-off (RMSEA = .14 [0.13, 0.14]). Thus, model fit indices were similar to the CFA results, with two out of three fit indices reaching acceptable levels, implying the factor structure is equivalent between those with and without a self-reported ADHD diagnosis. Both metric and scalar invariance held as assessed by ΔCFI and ΔRMSEA.

Thus, the MEWS showed full measurement invariance across sex and ADHD status at the scalar level, and we are satisfied that there is no substantial measurement bias.

5.4.2.3 Age

MIMIC analysis testing the direct effect of age on individual items suggested DIF for Item 12 ("*I can only focus my thoughts on one thing at a time with considerable effort*") as a function of age. Assuming equivalent levels of mind wandering, increasing age was associated with increased scores for this item (direct-effect = 0.01, p <.001); however, the magnitude of the direct effect is

small. Further, consideration should be given to the fact that Item 12 appeared last in the scale and the effect could be an artefact of this. Results therefore indicate that age is not a concern regarding measurement non-invariance. Regarding population heterogeneity, the MIMIC model suggested that mind wandering increased with age.

Thus, MGCFA and MIMIC indicate the MEWS is measurement invariant across sex, ADHD, and age.

Table 5.1 Standardised factor loadings for the 12-items for EFA (with oblimin rotation) and CFA and across sex and ADHD status, and Cronbach's alpha for the scale

	Item	Standardised Factor Loadings					
		EFA (*n*=742)	CFA (*n*=742)	Males (*n*=425)	Females (*n*=1059)	ADHD (*n*=198)	No ADHD (*n*=1181)
1.	I have difficulty controlling my thoughts	.83	.80	.83	.81	.75	.80
2.	I find it hard to switch my thoughts off	.82	.80	.82	.81	.80	.79
3.	I have two or more different thoughts going on at the same time	.74	.76	.69	.78	.73	.72
4.	My thoughts are disorganised and 'all over the place'	.85	.88	.85	.87	.80	.84
5.	My thoughts are 'on the go' all the time	.84	.84	.88	.83	.89	.82
6.	I experience ceaseless mental activity	.86	.82	.85	.84	.82	.82
7.	I find it difficult to think about one thing without another thought entering my mind	.88	.84	.87	.86	.83	.85
8.	I find my thoughts are distracting and prevent me from focusing on what I am doing	.87	.88	.89	.87	.80	.86
9.	I have difficulty slowing my thoughts down and focusing on one thing at a time	.91	.91	.90	.91	.82	.90
10	I find it difficult to think clearly, as if my mind is in a fog	.78	.79	.78	.78	.65	.77
11.	I find myself flitting back and forth between different thoughts	.88	.83	.83	.86	.76	.84
12.	I can only focus my thoughts on one thing at a time with considerable effort	.79	.79	.80	.79	.54	.78
Internal consistency	Cronbach's Alpha (α)	.95		.95	.95	.91	.94

Table 5.2 Multi-group CFA models for measurement invariance across sex and ADHD diagnostic status for the MEWS

	Measurement invariance model [a] (constraints)	CFI	ΔCFI	RMSEA	ΔRMSEA
Sex	Configural (no equality constraints)	0.968	-	0.141 (0.135, 0.147)	-
	Metric (factor loadings)	0.969	-.001	0.132 (0.127, 0.138)	.009
	Scalar (factor loadings and thresholds)	0.970	-.001	0.120 (0.115, 0.125)	.012
ADHD	Configural	0.960	-	0.138 (0.132, 0.144)	-
	Metric	0.964	-.004	0.125 (0.120, 0.131)	.013
	Scalar	0.964	.000	0.113 (0.108, 0.119)	.012

[a] See Supplementary Table S2 (Appendix D) for further detail on the constraints applied to each model.

5.4.3   Reliability and validity

Internal consistency for the 12-item scale was high for the complete sample (α = .95), with no improvement in the reliability index gained by omitting items. Item-total correlations were all above .69. Similar results were found across sex and ADHD status. For males and females α was .95, with no improvement in the reliability index gained by omitting items, and item-total correlations all >.64. Alpha was also high in those with ADHD (α = .91) and those without (α = .94), with no improvement in the reliability index gained by omitting items, and item-total correlations >.48 in those with ADHD and >.66 in those without ADHD.

Demonstrating convergent validity, the MEWS correlated moderately-to-strongly with spontaneous mind wandering (MW-S r = 0.76, p <.001), ADHD symptoms (inattention r = 0.76, p <.001; hyperactivity/impulsivity r = 0.71, p <.001), emotional lability (r = 0.44, p <.001), and impairment (r = 0.74, p <.001) (Table 5.3). It also demonstrated discriminant validity, with a weak, non-significant correlation with deliberate mind wandering (MW-D r = 0.05, p = .06) and a negative relationship with wellbeing (r = -0.41, p <.001).

We found elevated levels of mind wandering as measured by the MEWS in those with a self-reported diagnosis of ADHD compared to those without ADHD (p <.001, d = -1.17), with the same pattern of findings for measures of spontaneous mind wandering (MW-S) (p <.001, d = -.98), inattention (p <.001, d = -1.54), hyperactivity/impulsivity (p <.001, d = -1.42), emotional lability (p <.001, d = -.45), and impairment (p <.001, d = -1.47). We also found higher scores for wellbeing in those without ADHD compared to ADHD cases (p <.001, d = .35) (see Supplementary Table S3, Appendix D, for mean scores across subscales). ROC analysis examined the capacity of the MEWS to discriminate between those with and without ADHD. Area under the curve (AUC) was .81 (95% CI: .78, .84, p<.001); the closer the value to 1, the better the discriminant capacity of the measure, and so this indicates that in the current sample including individuals with self-reported ADHD the MEWS has good discriminant capacity. This was comparable to the inattention (AUC = .86, 95% CI: .84, .89) and hyperactivity/impulsivity rating scales in the sample (AUC = .83, 95% CI: .80, .86).

Regression analysis in the ADHD group examining if mind wandering (measured by the MEWS) accounts for unique variance in impairment beyond core ADHD symptoms found that inattention and hyperactivity/impulsivity accounted for 53.4% of the variability in impairment (R^2 = .53). The addition of mind wandering in the model led to a significant increase in the variability accounted for by the model ($R^2\Delta$ = .02), with an increase to 55.3%, $F\Delta$(1,194) = 8.34, p = .004. This indicates that mind wandering is having a small but significant effect beyond that of inattention and hyperactivity/impulsivity. Inattention was the most strongly associated (β = .56), followed by mind wandering (β = .19) and hyperactivity/impulsivity (β = .08). Only inattention and mind wandering were significantly associated with impairment in the model (p <.001 and p = .004, respectively).

Similar findings were found for the measure of wellbeing. Within those with self-reported ADHD, mind wandering accounted for unique variance in total wellbeing beyond core ADHD symptoms. Inattention and hyperactivity/impulsivity accounted for 10% of the variance in wellbeing (R^2 = .10). The addition of mind wandering as a predictor led to a significant increase in the variability accounted for by the model ($R^2\Delta$ = .04), with an increase to 15%, $F\Delta$(1,194) = 9.29, p = .003. Mind wandering was the most strongly associated (β = -.28, p = .003), followed by inattention (β = -.25, p = .009) and hyperactivity/impulsivity (β = .24, p = .005). This implies that excessive mind wandering in ADHD is having a small but significant independent negative effect on wellbeing beyond that accounted for by the core ADHD symptoms.

Table 5.3 Correlations between excessive mind wandering scores and rating-scale measures of spontaneous and deliberate mind wandering, inattention hyperactivity/impulsivity, emotional lability, impairment, and wellbeing

	MEWS	MW-D	MW-S	INN	HI	EL	IMP
MEWS	-	-	-	-	-	-	-
MW-D	.05	-	.	-	-	-	-
MW-S	**.76**	**.19**	-	-	-	-	-
INN	**.76**	.03	**.67**	-	-	-	-
HI	**.71**	.03	**.58**	**.72**	-	-	-
EL	**.44**	-.04	**.35**	**.41**	**.43**	-	-
IMP	**.74**	.006	**.63**	**.84**	**.68**	**.46**	-
WB	**-.41**	**.10**	**-.30**	**-.40**	**-.21**	**-.37**	**-.46**

Note. MEWS = Mind Excessively Wandering Scale; MW-S = Mind Wandering Spontaneous; MW-D = Mind Wandering Deliberate; INN = inattention; HI = hyperactivity/impulsivity; EL= emotional lability; IMP = impairment; WB = wellbeing.
Statistically significant correlations are presented in bold: significant at p<.001

Table 5.4 Mean scores (SD) for the study subscales comparing males and females with and without ADHD*

	ADHD				No ADHD			
	Males (n=76)	Females (n=122)	p	Cohen's d (95% CI)	Males (n=319)	Females (n=862)	p	Cohen's d (95% CI)
MEWS	26.34 (6.57)	25.38 (7.75)	.44	.13 (-.16, .42)	16.90 (9.98)	15.36 (8.53)	**.01**	.18 (.05, 0.31)
MW-S	23.41 (3.44)	23.47 (4.60)	.78	-.01 (-.30, .27)	18.99 (5.39)	17.96 (5.50)	**.006**	.19 (.06, .32)
MW-D	17.39 (7.07)	17.16 (6.35)	.78	.04 (-.25, .32)	18.16 (5.58)	17.47 (5.72)	**.008**	.12 (-.01, .25)
INN	19.92 (4.27)	18.30 (5.48)	**.045**	.32 (.03, .61)	11.34 (6.67)	8.80 (6.02)	**<.001**	.41 (.28, .54)
HI	15.70 (5.10)	15.31 (6.43)	.75	.06 (-.22, .35)	8.86 (5.46)	7.74 (4.92)	**.003**	.22 (.09, .35)
EL	3.63 (2.91)	4.29 (3.17)	.13	-.21 (-.50, .07)	3.02 (3.11)	2.65 (2.69)	**.04**	.13 (.002, .26)
IMP	2.02 (0.55)	1.90 (0.63)	.23	.20 (-.09, .49)	1.08 (0.72)	0.86 (0.70)	**<.001**	.31 (.18, .44)
WB	42.42 (13.77)	47.26 (12.92)	**.01**	-.37 (-.65, -.08)	48.24 (13.89)	51.09 (14.45)	**.008**	-.20 (-.33,-.07)

Note. MEWS = Mind Excessively Wandering Scale; MW-S = Mind Wandering Spontaneous; MW-D = Mind Wandering Deliberate; INN = inattention; HI = hyperactivity/impulsivity; EL = emotional lability; IMP = impairment; WB = wellbeing.
Statistical analysis adjusted for age.
Statistically significant findings are presented in bold.
*1379 participants answered the question regarding a previous diagnosis of ADHD.

5.4.4 Sex differences in those with and without self-reported ADHD

Overall, males had significantly higher scores across all scales (p range <.001 to .004, d range .12 to .44), except greater wellbeing reported by females (p <.001, d = -.25) and no significant difference in emotional lability (p = .17) (Supplementary Table S3, Appendix D). In those with self-reported ADHD, males and females showed similar symptom scores, except males with ADHD reported significantly greater levels of inattention (p = .045, d = .32) and lower wellbeing than females (p = .01, d = -.37) (Table 5.4). Among those without ADHD, males reported significantly greater symptom levels across all variables (p range <.001 to .04, d range .12 to .41) and lower wellbeing than females (p = .008, d = -.20).

5.5 Discussion

We validated the Mind Excessively Wandering Scale (MEWS) using a large population sample. The scale showed measurement invariance across sex, age and ADHD diagnostic status, suggesting the MEWS is a reliable and valid instrument measuring the same construct across the studied groups. Among those with ADHD, we found no evidence for sex differences in mind wandering, nor were there sex differences in levels of hyperactivity/impulsivity, emotional lability, or impairment. However, males with ADHD reported higher levels of inattention and lower wellbeing than females with ADHD. Among individuals without ADHD, males had higher scores across all ADHD related scale and reported significantly lower wellbeing than females.

In the current study, analysis involved a series of factor analysis models. EFA suggested that a 1-factor structure is appropriate for the MEWS. Model fit indices for the CFA model were acceptable, with three out of four fit indices suggesting acceptable fit for the unidimensional structure. The RMSEA exceeded the recommended cut-off, however this does not mean that one should automatically disregard the model (Lai & Green, 2016). It can be difficult to achieve good fit in large samples (Maccallum, Browne, & Sugawara, 1996; Schmitt, 2011) and fit indices should be interpreted with this in mind. Further, there is also debate regarding model fit indices and the 'rules of thumb', with a general consensus that strictly adhering to recommended cut-offs can lead to incorrectly rejecting an acceptable model (i.e., a Type I error) (Hooper et al., 2008) and that allowing model fit to drive the research process moves away from the theory-testing purpose of

structural equation modelling (Hooper et al., 2008; Schmitt, 2011). Thus, we believe the results support the MEWS as measuring one unified construct of excessive mind wandering.

This study is the first to test measurement invariance of the MEWS, which is important to establish for any new measure, and extends our previous findings. The MEWS had full scalar invariance across sex and ADHD diagnostic status. No sex differences were observed at the level of factor loadings or thresholds, indicating scalar invariance across sex in the total sample. This attests that the same latent construct of mind wandering is related to the items and their thresholds similarly for males and females. Measurement invariance also held in those with and without a self-reported diagnosis of ADHD (i.e., scalar invariance held). Thus, comparisons of mean scores across these groups is appropriate and meaningful, and any between group differences observed can be reliably interpreted as true differences in the latent construct of mind wandering. We also found scale items functioned similarly across age, but that increasing age may be associated with higher levels of mind wandering, so age should be considered as an important covariate in analyses of mind wandering.

Reliability and validity analysis showed the 12-item scale had high internal consistency in the total sample, as well as in males and females and those with and without self-reported ADHD. The MEWS demonstrated convergent validity, with moderate to strong correlations found between the MEWS and measures of core ADHD symptoms, impairment, and wellbeing (negative correlation). The MEWS showed strong correlation with another existing measure of spontaneous mind wandering but not with deliberate mind wandering, supporting the MEWS as specifically reflecting spontaneous mind wandering. Of note, the correlation between the MEWS and emotional lability was lower than demonstrated in our previous study, which may be due to different measures of emotional lability being employed in the studies. Regarding discriminant validity, both ROC analysis and examination of mean differences showed the MEWS distinguished between those with and without self-reported ADHD. Importantly, in the current sample the ROC analysis using the MEWS produced results comparable to those of the core ADHD symptom dimensions.

The National Collaborating Centre for Mental Health (NCCMH, 2009) emphasise the importance of linking symptoms to impairment, which may be a better measure of identifying those who would

benefit from treatment rather than somewhat arbitrary symptom counts. Replicating our previous findings, among adults with ADHD, mind wandering accounted for unique variance in impairment above that of core ADHD symptoms of inattention and hyperactivity/impulsivity. The ability for the MEWS to account for unique variance beyond core ADHD symptoms demonstrates the value of the measure and its potential clinical utility. Similar findings were also found for wellbeing, further emphasising the value of the scale. Thus, findings indicate the mind wandering is associated with both increased impairment and reduced wellbeing even after accounting for levels of inattention and hyperactivity/impulsivity.

Examination of sex differences showed that among those without ADHD males reported greater levels of mind wandering compared to females, but among those with ADHD, males and females reported similar levels. A similar pattern was found for inattention and hyperactivity/impulsivity, with the exception that among those with ADHD males reported more inattention than females. This is in line with recent findings amongst youth (Mowlem et al., 2018) showing higher ADHD symptoms in males than females in the general population, but similar symptom severity amongst those with a diagnosis, except for higher inattention in males. To our knowledge this is the first investigation of sex differences in those with and without ADHD in a population-based sample of adults, and we found that the pattern of sex differences for the behavioural ADHD symptoms in adults with and without ADHD is also reflected in the more internalised/subjective experience of excessive mind wandering.

Regarding impairment, males without ADHD reported greater impairment than females, but similar levels were reported among those with a self-reported ADHD diagnosis. Additionally, despite similar symptom levels and impairment in males and females with ADHD, females with ADHD reported significantly greater wellbeing, potentially indicating differing perceptions of behaviour in males and females with ADHD. In youth, studies show parents may under-rate ADHD symptoms and impairment in girls with ADHD compared to boys, suggesting sex-specific biases in perceptions of behaviour (Abikoff et al., 2004; Meyer et al., 2017). It is possible that differing perceptions of behaviours and impairment in males and females also occurs in adulthood. This requires further investigation.

A strength of the current study is the large sample size including a large age range and representation of females, both of which are often a limitation of studies in the ADHD literature. However, some limitations should be considered. First, despite the online survey being a general population sample, it is not necessarily representative of the general population, but of those who chose to participate in an online survey. Our sample included significantly more females than males suggesting that females may be more willing to participate in such studies. Further studies should examine if results are replicated across other populations. Second, our definition of ADHD was based on self-report and not clinical diagnosis data. However, this approach has previously been employed in a survey design (Hesson & Fowler, 2018), and was adopted in the most recent large-scale genome-wide association study of ADHD using 23andme (Demontis et al., 2017). In addition, our findings replicate those of our previous study that included a clinical sample of adults with ADHD (Mowlem et al., 2016).

Enhancing our understanding of the broader range of symptoms or problems associated with ADHD and the phenomenology that underlies ADHD symptomatology has the potential to aid diagnosis and inform targets for interventions. Valid and reliable assessment of disorders is a prerequisite for clinical treatment and intervention. The MEWS has been shown to be a reliable and valid measure of mind wandering in ADHD that discriminates between those with and without ADHD, with satisfactory sensitivity and specificity, and specific association with functional impairment. Finding measures to assess adult ADHD, a disorder primarily defined in behavioural terms, is of value, and mind wandering could be more useful when self-report is possible as it is the experience of the internal mental states rather than observed behaviours. The MEWS shows promise as a brief screening tool in the general population and could be a potential target for monitoring of treatment effects.

The replicated finding that mind wandering had an independent effect on impairment beyond that of core ADHD symptoms of inattention and hyperactivity/impulsivity, indicates that symptoms of mind wandering are strongly linked to impairment and so may be an important target for therapeutic interventions. Further studies are needed to establish such interventions, but mindfulness training could be an area of future emphasis.

Chapter 6. Discussion and conclusions

This thesis sought to further our understanding of sex differences in ADHD across youth and adulthood. The main aims were to examine whether: 1) different factors are associated with meeting diagnostic criteria in females versus males, 2) sex-dependent biases in parental perceptions of ADHD symptoms exist, 3) the predictive associations of symptoms on being diagnosed and treated for ADHD differs in males and females, and 4) investigate whether a new measure based on the internal subjective experience of ADHD - excessive mind wandering - could have clinical utility in ADHD diagnosis and add to our understanding of sex differences in the manifestation of ADHD. The specific findings, limitations, and implications of each individual empirical study have been discussed in detail within their respective chapters and will not be repeated here. Rather, this chapter summaries the key findings and draws them together to consider the wider research and clinical implications of the work presented in relation to individuals with ADHD. I then provide an overview of the general strengths and limitations of this body of work, including methodological considerations, and suggest future directions for research.

6.1   Summary of key findings and implications

The first empirical chapter (Chapter 2) in this thesis used a population-based sample to examine if, amongst a group of children with comparably elevated ADHD symptoms, different factors influence whether females and males meet diagnostic criteria. ADHD diagnosis was derived from an investigator-rated semi-structured interview; thus the children meeting diagnostic criteria were not ascertained from clinical settings, removing potential bias related to factors influencing referral to clinics. The findings showed that females meeting diagnostic criteria for ADHD had higher rated emotional, conduct, and peer problems, total problem scores, and complaints about hyperactivity at school compared to females with high symptoms that did not meet diagnostic threshold. Although similar differences were observed in males (except for emotional problems), effect sizes were greater in females. These results suggest that factors which distinguish females who meet full ADHD diagnostic criteria from high-symptom peers who do not may be somewhat sex-specific, and additional behavioural and emotional problems may play a larger role in distinguishing diagnosed from high-symptom females than the equivalent male comparison.

Potentially females' ADHD symptoms may need to be made more prominent by additional behavioural problems for them to display clinically recognisable ADHD behavioural symptoms. Furthermore, the prominence of emotional problems for females meeting diagnostic criteria, which is in line with previous findings (Novik et al., 2006), suggests this characteristic is more specific to the female phenotype of ADHD and females may express their difficulties differently to males with ADHD.

Additionally, sex differences in parental perceptions of ADHD behaviours and impairment were demonstrated. Despite the objective investigator-rated interview measure of impairment distinguishing between the diagnosed and high-symptom groups of females, parent ratings of impairment did not. That is, parents rated females meeting diagnostic criteria for ADHD as having similar levels of impairment as females who did not meet diagnostic threshold for ADHD. However, both measures distinguished the two groups of males. In addition, amongst children meeting diagnostic criteria for ADHD, parents were found to under-rate females' hyperactive/impulsive symptoms compared to the more objective accounts from the diagnostic interview, with the opposite pattern observed in males. These results are in line with those of a previous study comparing parent-ratings of ADHD to an objective classroom observational measure which found that, despite comparable levels of ADHD symptoms in males and females based on objective assessment, parent-ratings reflected observed ADHD status less well in females (Meyer et al., 2017). These findings suggest the existence of sex-dependent biases among parental perceptions of ADHD symptoms and that parents may be less sensitive to impairment in females, perhaps due to it being expressed differently to in males.

Following on from Chapter 2, the second empirical study (Chapter 3) also investigated sex differences related to childhood ADHD diagnosis in a population-based sample, but uniquely this sample could be linked to clinical diagnoses data obtained from national population registries. Thus, a clinical sample was available, but participants had not been ascertained via clinics and so are representative of all those receiving a clinical diagnosis of ADHD, overcoming a key methodical issue in this research area. Specifically, Chapter 3 investigated whether the predictors of ADHD clinical diagnosis and pharmacological treatment differ in males and females. At the population level, compared to females, males were found to have higher scores for all measured symptom domains (inattention, hyperactivity/impulsivity, conduct, and learning problems), more males than

females received a clinical diagnosis of ADHD, and clinically diagnosed males and females showed similar symptom severity. Symptom severity for all domains increased the likelihood of having a clinical diagnosis of ADHD in both males and females. Additionally, significant sex-by-symptom interactions on diagnostic and treatment status were found for hyperactivity/impulsivity and conduct problems, such that these behaviours were stronger predictors of clinical diagnosis and prescription of pharmacological treatment in females. These findings, using one of the largest datasets to date to investigate sex differences in ADHD, suggest that females with ADHD may be more easily missed in the ADHD diagnostic process and less likely to be prescribed medication in the absence of prominent externalising problems.

The sex differences observed in ADHD led me to think more about the expression of ADHD and how investigating additional symptoms and ways to measure them could increase our understanding of whether males and females manifest their ADHD differently. Thus, the third and fourth empirical studies in this thesis (Chapters 4 and 5) investigated the 'symptom' of excessive mind wandering in ADHD.

Chapter 4 evaluated the psychometric properties of a newly developed measure of mind wandering - The Mind Excessively Wandering Scale (MEWS) – created based on patients' reports of their internal, subjective experience of ADHD. This is the first study published using this scale, and I evaluated the MEWS in two independent case-control samples. The findings from both samples indicated a unidimensional structure to the MEWS which accounted for between 62 – 70% of the variance, and that the scale has high internal consistency and good test-retest reliability.

Consistent with previous findings (Franklin et al., 2014; Seli et al., 2015; Shaw & Giambra, 1993; Weyandt et al., 2003), investigation of case-control differences revealed significantly elevated levels of mind wandering in individuals with ADHD compared to controls. Furthermore, the MEWS successfully discriminated between cases and controls with high sensitivity (~.9) and specificity (~.9), as shown by ROC analysis. Importantly, these differences were comparable to those of existing scales used in assessment of ADHD, which demonstrates potential clinical utility of the scale. However, the finding that adds weight to the potential value of the MEWS was that mind wandering contributed independently to functional impairment, beyond the core symptoms of

inattention and hyperactivity/impulsivity. Further, in the second sample, mind wandering had the most impact on impairment in the model. In the subset of individuals with ADHD who were treated with methylphenidate at follow-up, a significant reduction in mind wandering scores was found compared to the baseline medication-free period. These findings suggest that excessive mind wandering is a common co-occurring feature of adult ADHD that has specific effects on impairment, and that the MEWS could have clinical utility as an additional screening tool in adult ADHD assessment and could also be used for treatment monitoring.

Following on from Chapter 4, the final empirical study (Chapter 5) further validated the MEWS in a large general population sample and examined sex differences in the manifestation of adult ADHD. As in Chapter 4, findings revealed a unidimensional structure to the MEWS, with confirmatory factor analysis indicating good model fit. Additionally, I assessed measurement invariance to examine whether the scale is capturing fundamentally the same construct across sex, ADHD status, and age. Measurement invariance is rarely tested in empirical studies of psychiatric disorders (Orri et al., 2016), yet a lack of invariance can render group comparisons (e.g., cases vs controls) meaningless and lead to incorrect interpretations of differences (Marsh et al., 2013; Orri et al., 2016). This study is the first to examine measurement invariance of the MEWS. Across sex, ADHD status and age, I found the MEWS to be measurement invariant, giving confidence that any subsequent between-group comparisons would be meaningful. Reliability and validity analyses indicated strong internal consistency for the whole sample and across sex and ADHD status. Further replicating the previous findings (Chapter 4; Mowlem et al., 2016), mind wandering was elevated in individuals with ADHD compared to those without, and the MEWS showed good case-control discriminatory capacity and accounted for unique variance in impairment beyond the core ADHD symptoms. Strengthening the latter finding, I also found mind wandering to contribute independently to wellbeing.

Sex differences in mind wandering in those with and without ADHD were also examined, along with the symptom dimensions of inattention, hyperactivity/impulsivity, emotional lability, impairment, and wellbeing. Among those without ADHD, males reported significantly greater symptom levels across all variables and lower wellbeing compared to females. Conversely, in individuals with self-reported ADHD, males and females demonstrated similar scores, except for greater levels of inattention reported by males (consistent with the findings from Chapter 3 in

children) and lower wellbeing compared to females. To my knowledge, this is the first investigation of sex differences in adult ADHD in a population-based sample including those with and without an ADHD diagnosis, and adds to the limited literature in this field. The findings further support mind wandering as a common co-occurring feature of ADHD, and the MEWS as an instrument that could aid the screening and diagnostic process. Moreover, the findings show that the pattern of sex differences observed for the behavioural symptoms of ADHD and impairment are also reflected in the internalised and subjective experience of excessive mind wandering.

6.2   Wider themes and their implications

The literature is clear in identifying that females with ADHD may be underdiagnosed compared to males. However, it is unclear whether this is truly because females are less likely to be affected or whether there are biases in the referral and diagnostic process leading to under-referral and under-identification of females with ADHD, especially in youth. The sex ratio balances out in adulthood, but the diagnosis in adulthood is still relatively rare in comparison to youth and is based on criteria developed for diagnosis in children and adolescents. Taken together, the findings from this thesis have highlighted some emerging themes regarding these issues, discussed below.

6.2.1   Referral and diagnosis of females with ADHD symptoms

6.2.1.1   Sex-specific biases could be leading to under-recognition and under-diagnosis of females

The findings from Chapters 2 and 3 identify a potential link to the under-recognition and/or under-diagnosis of ADHD in females compared to males. In Chapter 3, more males than females had a clinical diagnosis of ADHD (2.5:1), yet among those from the population the ratio based on symptomatic criteria was slightly lower (1.8:1). Among children in the population with elevated symptoms, a higher percentage of the males had a clinical diagnosis compared to the percentage of the females. In Chapter 2, the ratio of diagnosed to high-symptom females was 0.65:1 compared to 1.5:1 for males, suggesting that males with high symptoms are more likely to meet diagnostic criteria than females. Furthermore, Chapter 3 found that externalising problems were stronger predictors of ADHD diagnosis in females compared to males, yet in Chapter 2 parents were shown to under-rate externalising problems in females and had a tendency to over-rate

them in males. These findings are in line with studies showing that parents perceive the ADHD criteria as being descriptive of males (Ohan & Johnston, 2005), and that externalising behaviours drive referral (Biederman et al., 1999). Additionally, parents' ratings of their child's impairment demonstrated a sex-specific bias, with lower rated impairment in females meeting diagnostic criteria compared to males meeting diagnostic criteria, and no differences in impairment ratings shown between high symptom and diagnosed females, neither of which were in line with findings based on the objective interview measure.

As discussed, behavioural diagnoses can bring issues of symptom interpretation and perception from individuals key to the diagnostic process, and the tendency to view ADHD as a predominantly male disorder can affect how behaviour in males and females is perceived by individuals key to the diagnostic process (such as parents and teachers). If a male stereotype of ADHD is the norm, then it is possible that parents and teachers may not as readily recognise manifestations of ADHD in females compared to males. Thus, potentially only the most severe females or those whose symptoms manifest as disruptive behaviours will be identified. In line with this, and based on the findings from this thesis, the high sex ratio in diagnostic rates of ADHD could therefore partly reflect: 1) sex-specific stereotypes operating in the referral process due to parents not judging females to be as impaired or to demonstrate as many externalising symptoms, and 2) bias in the current diagnostic criteria or the way they are applied to males and females in clinical settings, as if the diagnostic criteria are biased or poorly defined for females compared to males (Williamson & Johnston, 2015) then females will be more likely to have a diagnosis if they have externalising symptoms. Further, clinicians use parental report in clinical assessment, and if parents are less sensitive to ADHD-type behaviours in females and more attuned to notice and endorse symptoms in males, even if the rates of ADHD behaviours are similar in males and females, females may be missed in the referral and diagnostic process. Overall these results are consistent with explanations of a sex bias in the recognition of symptoms of ADHD that have been argued to contribute to the under-referral and under-diagnosis of females (Biederman et al., 2005; Ohan & Johnston, 2005). Furthermore, this has implications for females with ADHD receiving appropriate treatments, and it was also the case that externalising behaviours were stronger predictors of receiving pharmacological treatment in females. It is also entirely possible that ADHD occurs more frequently in males as well as being underdiagnosed in females.

Given the need for early identification to optimise treatment outcomes, the negative long-term outcomes associated with ADHD that are likely to be increased in individuals whose symptoms are untreated, and that those with undiagnosed or subthreshold ADHD (failure to meet full diagnosis) are unlikely to access services from which they would benefit, the current findings identify a need for improving awareness that females are also affected by ADHD. It is important that parents and clinicians are sensitive to the fact that females with ADHD may not present in the same ways as males. By increasing our knowledge of sex differences in ADHD, and working towards improved recognition of females, the negative societal impact of ADHD can potentially be reduced.

Another message to draw from the work in this thesis is the importance of reliable measures for screening and diagnosing ADHD in both childhood (specifically to ensure that females are not missed) and adulthood (to ensure that adults with ADHD are effectively screened), in both research and clinical practice. As shown in Chapter 2, some diagnostic tools, such as parent rating-scale measures, may lead to underestimating females' symptoms and impairments and contribute to their under-diagnosis. Further, it can mean that females are less likely to be included in research studies of ADHD or to be given ADHD case status in a study, as many population-based studies derive diagnosis based on parent-rating scales. The use of structured diagnostic interviews for subject identification when exploring sex differences in research on ADHD has been highlighted as a necessity (Gaub & Carlson, 1997).

6.2.1.2 Symptom manifestation could be leading to lower rates of diagnosis in females

As previously detailed in this thesis, it has also been proposed that the observed sex differences in referral and diagnosis in youth results from females being more likely to present with an internalising presentation of ADHD, comprising predominantly inattentive symptoms, compared to an externalising set of symptoms in males (Arnold, 1996; Quinn, 2008). This thesis found that across youth (Chapter 3) and adulthood (Chapter 5), it was not the case that females had more severe inattention than males. In fact, in those with a diagnosis of ADHD males had higher inattention scores than females. However, in Chapter 3, at the population level females were found to be more likely to have the inattentive presentation compared to males. This suggests that females do not have more inattention than males, but that they are less likely to have as many hyperactive/impulsive symptoms, and so mostly fall in the inattentive category. As primarily

inattentive symptoms tend not to be rated as being as impairing as the externalising symptoms (Coles et al., 2012; Willcutt, 2012), individuals with a primarily inattentive presentation of ADHD may be less frequently referred for services (Nussbaum, 2012). The findings from Chapter 3 appear to suggest that this is the case, as despite at the population level more females than males had the inattentive presentation, at the clinical level the combined presentation was most common in both sexes, again speaking to the view that externalising behaviours drive referral. Of note, this could also affect males with an inattentive presentation.

Currently, each of the symptoms listed in the DSM criterion A (which details the two symptom dimensions each comprising nine symptoms; see Table 1.1) carries the same weight. Recent work has suggested that inattention drives hyperactivity/impulsivity, but not the converse (Sokolova et al., 2016), and it could be argued that the inattentive items should be more heavily weighted than the hyperactivity/impulsivity items. More research is needed to replicate this finding and investigate it further, but if this were to be the case then potentially more females with ADHD would receive a diagnosis, but it should not miss those with externalising presentations if inattention drives hyperactivity/impulsivity.

6.2.1.3   Normative differences could lead to less females being diagnosed

Studies in clinical samples tend to show that males and females have similar severity (Gaub & Carlson, 1997), but in population-based sample males tend to have higher ratings (Larsson et al., 2012; Levy et al., 2005; Martin et al., 2014). This suggests that females will need a greater severity of symptoms to reach and pass the diagnostic threshold compared to the norm for females, whereas males generally have a higher level of symptoms and will not require the same increase in symptoms from their norm to reach diagnostic threshold. In Chapters 3 and 5, at the population level males scored higher than females across all symptoms domains – showing greater symptom severity – whereas similar symptom severity was demonstrated at the clinical level (except for greater inattention in males, as mentioned). In Chapter 2, regarding traits relevant to the pathology of ADHD, the magnitude of difference in scores between females meeting diagnostic threshold and females with comparably high ADHD symptoms not meeting threshold was greater than in the equivalent groups of males. Taken together, these findings are indicative of normative sex differences and demonstrate that females, who overall have lower base rates of ADHD

symptoms and correlates, may have to deviate further from their group norm to reach diagnostic threshold. I also extended previous findings by showing that the pattern of sex differences for the behavioural ADHD symptoms in those with and without ADHD seems to be reflected in the more internalised experience of excessive mind wandering, at least in adulthood.

Due to the replicated finding that females generally have a lower intensity of symptoms, it could be argued that sex-specific modification in the severity of symptoms required for diagnosis should be implemented (Staller & Faraone, 2006). Further research would be beneficial to establish the most appropriate thresholds for the diagnosis of ADHD and if it should differ for females. However, whether it is imperative to establish if a categorical decision for the presence of a disorder should be based on normative comparisons (i.e., if the child is more severe than children of the same sex and age) is debateable if more emphasis were to be placed on impairment (Frick & Nigg, 2012). Despite impairment measures forming a key component of the referral and diagnostic process, current criteria still focus on the number of symptoms rather than a more precise definition of functional impairment (Cortese & Coghill, 2018). This is an important line of inquiry given it is anticipated that there are a substantial number of youth in the community who do not meet full symptom criteria for ADHD but experience significant functional impairment and would benefit from treatment (Polanczyk et al., 2015). This clearly indicates the importance of managing diagnostic thresholds effectively as failure to meet full diagnosis limits access to a range of services, such as school accommodations, despite the association of subthreshold symptoms with real world impairment (Angold et al., 1999; Balazs & Kereszteny, 2014; Bussing et al., 2010; Faraone, Biederman, Spencer, et al., 2006; Hong et al., 2014; Noren Selinus et al., 2016).

6.2.2   Additional symptoms could aid screening for ADHD in adults

Currently, there are no biomarkers to determine ADHD and the diagnosis is made when a set of defined behavioural symptoms and criteria for onset, course and impact have been met which are very much based on childhood research. However, ADHD is now recognised to occur in adulthood (Asherson et al., 2016; Biederman et al., 2010; Faraone, Biederman, & Mick, 2006). In this age group diagnosis is usually made based on self-report, compared with the parent report that is a key source of information for childhood ADHD diagnosis. Evidence shows that informant report tends to be more accurate than self-report and that adults may underrate their symptoms

(Asherson et al., 2016; Du Rietz et al., 2017; Merwood et al., 2013). A potential reason for this discrepancy is that it is more difficult for an individual to reflect upon the behavioural symptoms that currently characterise ADHD diagnosis, such as if others think that you "do not listen to when spoken to directly", compared to a parent reporting on such symptoms. Reporting on an internal, subjective mental state could be a more accurate way to capture self-report of ADHD, yet current screening tools for adult ADHD comprise rating scales largely of behaviours.

In conjunction with existing findings in the literature (Franklin et al., 2014; Seli et al., 2015; Shaw & Giambra, 1993; Weyandt et al., 2003), the results from Chapters 4 and 5 of this thesis suggest that adults with ADHD frequently experience excessive and uncontrolled mind wandering, which appears to be a strong predictor of the daily functional difficulties they experience. This demonstrates that individuals with ADHD also present with subjective psychopathology that goes beyond behavioural descriptions, which may form part of the core symptomatology of ADHD.

Additional measures to aid assessment and monitoring of adult ADHD and provide new insights into the disorder in this age group is of considerable relevance to research and clinical practice (Asherson et al., 2016). The current findings show the significance of mental phenomena in the disorder, its specific association with impairment, and the validation of a measure pertaining to this. Thus, it is believed that the MEWS could have utility as a screening tool to incorporate into clinical practice and research studies of ADHD to assist with accurate diagnosis in adulthood. The National Institute for Health and Care Excellence (NICE) clearly states the importance of linking symptoms to impairment, and if, as implied here, the MEWS is potentially explaining a variety of deficits not easily accounted for by the core symptom dimensions, this further strengthens its potential utility. Moreover, it could be argued that some of the current symptoms used to define ADHD are conflated with impairment. For example, losing things, being forgetful, and being disorganised are 'symptoms' of ADHD, yet could easily be considered impairments. Thus, the criteria are not exclusively describing a symptom but behaviours that could be prone to adaptation. The current symptoms may not be sensitive to the underlying disorder, in that if individuals have developed adaptive skills to manage the symptoms, then the symptoms may not be as apparent. Self-reflection on an internal mental state which is independent of adaptive skills that could modify behavioural symptoms, may be more sensitive or accurate. Following this line of

thinking, it can be argued that mind wandering is entirely different from measures of impairment as it is only reflecting a subjective experience of the flow of thoughts.

As it was shown that the MEWS correlates highly with the existing core behavioural symptoms specified in the ADHD diagnostic criteria, by-and-large the MEWS may be picking up the same symptoms (it is possible that it could underlie, and thus lead to the ADHD symptoms, or it could be another reflection of inattention/distractibility). However, as MEWS scores also distinguished between cases and controls with high sensitivity and specificity, potentially it could pick up individuals who may otherwise be missed or receive a delayed diagnosis, for example those with less overt behavioural presentations of ADHD or those who lack confirmation of behavioural symptoms from additional informants. Furthermore, adults may find it easier to accurately report mind wandering than the traditional DSM symptoms of inattention and hyperactivity/impulsivity, and so the MEWS may enable more accurate self-report of ADHD. If self-report is the main source of information for diagnosis (as is often the case in adulthood), then questionnaires based more on internal experiences that the individual can better reflect on themselves may be more appropriate. However, it is important to reiterate that currently we do not recommend the routine use of the MEWS to identify patients with ADHD until the scale has been comprehensively evaluated in other psychiatric disorders with overlapping clinical features (see section 6.4.3.1). The possibility that mind wandering could especially aid in the diagnosis of females with ADHD was discussed in Chapter 5, however, the findings were not clear that this was the case, since levels of mind wandering were found to be similar in males and females with ADHD.

The finding that mind wandering contributes to functional impairment beyond the core symptoms of ADHD also has implications for treatment. First, given that mind wandering scores reduced when individuals with ADHD took pharmacological treatment (Chapter 4), the MEWS could be effectively used to monitor treatment outcomes. Second, mind wandering itself could be a treatment target, and interventions such as mindfulness that are likely to reduce levels of mind wandering (Bachmann, Lam, & Philipsen, 2016), could also reduce impairment. For example, it has recently been shown that mindfulness increased nonreactivity to inner experience in those with ADHD (Hoxhaj et al., 2018).

The findings could also have implications for the DSM. As previously mentioned, the DSM-5 defines ADHD almost entirely by reports of behaviours, and mind wandering is only briefly mentioned as one example of distractibility (American Psychiatric Association, 2013). Further, the DSM has only recently been adapted to facilitate diagnosis in adulthood, which included simply adding descriptions of how the existing defined symptoms could affect adults (i.e., instead of leaving seat at school, also including leaving seat in the workplace) as opposed to a set of criteria specifically based on adulthood symptoms. With future work, potentially two sets of criteria could come to exist, one for diagnosis in children and adolescents and one for adults. For example, in adulthood greater emphasis could be placed on internal mental states as opposed to observable behaviours, given it may help them report their symptoms. This is not implying that they are two different disorders, but that diagnosing a disorder in childhood and adulthood is quite a different process. Further, even though the underlying psychopathophysiology is likely to be largely the same and that largely the same 'symptoms' will be specified, the criteria could be more tailored to the way the symptoms present in each age group and based on more robust research on the manifestation of the disorder in adulthood. However, it could be challenging to decide the point at which childhood/adolescence turns into adulthood (Blakemore & Choudhury, 2006; Johnson, Blum, & Giedd, 2010).

6.3   Methodological considerations: strengths and limitations

Each of the empirical chapters within this thesis includes a brief discussion of the main limitations and strengths relevant to that study. In the following section I describe in more detail the methodological considerations that apply to the research throughout this thesis.

6.3.1   Sample sizes

The research undertaken in this thesis capitalises on several strengths of the datasets used to advance knowledge on sex differences in ADHD. The large size of the samples used in Chapters 3, 4 and 5 is a key strength of this body of work. The population-based sample of over 19,000 children used in Chapter 3 (The Child and Adolescent Twin Study in Sweden; CATSS) is one of, if not the, largest epidemiological studies used to investigate sex differences in ADHD which meant a more balanced representation of males and females. Many studies in ADHD are primarily, if not

exclusively, made up of male participants meaning the findings may not generalise to females with ADHD or ADHD symptoms. Also, although the size of the case-control samples (MIRIAD and OCEAN) used in Chapter 4 who completed the MEWS were modest, they enabled initial validation of a new measure. Further, I replicated the findings in a much larger sample of 1484 individuals (Chapter 5).

Recruiting participants and administering measures online (as I did in Chapter 5), where much larger and more representative samples are (in principle) readily available offers an attractive prospect (Gosling, Vazire, Srivastava, & John, 2004). However, despite these benefits, it is recognised that online surveys are not without their obstacles. For example, there exists a trade-off between increased sample size and potentially decreased data quality (Germine et al., 2012). That said, such issues tend to be more of a concern for performance-based cognitive and perceptual measures (Germine et al., 2012), and there have been studies demonstrating the validity and reliability of web-based questionnaire measures (Chiorri & Vannucci, 2017; Gosling et al., 2004; Haworth et al., 2007). Additionally, studies comparing questionnaires completed in the lab versus online have found no significant or systematic differences in results (Casler, Bickel, & Hackett, 2013). The findings from Chapter 5 regarding the psychometric properties of the MEWS when administered online replicate the findings from Chapter 4 where the MEWS was administered face-to-face, providing confidence of psychometric equivalence and that online administration did not sacrifice data quality.

In Chapter 2, even though the sample size for the female groups was modest (n=32 and 49), this was still sizeable for a study investigating sex differences in ADHD. Despite selection of participants from the wider TEDS sampling frame, there was a mismatch in the number of males (n=121 and 81) to females. The reason for the smaller number of females was not arbitrary; rather it was due to less females being identified as having high ADHD symptoms or meeting the diagnostic criteria. Furthermore, this study involved secondary analysis of existing data and the study was not originally designed for the purposes of sex difference analysis. Larger-scale investigations are required.

6.3.2 Age range

The studies in this thesis investigate ADHD in both youth and adulthood, acknowledging the presence of the disorder across the life trajectory. As a limit of the current sex differences literature in ADHD is that most studies focus on children and adolescents (Davies, 2014), the study of ADHD in adulthood in Chapters 4 and 5, and specifically investigation of sex differences in Chapter 5, offers a novel aspect to this research. Further, the participants from the online survey presented a wide age range (16 – 83 years), which is a benefit given that most studies of adult ADHD focus on early and middle adulthood. However, it is acknowledged that the broad age-range sampled may contribute to greater age-related variability in measures of interest, potentially masking some meaningful results, especially as analyses were run controlling for age to account for any of these effects. That said, the MEWS was found to be measurement invariant across age (Chapter 5), but future studies may wish to investigate more homogeneous groups. It is acknowledged that the samples in Chapters 2 and 3 were restricted to childhood, and the samples in Chapters 4 and 5 were restricted to adulthood and so each set of results may not generalise to other age groups than those studied in the specific chapters. Notably however, the sex differences analyses in adulthood (Chapter 5), replicated the findings from childhood (Chapter 3).

6.3.3 Diagnostic classification

Most population-based studies rely solely on parent or teacher rating scales to classify participants with and without ADHD. Such rating-scale measures of child behaviour reflect the perspective of untrained raters, which may be prone to sex-specific biases and perceptions of behaviours (Meyer et al., 2017). The PHAD study was unique in extending existing methodology used in population-based samples by incorporating a detailed, 'gold-standard', objective diagnostic measure of ADHD. In the CATSS study, participants were linked to National Registry Data on whether they had a clinical ADHD diagnosis. Linking a population-based sample to clinical data for which there is not an ascertainment bias in this way overcomes limitations of using one source of information on ADHD alone (i.e., clinical data or parent-ratings). Additionally, the online survey study is a population-based sample with data from participants who self-reported a diagnosis of ADHD, but who were not clinically ascertained. Although self-report may be considered a less reliable source

of information (as opposed to confirmation from clinical notes) previous studies have successfully taken this approach; for example the most recent large-scale genome-wide association study of ADHD found high genetic correlation (r_g = 0.65) between self-reported cases of ADHD and those with an established clinical diagnosis (Demontis et al., 2017).

Thus, the population-based studies used in this thesis uniquely reconcile trade-offs between epidemiological and clinical samples. They overcome some of the limitations of population-based samples that diagnose based on rating-scales alone, and of clinical samples where ascertainment bias exists, both of which could have implications specifically for studies of sex differences in ADHD. This is especially pertinent given that findings from Chapter 2 showed differences in parental ratings of males and females meeting diagnostic criteria for ADHD based on investigator-rated interview.

6.3.4   Dimensional and categorical definitions of ADHD

Another strength of the studies in this thesis is that they employed both dimensional (symptoms and impairment ratings) and categorical (diagnostic cut-off) definitions of ADHD. For example, in Chapters 2, 3 and 5, categorical analyses compared males and females based on clinical cut-offs of ADHD and all chapters compared those with and without ADHD (obtained through diagnostic interview, national registry data, or self-report - as detailed in section 6.3.3). A strength of Chapters 4 and 5 was that they employed both approaches by looking at how the measures of mind wandering were associated with the continua of ADHD symptoms and impairment, as well as investigating case-control differences. In light of the converging evidence that the symptoms of ADHD are quantitative traits distributed continuously throughout the population (Frazier, Youngstrom, & Naugle, 2007; Haslam et al., 2006; Larsson et al., 2012; Levy et al., 1997; Lubke et al., 2007; Salum et al., 2014), and given the complexity of ADHD, adopting both approaches is valuable to obtaining a more complete understanding of ADHD.

Studies employing a categorical approach better reflect clinical diagnostic discriminations between 'affected' and 'unaffected' individuals that are likely to be implemented in the 'real-world'. However, a fundamental conceptual issue relevant to the study of ADHD is that the diagnostic threshold is somewhat arbitrary, socially constructed, and a practical clinical tool, rather than an

etiologically or biologically-based definitive delineation of disorder presence vs. absence. A dimensional approach enabled investigation of ADHD in population-based samples unselected for clinical extremes for epidemiological research, reducing the risk of ascertainment bias so often associated with clinical samples. It also allowed examination of ADHD symptoms and impairment separately (such as in Chapters 2, 4 and 5). This is valuable given the heterogeneity of ADHD and given: 1) the possibility that individuals who fall just below the threshold may have significantly impairing symptoms, 2) that individuals within a diagnostic category can vary greatly with regard to symptom severity and impairment, and 3) that individuals with high symptoms will not always experience significant impairment (Barry, Lyman, & Klinger, 2002; Frick & Nigg, 2012). The categorical approach to diagnosis can be seen to ignore these variations (Frick & Nigg, 2012). In Chapter 2 I aimed to address some of these factors in the study design. For example, the sample included a group of children who had comparably high levels of ADHD symptoms to those meeting diagnostic criteria, but it was not assumed that they would not experience impairment. It also acknowledged that children within a diagnostic category can differ with regard to impairment, specifically to address sex differences and understand if different factors characterise males and females within the ADHD diagnostic group.

6.3.5   Rater effects

In Chapters 2 and 3 of this thesis, ADHD symptom ratings were based on parent report; although it is important to note that the diagnosis of ADHD was not based on parent ratings alone. Measurement error is a contentious issue in psychopathology assessment. Whilst parent-rated reports of ADHD-symptoms have the highest and most consistent heritability estimates compared to self- and teacher- ratings (Nikolas & Burt, 2010; Sibley, Pelham Jr, Gnagy, et al., 2012) and previous studies show greater agreement with objective markers of ADHD outcomes, as well as superior predictive validity on long-term outcomes compared to self-reports (Barkley, Fischer, Smallish, & Fletcher, 2002; Du Rietz et al., 2016), this is not to say that sex-specific stereotypes are not influencing interpretations of behaviours by parents (Meyer et al., 2017). Indeed, in Chapter 2 I found some evidence that parents may underrate females' ADHD symptoms compared to more objective measures and over-rate males. This was only investigated for ADHD symptoms, but the possibility that this was also the case for other measures, such as the Strengths and Difficulties

Questionnaire (SDQ), cannot be excluded. It is also possible that parent-ratings may have shown rater bias in the other direction for behaviours that are deemed more stereotypically female, such as prosocial behaviour. It is important that in both clinical practice and research there is an awareness of the role of perceptions in informant ratings, and all informant report is subject to some degree of bias.

The use of self-report for the mind wandering measure in Chapters 4 and 5 represents a strength of this work, as the use of parent-report or other external informant report may not provide an optimal assessment of internalising symptoms which can go unnoticed by external informants.

6.3.6   Generalisability

The studies in Chapters 2, 3 and 5 used population-based samples, and these types of studies are designed to provide results that can be generalised to individuals with the disorder in the general population, but it means that the findings may be less generalisable to clinical cohorts. This may be most obvious regarding sex differences in ADHD as the ratio of males to females with ADHD is much smaller in population-based samples compared to clinical samples. This suggests that more females are affected with ADHD than reflected in clinical samples, and so the findings from investigations in clinical samples may not be wholly representative of the population with ADHD. The scientific research literature on ADHD consistently illustrates the trade-off between clinical and epidemiological methodologies (Bauermeister et al., 2007), and as discussed, clinical samples can be unrepresentative of the general population with ADHD, especially if we are missing or mis-diagnosing many females with ADHD.

However, an important question is whether (and why) we are failing to diagnose ADHD in females. To address this, we need to clarify whether the current gender disparity is reflective of true etiological differences and/or a reflection of problems with a male-focused conceptualisation, recognition, and assessment process of ADHD. If we only study clinical samples, this will not provide information about non-referred individuals and females with ADHD may be missed, thus limiting our understanding of the disorder in general, and in females. The population-based datasets used in this thesis had a good female representation. Many studies in ADHD are primarily, if not exclusively, male samples and results many not generalise to females with ADHD or ADHD

symptoms. Thus, by using datasets that are both population-based and with strong female representation, the findings from the empirical studies in this thesis are more representative of all individuals with ADHD, including females.

Finally, a concern when using twin samples is that it may limit generalisability to singletons. For example, relative to singletons, twins are more likely to have lower birth weight (Bhutta, Casey, Cradock, Anand, & Cleves, 2002; Pettersson et al., 2016) and be born preterm, both of which show association with later ADHD diagnosis (Aarnoudse-Moens, Weisglas-Kuperus, van Goudoever, & Oosterlaan, 2009; Bhutta et al., 2002; D'Onofrio et al., 2013; Johnson, Hollis, et al., 2010). Prior studies examining the generalisability of research using twin samples to singletons have reported mixed results regarding the effect of twin status on ADHD risk, with some studies showing differences between twins and non-twin sibling pairs regarding ADHD symptomatology and implicating a twin-specific effect (Ehringer, Rhee, Young, Corley, & Hewitt, 2006; Levy et al., 1997), and other studies not showing a difference (Moilanen et al., 1999). Importantly, the prevalence of ADHD observed in Chapter 3 (3.2%) using a twin sample was in the range reported in non-twin samples (Polanczyk et al., 2015), giving confidence in the generalisability of the findings. This also has implications statistically. Using twin samples means you have clustered data (i.e., the inclusion of two individuals per family), violating the assumption of independence of observations for the outcome. If unaccounted for in analysis this can lead to biased standard errors of the estimated regression coefficients. I addressed this by employing statistical techniques which produce robust standard errors in Stata. This is beneficial as it allows the use of all available data, rather than just one twin in each pair which can severely impact sample size. Nevertheless, it is important to replicate findings in non-twin samples.

6.3.7 Effect sizes, significance thresholds, and multiple testing

Following scientific convention, the analyses in this thesis used a $p<0.05$ significance threshold to judge statistical significance. Trend level associations are also acknowledged (i.e., $p>0.05$ and <0.10). The significance threshold is somewhat arbitrary (Hackshaw & Kirkwood, 2011) and there have been growing calls for researchers to focus on effect sizes and confidence intervals during the interpretation of findings. Thus, although the conventional threshold was used to judge the significance of results, I paid due attention to effect sizes.

The data analyses in this thesis did not apply a correction for multiple testing. This is specifically relevant to Chapters 2 and 3. Although within each study several statistical tests were conducted, the choice was made not to employ a correction for multiple testing because this alters the statistical inference of a study from the testing of a number of specific hypotheses to a test of the universal null hypothesis (i.e., testing that the null hypotheses across all the variables are simultaneously true) (Biederman et al., 2005; Perneger, 1998; Rothman, 1990; Savitz & Olshan, 1995). In the studies within this thesis, differences in specific variables among males and females could have important interpretive consequences and so testing the universal null hypothesis was not of interest. Furthermore, the main focus was sex differences as opposed to differences between the multiple variables. Other drawbacks also include an increase in the type II error rate (false negative findings) (Perneger, 1998; Rothman, 1990) and issues regarding how many tests should be included in the adjustment (Perneger, 1998). In addition, common multiple testing corrections such as Bonferroni assume that hypotheses are uncorrelated (or unrelated), which is not the case in studies such as these where all hypotheses relate to the overarching question of sex differences. However, due to the exploratory nature of these analyses, further replication of the results from this thesis is important to validate findings and before beginning to make strong assertions regarding implications for clinical practice.

6.4   Future directions

6.4.1   Replication

To test reproducibility of the findings from this thesis, future observational studies should test for replication of the specific findings in large independent samples. My study of children with comparably high levels of ADHD who did and did not meet diagnostic criteria is, to my knowledge, the first empirical study of its kind. Specifically, the use of a detailed objective investigator-rated interview to obtain diagnostic information in a population-based sample complemented by parental-rating scales was a novel aspect. Although findings are interpreted conservatively given potential limitations, such as modest sample size, the initial evidence (namely larger effect sizes in diagnosed vs high-symptom females as compared to males) suggests that meaningful sex differences could be captured in future studies with larger samples. Ideally, this would involve a

population-based sample for whom all participants receive a detailed diagnostic interview (as opposed to a selected high-risk sub-sample), and information would be gathered on individuals who were actually referred to clinical services. Such studies would add to our ability to uncover potential sex-specific biases in the ADHD referral and diagnostic process. Chapter 3 was carried out using data from the Swedish population, and findings regarding sex differences between males and females in the population but not in those with a clinical diagnosis replicate previous studies (Arcia & Conners, 1998; Biederman et al., 2002; Gaub & Carlson, 1997; Graetz et al., 2005; Ramtekkar et al., 2010; Sharp et al., 1999). Generalisability to countries with similar demographics and healthcare access is likely to be high. However, it is important to see if results from a country with universal healthcare coverage (as in Sweden) are replicated in other countries.

As mentioned in section 6.3.1, Chapter 5 replicated the findings of Chapter 4 in a larger, population-based sample, which is a strength of this body of work. However, to my knowledge this was the first study of sex differences in those with and without ADHD in a population-based sample of adults, and so requires replication - although the results did replicate my findings in youth from Chapter 3. Further studies are also needed to extend the findings, for example though experimental paradigms or using experience sampling techniques. Potentially this could provide further information on differential manifestation of ADHD as a function of sex.

6.4.2   ADHD sex differences research

6.4.2.1   Alternative diagnoses in ADHD, and specifically females

It is imperative to establish whether females with ADHD are being overlooked. The studies in Chapters 2 and 3 of this thesis looked at sex differences in ADHD in relation to associations with diagnosis. Whilst the study design and findings enabled speculation and inferences to be made regarding potential biases in the referral process, neither had explicit information on actual referral. A valuable next step in this line of research would be to interrogate the issue of sex differences in referral for ADHD behaviours. Following from this is the question of whether females with ADHD symptoms are being referred but receiving alternative diagnoses, which would imply potential biases in the diagnostic process. If it is the case that females with ADHD are being missed by current diagnostic processes, there is a high possibility that they are misdiagnosed with

other conditions (e.g., anxiety, depression) and/or that diagnostic over-shadowing is occurring from genuine co-morbidities (e.g., anxiety, depression, anorexia, learning disability) (Quinn & Madhoo, 2014). Recently, it was shown that amongst children who had received a clinical diagnoses of anxiety or depression (based on administrative data), females had a higher burden of the genetic variants associated with increased risk for ADHD compared to males (Martin, Taylor, et al., 2018). Such findings indicate the possibility that females at genetic risk for ADHD may be underdiagnosed and receive alternative diagnoses such as anxiety or depression.

The studies in this thesis were not able to examine the likelihood of children, and specifically females, being given alternative diagnoses. Leveraging registry data would offer a great opportunity to explore these questions in more detail. For example, one could examine whether females versus males with high ADHD symptoms are more likely to receive alternative diagnoses and whether certain presentations or manifestations of ADHD are associated with higher likelihood of alternative diagnoses in both sexes, and more so in females than males. This could potentially indirectly shed light on referral bias, as if most children who meet symptomatic criteria for ADHD from the population are observed in the national registry data for having a psychiatric diagnosis (not necessarily ADHD), then this would suggest that the children are being referred, but that not all are receiving an ADHD diagnosis. Such studies could also strengthen our understanding of whether the current diagnostic criteria for ADHD and/or clinical practice are somewhat biased towards a male presentation of ADHD. However, it is important to note that although national registry data is an incredibly valuable resource, there is a need for data on more than just the diagnostic code. For example, inclusion of phenotypic information to enable a greater understanding of why the diagnosis was made - especially with diagnoses that are so heterogeneous in nature. The proposed study findings could further inform our understanding of the way clinicians recognise ADHD symptoms and potentially apply the diagnostic criteria, and would benefit those working in this field in terms of improving understanding and recognition of ADHD in females.

6.4.2.2 Qualitative study of clinicians, teachers, parents, and individuals with high ADHD symptoms

To understand more about sex differences in ADHD and potential differences in referral, diagnosis, and treatment for males and females with ADHD, I believe it would be informative to carry out a qualitative study. This could provide rich data from a variety of informants, including clinicians, teachers, parents of children with ADHD or high ADHD symptoms, and individuals with ADHD, and potentially uncover issues not revealed in quantitative studies, such as the experiences and unmet social needs of females with ADHD or high ADHD traits, and potential masking and compensatory mechanisms amongst females (Quinn & Madhoo, 2014). If it is not known what these are, then they are unlikely to be measured in quantitative studies. In Chapter 2, the possibility that in the presence of positive social behaviour females' symptoms may be 'masked' making them appear less impaired was discussed. Furthermore, studies have suggested that behaviour in the home versus school environment may be more different in females than males (Meyer et al., 2017). Qualitative studies hold promise for understanding more about these hypotheses and such findings could, for example, influence clinical aspects of ADHD assessment and help educators maximise students' compensatory skills. This improved information could lead to better recognition and theoretical understanding of the female presentation of ADHD.

Qualitative studies could also increase understanding about treatment decisions. In Chapter 3, it was not possible to take into consideration the influence of parental preference for treatment. That is, prescribing medication (or not) for a child with ADHD could be influenced by whether a parent wishes their child to receive alternative forms of treatment first or if they deem the behaviour of the child to be problematic enough to warrant pharmacological treatment, rather than being exclusively decided by the clinician as a result of assessment. Such decisions could differ based on the child's sex and I was not able to examine such underlying nuances in treatment. This type of information could influence targeting of service provision for females and their families.

6.4.2.3 Longitudinal studies of sex differences in ADHD

The studies included in this thesis are cross-sectional. It is important to examine how the symptoms of ADHD and associated traits differ from normal behaviour at different developmental periods and understand if the diagnostic criteria are effectively reflecting these differences, including as a function of sex. Findings from such studies may inform our understating of maturational effects, for example whether onset of ADHD is later in females (Agnew-Blais et al., 2016) and if there are gendered maturation differences in the trajectory of ADHD symptoms and associated traits (Nussbaum, 2012) which would add to understanding of why ADHD would emerge later in adolescence for females. It could be that as life gets more complex, for example during adolescence and young adulthood when social demands may increase and/or there are changes in the environment and support system (e.g., leaving home and no longer living with parents), potential compensatory mechanisms employed by females with (undiagnosed) ADHD come undone. It could also be that there are different developmental processes that we do not yet fully understand. The findings from this thesis also indicate a need for increased understanding of the complex aetiological and developmental relationship between ADHD and internalising symptoms in males and females which could be addressed with longitudinal data. For example, examining whether these co-occurring symptoms develop as a consequence of untreated ADHD or are independent of ADHD.

6.4.3 Mind wandering research

6.4.3.1 Specificity of mind wandering to ADHD

Despite the research in this thesis strongly supporting the notion that adults with ADHD frequently experience excessive spontaneous mind wandering, the sensitivity and specificity of the MEWS for the ADHD diagnosis compared to other clinical diagnoses is not clear. Future studies are required to not only evaluate the psychometric properties of the MEWS in populations with other clinical disorders, but to determine the discriminant validity of the scale (and mind wandering) in those with ADHD compared to individuals with other psychiatric diagnoses. Given that mind wandering has been shown in other conditions, such as obsessive compulsive disorder (Seli et al., 2017), it may also be that the nature of the mind wandering experience differs in different psychiatric

diagnoses groups. For example, in ADHD it may just be a general tendency to mind wander and constantly have your thoughts on the go and flitting around, whereas in other disorders it may be driven by negative cognitions and rumination and only present itself in specific contexts.

6.4.3.2 Mind wandering in children

The research on mind wandering in this thesis explored the phenomenon in adults with ADHD. Given the link between mind wandering and impairment and wellbeing, it is of interest for future work to explore mind wandering in children. This is a complex undertaking and it is unclear if investigation of mind wandering in child ADHD populations is conceivable, although a recent study has begun to explore this (Van den Driessche et al., 2017). It is possible that children could describe the experience of a subjective mental state that reflects mind wandering but may not be able to conceptualise it, understand what it actually is, or reliably and validly report on it.

Nevertheless, this is an important line of research to pursue given that parents may be better at recognising and reporting on externalising behaviours compared with internalising problems (Husky et al., 2017; Van Der Meer, Dixon, & Rose, 2008). Furthermore, children as young as 6 have been shown to be capable of providing valid reports of their mood and feelings (Ialongo, Edelsohn, & Kellam, 2001; Rebok et al., 2001; Ringoot et al., 2017). The necessity for mental health screening efforts in youth are highlighted by the fact children and adolescents rarely disclose (spontaneously) their emotional distress to an adult (Husky et al., 2017; Van Der Meer et al., 2008; Vander Stoep et al., 2005). Thus, additional ways of measuring internalising symptoms that are causing distress hold potential. However, measures such as the MEWS would clearly need to be adapted for use in children; for example, with computerised, cartoon-like self-report methods (Husky et al., 2017).

Previous longitudinal research has revealed a greater developmental decline in hyperactive-impulsive than inattentive symptoms (Biederman et al., 2000; Larsson et al., 2006). Given that mind wandering may underlie the inattentive behavioural symptoms of ADHD (Biederman et al., 2017; Bozhilova et al., 2018; Jonkman et al., 2017), exploring longitudinally the relationship between mind wandering and ADHD and if its frequency differs across the developmental trajectory, could add to our understanding of the underlying etiological mechanisms of ADHD. This

could help answer questions regarding whether excessive mind wandering in ADHD is an epiphenomenon of the processes that lead to ADHD symptoms or has a more direct causal role in generating the symptoms and impairments of ADHD. Additionally, such a study could incorporate investigation of potential sex differences in mind wandering across the developmental trajectory. Understanding of the maturational processes could potentially aid diagnosis and guide intervention.

6.4.3.3 The association of mind wandering in ADHD with positive traits

ADHD poses an evolutionary paradox, in that despite being strongly associated with negative long-term outcomes and functional impairments, it persists in the population with a substantial worldwide prevalence rate. By definition, mental health disorders are maladaptive and impairing, and so a negative stance tends to be taken when investigating ADHD in terms of focusing on investigation of the associated impairments and adverse outcomes. However, for a 'disorder' to be so highly prevalent in a population suggests it is not exclusively maladaptive and certain advantages and adaptive characteristics of ADHD traits may exist. For example, we know that some individuals with high levels of ADHD symptoms are able to excel in the workplace if they select jobs that take advantage of some of the characteristic features of ADHD, and adults with ADHD may choose specific types of jobs that best suit their symptoms (Wiklund, Patzelt, & Dimov, 2016).

Despite mind wandering often being associated with negative symptoms of ADHD, mind wandering is not always detrimental, and may confer functional benefits in some circumstances (Mooneyham & Schooler, 2013). Both ADHD and mind wandering demonstrate association with creativity (Baird et al., 2012; White & Shah, 2006, 2011), and those with ADHD are more likely to report interesting mind wandering episodes (Franklin et al., 2014). Mind wandering could therefore be accounting for the creativity often demonstrated in ADHD, and this is an interesting area for future research.

There is very little research on the strengths and positive aspects of adult ADHD (Wiklund et al., 2016; Wilmshurst, Peele, & Wilmshurst, 2010), and it is important to understand more about potential positive characteristics of ADHD and how individuals may take advantage of their

symptoms. Of note, this is not to downplay the impairing nature of ADHD and the many difficulties experienced by those living with ADHD, but instead recognising that there is value in showing that ADHD is not solely adverse, supporting the reduction of stigma of mental health disorders and the design of interventions and supportive environments that enhance wellbeing.

6.5   Conclusion

The research presented in this thesis contributes to our understanding of sex differences in ADHD and provides further insight into the nature of the disorder. In particular, it makes a significant contribution to our understanding of potential sex-specific biases in the referral and diagnostic process, and the literature on ADHD and mind wandering. The findings suggest females may be more easily missed in the referral and diagnostic process due to sex-specific biases in the interpretation of symptoms by parents, and in the absence of prominent externalising behaviours and additional co-occurring problems. Further, the findings show that mind wandering - as measured by a newly developed scale - is a common co-occurring symptom of ADHD with specific implications for the functional impairment experienced. Overall, the results of this thesis highlight the need for increasing awareness and knowledge of ADHD in females amongst parents, teachers, and clinicians, a careful approach in the assessment of females with symptoms of ADHD, and the clinical utility of a newly developed measure of mind wandering in the assessment of adults with ADHD. It is a public health concern if individuals with ADHD are being missed and not gaining access to serves and treatment that they could benefit from, and thus being at greater risk for the adverse outcomes associated with ADHD. I hope that information gained about sex differences in ADHD can improve understanding of ADHD in females and encourage and guide future research into this important area of mental health.

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Appendix A: Supplementary material for Chapter 2

Online Supplementary Material

Mowlem, F.D., Agnew-Blais, J., Taylor, E., & Asherson, P. Do different factors influence whether girls versus boys meet ADHD diagnostic criteria? Sex differences among children with high ADHD symptoms.

Additional sample information

The Developmental Pathways to Hyperactivity and Attention Deficit Study (PHAD)

PHAD is a spin-off study from the larger Twins Early Development Study (TEDS) [1]. The primary aim of PHAD was identifying early neuroimaging and cognitive markers underlying risk for ADHD. Twins from the TEDS sampling frame were screened for ADHD symptoms at age 7 years using combined parent and teaching ratings on the hyperactivity/inattention subscale of the Strengths and Difficulties Questionnaire (SDQ), plus three additional items addressing attention and hyperactivity and impulsivity problems ('notices small details', 'has difficulty completing activities', 'has difficulty waiting for things'). The SDQ is frequently used in both clinical and research assessments of ADHD and as a measure to detect children at high risk of mental health problems especially using multiple informants [2–4]. Twins at risk of ADHD were identified if at least one twin in each twin-pair scored in the top 15% of the TEDS population. Families were excluded if they had withdrawn from TEDS or were uncontactable, were involved in other TEDS spin-off studies, or if medical exclusions applied. Opposite sex-pairs were excluded as the original objective of the study was to compare within twin-pair cognitive and neuroimaging findings for ADHD, while removing the potential confounding effect of sex differences. This led to 861 families being selected from TEDS where at least one twin was at risk of ADHD. Of these, 690 families agreed to participate in a further screening telephone interview, based on which 200 families were excluded: 67 due to reports of at least one twin having a learning disability, autistic spectrum disorder, or a neurological disability, and 133 who reported having no problems at home or school, or problems in only one setting. Of the remaining 490 families, 345 parents completed an ADHD symptom

checklist based on DSM-IV criteria [5], based on which 138 families were excluded where neither twin met the required symptom threshold (score >22). This left a sample of 207 families with at least one twin with high levels of ADHD symptoms. 196 families with children identified as being at risk for ADHD (comprising 276 boys and 116 girls) completed the Parental Account of Childhood Symptoms (PACS) diagnostic interview.

Additional information on study measures

PACS diagnosis

As in previous studies using the PACS [6, 7], an ADHD diagnostic algorithm combined data from the PACS and the Conners' teacher-rating scale for DSM-IV ADHD symptoms to apply a research diagnosis of ADHD. Children were 'diagnosed' if sufficient items were identified to fulfil DSM-5 criteria, and both impairment (based on severity of symptoms identified in the PACS) and pervasiveness (based on the presence of ADHD symptoms in more than one setting using information from the PACS and the Teacher Conners') were present. Situational pervasiveness outside the home setting is also captured in the PACS interview.

Impairment: SDQ Impact supplement

Parents are first asked 'Overall, do you think that your child has difficulties in one or more of the following areas: emotions, concentration, behaviour or being able to get on with other people?'. Subsequent items include: 'Difficulties upset or distress child', 'Interfere with home life', 'Interfere with friendships', 'Interfere with classroom learning', and 'Interfere with leisure activities'. If 'no' is answered to the first question then the subsequent questions are not asked and the impact score is automatically scored as '0'.

Supplementary Fig. S1 Graphical representation of the sex-by-diagnostic status interactions that approached significance
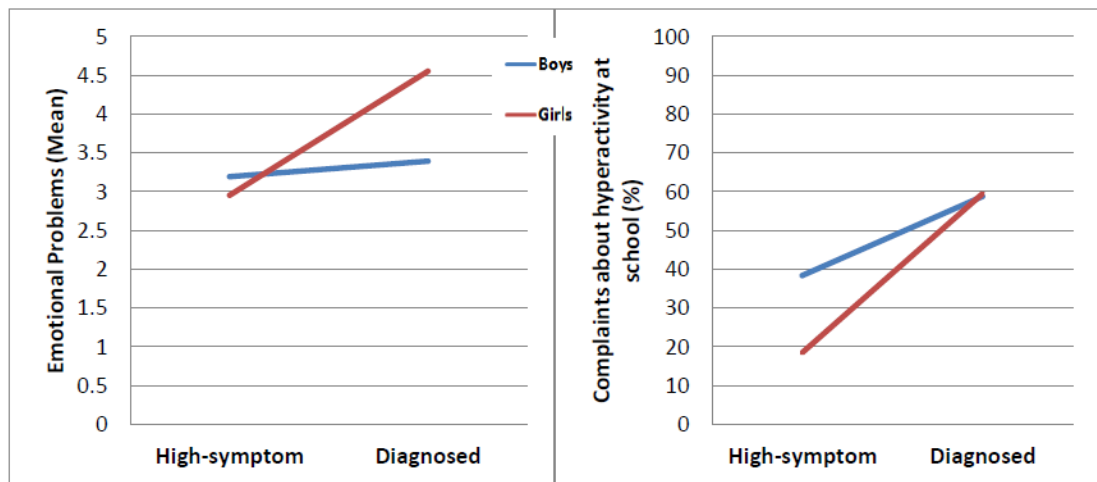
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Appendix B: Supplementary material for Chapter 3

Mowlem, F.D., Rosenqvist, M.A., Martin, J., Lichtenstein, P., Asherson, P., & Larsson, H. (2018). Sex differences in predicting ADHD clinical diagnosis and pharmacological treatment. *European Child & Adolescent Psychiatry.*

Supplementary Table 1. Characteristics of males and females in the entire sample (means and SD unless otherwise stated)

Characteristic [a]	Overall (n=19,804)	Males (n=10,029)	Females (n=9,775)	p	Cohen's d
Total ADHD	2.06 (3.13)	**2.49 (3.46)**	**1.62 (2.68)**	**< .001**	0.28
Inattention	1.05 (1.75)	**1.29 (1.92)**	**0.81 (1.52)**	**< .001**	0.28
Hyperactivity/ Impulsivity	1.01 (1.71)	**1.20 (1.88)**	**0.81 (1.48)**	**< .001**	0.23
Conduct	0.10 (0.37)	**0.12 (0.41)**	**0.08 (0.32)**	**< .001**	0.11
Learning	0.27 (0.61)	**0.30 (0.63)**	**0.25 (0.58)**	**< .001**	0.08

Bold data signify statistical significance of the tests

All models were adjusted for familial clustering, year of birth, and SES

[a] Data were missing on some variables; all available data were used in analysis

Supplementary Table 2. Characteristics of clinically diagnosed males and females stratified by medication prescription (based on the Prescribed Drug Register) (means and SD)

Characteristic [a]	Males		Females	
	Prescribed medication (n=396)	Not prescribed medication (n=70)	Prescribed medication (n=156)	Not prescribed medication (n=28)
Inattention	4.67 (2.82)	4.25 (2.72)	4.23 (2.97)	2.79 (2.67)
Hyperactivity/Impulsivity	4.25 (3.20)	3.41 (2.88)	4.10 (3.23)	1.88 (2.03)
Conduct problems	0.58 (0.99)	0.58 (0.90)	0.70 (1.08)	0.25 (0.48)
Learning problems	0.98 (1.01)	0.96 (1.08)	1.07 (1.12)	1.30 (1.15)

[a] Data were missing on some variables; all available data were used

Appendix C: Supplementary material for Chapter 4

Mowlem, F.D., Skirrow, C., Reid, P., Maltezos, S., Nijjar, S.K., Merwood, A., Barker, E., Cooper, R., Kuntsi, J., & Asherson, P. (2016). Validation of the Mind Excessively Wandering Scale and the relationship of mind wandering to impairment in adult ADHD. *Journal of Attention Disorders.*

Recruitment process for the OCEAN study (Study 2)

Controls

Controls were recruited via recruitment circulars and advertisements in the local community.

Cases

Recruitment occurred through four sources:

1. Recruitment through South London and Maudsley NHS Trust (SLaM): The medical records of patients (either follow-up patients or those on the waiting list) from the SLaM Adult ADHD Service were screened for eligibility, using the inclusion and exclusion criteria, by a member of the OCEAN research team who held honorary clinical contracts. In addition previous ADHD study databases were also screened for suitable participants. Those deemed eligible were sent study information sheets, invitations, a response slip and a stamped addressed envelope. Where no response slip was returned, participants were contacted by telephone to determine their interest in participating. Those who expressed an interest in participating in the study completed a telephone screening (detailed below). If deemed suitable following the telephone screening and if a Conners Adult ADHD Diagnostic Interview for DSM-IV (CAADID: a structured clinical interview for the 18 ADHD symptoms in childhood and adulthood) (Epstein *et al.* 2001) had been completed as part of their diagnostic assessment at SLaM, then they were invited into the trial and their baseline assessment was booked. If a CAADID were not completed as part of their diagnostic assessment it was completed over the phone by a member of the research team. If the patient was on the waiting list then a research diagnostic assessment was carried out by P. Asherson and R. Copper (detailed below).

2. Online questionnaire: In order to recruit undiagnosed patients an online screening questionnaire was set-up (http://neuroknowhow.com/adhdoraddquestionnairepage/) (although this link has now been disabled). This was established by a study participant who runs the website 'neuroknowhow' (http://neuroknowhow.com/aboutus/) which provides services and online help for those with neurodevelopmental difficulties such as ADHD, dyslexia, and dyspraxia. The

screening questionnaire consisted of the six questions in Part A of the(ASRS) which have been found to be the most predictive of ADHD (Kessler *et al.* 2005). Those who screened above the threshold for ADHD were asked to complete the Barkley Childhood Behaviour Scale. If they scored positive for 6 or more symptoms of either or both domains of inattention or hyperactivity/impulsivity then a research assessment was conducted (see below).

3. Online advertisements: Participants were also recruited from advertisements on the ADHD support websites AADD-UK (Adult ADHD-UK) (http://aadduk.org/about/) and ADDISS (The National Attention Deficit Disorder Information and Support Service) (http://www.addiss.co.uk/). We were also contacted from participants who saw the trial registered on clinical trials.gov (identifier: NCT01750307). If these participants had an existing diagnosis we asked them to send us a copy of their diagnostic assessment report. If inclusion/exclusion criteria were met then the CAADID (Epstein *et al.* 2001) was completed by a member of the research team. If the participants did not have an existing diagnosis and screened above threshold for ADHD on the ASRS (Kessler *et al.* 2005) and Barkley's Childhood Behaviour Scales (Barkley 1998) then a research assessment was conducted (see below).

4. Recruitment through other doctors: We attended the clinical team meetings at the Maudsley Adult ADHD Clinic to communicate the study to members of the healthcare team and ask if they had any suitable patients and if they could let their patients know about the study. The study was also circulated to clinicians on the email list of the UK Adult ADHD Network (UKAAN).

Telephone screening

Both ADHD and control participants underwent a structured telephone screening of exclusionary criteria, which consisted of detailed questions assessing any previous or current mental health problems including: presence, treatment for or diagnosis of anxious, depressive and manic/hypomanic symptoms, physical health problems, neurological problems, drinking and drug habits, use of omega-3 or 6 supplements, and any known allergies to fish.

Research assessment

Undiagnosed participants who met inclusion/exclusion criteria were asked to complete (over the telephone) the CAADID (Epstein *et al.* 2001). In line with DSM-5, symptom onset and chronicity was established before age 12 and in adulthood, the presence of a minimum of 5 symptoms of inattention and 3 symptoms of hyperactivity/impulsivity were established (*American Psychiatric Associations 2013*). The CAADID was also completed (over the telephone) with someone who knew the participant in childhood, most commonly a parent. The CAADID was then reviewed by P. Asherson, an experienced consultant psychiatrist specialising in adult ADHD, who approved the participants prior to inviting them into the study. In addition, P. Asherson met participants at their baseline assessment to review and confirm the diagnosis. Participants were then provided with a letter from P. Asherson detailing the outcome of the research assessment. Participants who had not yet been referred or diagnosed for adult ADHD could then, if they wished, use this letter to

help gain a referral for a formal adult ADHD assessment, although they were asked to not begin medication for the duration of the trial if they wished to take part.
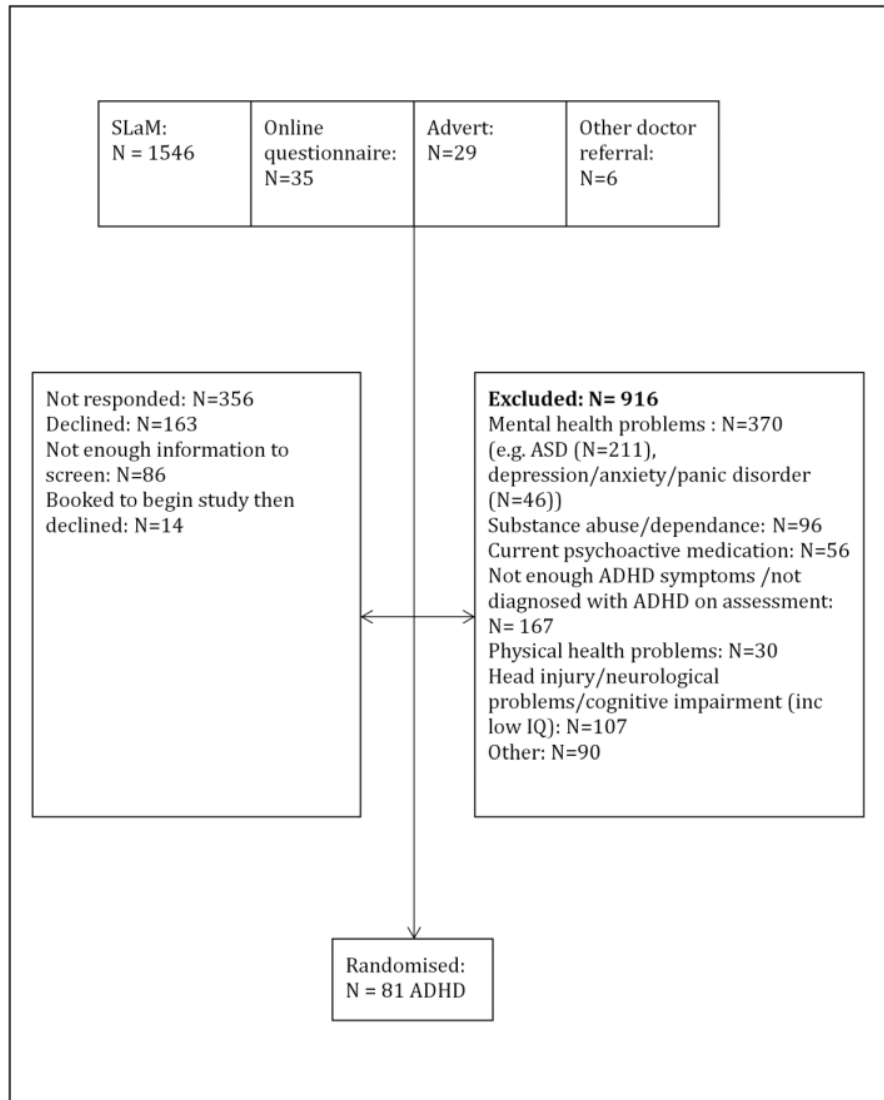
Supplementary Figures:
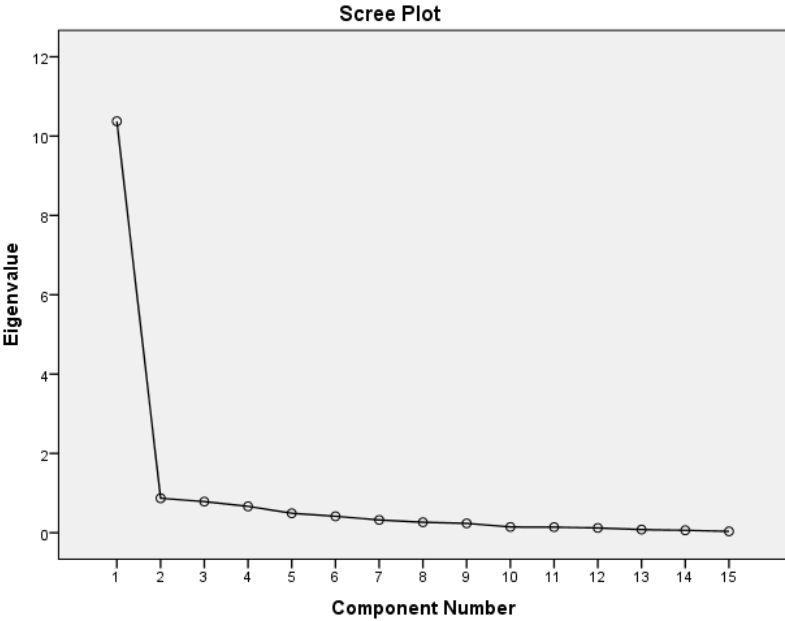
Supplementary Figure 1. *Scree plot produced during Factorial Analysis for Study 1 indicating a one-factor solution.*
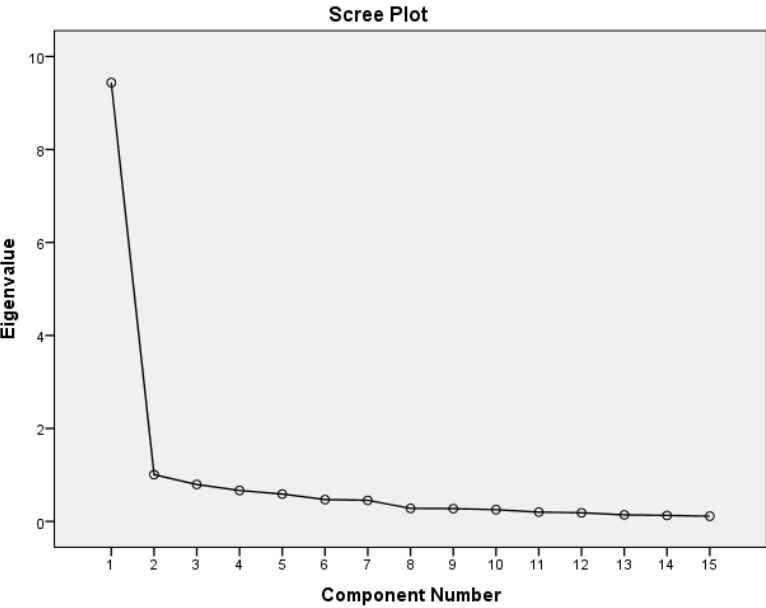
Supplementary Figure 2. *Scree plot produced during Factorial Analysis for Study 2 showing a one-factor solution.*

Supplementary Tables

Supplementary Table 1. *Case-control differences for mind wandering (MEWS), inattention (INN), hyperactivity/impulsivity (HI), emotional lability (EL), and impairment (IMP) at Time 2 and 3*

	Study 1							*Study 2*						
	ADHD			Control				ADHD			Control			
	N	M	SD	N	M	SD	*p*	N	M	SD	N	M	SD	*p*
Time 2														
MEWS	24	18.87	10.15	36	5.44	7.13	<.0001	68	24.09	10.60	-	-	-	-
INN	30	15.17	6.54	38	3.26	3.41	<.0001	68	23.25	7.91	-	-	-	-
HI	29	11.76	6.00	38	2.71	2.78	<.0001	68	17.10	6.36	-	-	-	-
EL	30	39.03	10.84	39	23.26	9.46	<.0001	68	21.56	10.65	-	-	-	-
IMP	30	0.87	0.41	38	0.26	0.29	<.0001	68	0.95	0.50	-	-	-	-
Time 3														
MEWS	-	-	-	-	-	-	-	55	24.62	11.10	-	-	-	-
INN	-	-	-	-	-	-	-	54	23.65	7.52	-	-	-	-
HI	-	-	-	-	-	-	-	54	17.11	6.43	-	-	-	-
EL	-	-	-	-	-	-	-	55	20.58	11.69	-	-	-	-
IMP	-	-	-	-	-	-	-	55	0.90	0.51	-	-	-	-

Supplementary Table 2. *Case-control differences for each domain of impairment at each time point*

| | Study 1 | | | | | | | Study 2 | | | | | | |
| | ADHD | | | Control | | | | ADHD | | | Control | | |
Time 1	N	M	SD	N	M	SD	*p*	N	M	SD	N	M	SD	*p*
Family Life	41	1.04	0.66	47	0.25	0.34	<.0001	80	1.17	0.76	30	0.23	0.30	<.0001
Work	39	1.31	0.63	39	0.22	0.39	<.0001	68	1.27	0.74	26	0.11	0.19	<.0001
School	31	1.90	0.61	38	0.37	0.46	<.0001	40	1.88	0.64	10	0.18	0.28	<.0001
Life-Skills	47	1.47	0.53	41	0.40	0.40	<.0001	80	1.50	0.64	30	0.27	0.25	<.0001
Self-Concept	47	1.69	0.87	41	0.56	0.55	<.0001	80	1.78	0.92	30	0.43	0.54	<.0001
Social	47	1.01	0.59	41	0.20	0.28	<.0001	80	1.09	0.69	30	0.12	0.19	<.0001
Risk Taking	47	0.65	0.49	41	0.23	0.26	=.001	80	0.64	0.46	30	0.16	0.19	<.0001
Time 2														
Family Life	30	0.59	0.44	38	0.24	0.39	<.0001	67	0.85	0.70	-	-	-	-
Work	27	1.04	0.56	24	0.17	0.26	<.0001	54	0.91	0.68	-	-	-	-
School	20	1.56	0.74	24	0.32	0.51	<.0001	26	1.41	0.79	-	-	-	-
Life-Skills	30	1.00	0.55	38	0.40	0.51	<.0001	68	1.27	0.62	-	-	-	-
Self-Concept	29	1.30	0.79	38	0.51	0.52	<.0001	68	1.49	0.98	-	-	-	-
Social	29	0.71	0.48	38	0.18	0.25	<.0001	68	0.82	0.62	-	-	-	-
Risk Taking	29	0.40	0.38	38	0.18	0.21	=.001	68	0.49	0.43	-	-	-	-
Time 3														
Family Life	-	-	-	-	-	-	-	54	0.81	0.70	-	-	-	-
Work	-	-	-	-	-	-	-	42	0.89	0.73	-	-	-	-
School	-	-	-	-	-	-	-	16	1.33	0.88	-	-	-	-
Life-Skills	-	-	-	-	-	-	-	55	1.23	0.65	-	-	-	-
Self-Concept	-	-	-	-	-	-	-	55	1.33	0.92	-	-	-	-
Social	-	-	-	-	-	-	-	55	0.80	0.68	-	-	-	-
Risk Taking	-	-	-	-	-	-	-	55	0.46	0.37	-	-	-	-

Supplementary Table 3. *ROC Analysis curve coordinates showing sensitivity and specificity of the 15-item MEWS in the MIRIAD study. Optimum balance of sensitivity (.88) and specificity (.88) is at threshold 15.00*

Test result	Sensitivity	1 - Specificity
-1.00	1.000	1.000
.50	1.000	.667
1.50	1.000	.583
2.50	.920	.542
3.50	.880	.292
5.00	.880	.250
6.50	.880	.208
10.50	.880	.167
15.00	.880	.125
16.50	.840	.125
18.50	.800	.083
22.00	.800	.042
24.50	.680	.042
25.50	.600	.000
27.00	.440	.000
28.50	.400	.000
29.50	.360	.000
30.50	.280	.000
32.00	.240	.000
33.50	.160	.000
35.00	.120	.000
37.50	.040	.000
40.00	.000	.000

Supplementary Table 4. *ROC Analysis curve coordinates showing sensitivity and specificity of the 15-item MEWS in the OCEAN study. Optimum balance of sensitivity (.90) and specificity (.90) is at threshold 15.00*

Test result	Sensitivity	1 - Specificity
-1.00	1.000	1.000
.50	1.000	.931
1.50	1.000	.759
2.50	1.000	.724
3.50	1.000	.655
4.50	1.000	.621
5.50	.987	.552
7.00	.987	.379
8.50	.987	.345
9.50	.987	.310
10.50	.975	.241
11.50	.949	.207
13.00	.924	.207
14.50	.911	.138
15.50	.899	.103
17.00	.848	.103
18.50	.810	.069
19.50	.785	.069
20.50	.759	.069
21.50	.759	.034
22.50	.734	.000
23.50	.684	.000
24.50	.671	.000
25.50	.633	.000
26.50	.582	.000
27.50	.557	.000
28.50	.443	.000
29.50	.418	.000
30.50	.354	.000
31.50	.329	.000
32.50	.304	.000
33.50	.278	.000
34.50	.253	.000
35.50	.215	.000
37.00	.177	.000
38.50	.152	.000
39.50	.139	.000
40.50	.127	.000
41.50	.076	.000
42.50	.063	.000
43.50	.025	.000
45.00	.000	.000

Supplementary Table 5. *ROC Analysis curve coordinates showing sensitivity and specificity of the 12-item MEWS in the OCEAN study. Optimum balance of sensitivity (.89) and specificity (.90) is at threshold 15.00*

Test result	Sensitivity	1 - Specificity
-1.00	1.000	1.000
.50	1.000	.897
1.50	1.000	.759
2.50	1.000	.724
4.00	1.000	.483
6.50	.987	.345
8.50	.975	.276
9.50	.937	.207
10.50	.924	.172
11.50	.911	.138
12.50	.886	.103
13.50	.873	.103
14.50	.848	.103
15.50	.835	.069
16.50	.797	.069
17.50	.785	.000
18.50	.759	.000
19.50	.722	.000
20.50	.684	.000
21.50	.646	.000
23.00	.570	.000
24.50	.494	.000
25.50	.430	.000
27.00	.342	.000
28.50	.316	.000
29.50	.266	.000
30.50	.215	.000
31.50	.177	.000
32.50	.152	.000
33.50	.127	.000
34.50	.114	.000
35.50	.063	.000
37.00	.000	.000

Supplementary Table 6. *Cross-scale correlations between the mind wandering (MEWS), inattention (INN), hyperactivity/impulsivity (HI), emotional lability (EL), and impairment (IMP) rating scales in cases and controls*

Study 1								
Time 1	INN		HI		EL		IMP	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
MEWS	0.50*	0.87***	0.38	0.81***	0.63**	0.74***	0.56**	0.75***
INN			0.62***	0.77***	0.48**	0.66***	0.58***	0.68***
HI					0.61***	0.64***	0.59***	0.69***
EL							0.53***	0.77***
Study 2								
Time 1	INN		HI		EL		IMP	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
MEWS	0.50***	0.38*	0.36**	0.23	0.58***	0.65***	0.67***	0.56**
INN			0.46***	0.35	0.23**	0.52**	0.46***	0.57**
HI					0.13	0.35	0.23*	0.59**
EL							0.62***	0.56**

* $p < .05$, ** $p < .01$, *** $p < .001$

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Appendix D: Supplementary material for Chapter 5

Mowlem, F.D., Agnew-Blais, J., Pingault, JB, & Asherson, P. Evaluating a scale of excessive mind wandering among males and females with and without ADHD from a population sample.

Supplementary Table S1. Details of the study measures

Supplementary Table S2. Details of the constraints applied to the 3 models used to test measurement invariance

Supplementary Table S3. Mean scores (SD) for the study subscales stratified by sex and self-reported ADHD diagnostic status, comparing males to females, and those with ADHD to those without ADHD

Supplementary Fig S1. Scree plot for EFA

Supplementary Table S1. Details of the study measures

Measure	Length	Scoring	Maximum score	Cronbach's alpha
The Mind Excessively Wandering Scale (MEWS) [1]	12 items	4-point likert scale *Not at all or rarely* [0], *Some of the time* [1], M*ost of the time* [2], N*early all of the time or constantly* [3]	36	.95
The Mind Wandering Spontaneous Scale (MW-S) [2]	4 items	7-point likert scale *Rarely* [1] to *A lot* [7], or *Almost never* [1] to *Almost always* [7]	28	.86
The Mind Wandering Deliberate Scale (MW-D) [2]	4 items	7-point likert scale *Rarely* [1] to *A lot* [7]*, or Not at all true* [1] *to Very true* [7]	28	.84
Barkley Adult ADHD Rating Scale [3]	18 items (9 items for inattention, 9 items for hyperactivity/impulsivity)	4-point likert scale *Never or Rarely* [0], *Sometimes* [1], *Often* [2], *Very Often* [3]	54 (27 per subscale)	Entire scale: .93 Inattention: .92 Hyperactivity: .86
Barkley Current Behaviour Scale Self-report [3]	10 items	4-point likert scale *Never or Rarely* [0], *Sometimes* [1], *Often* [2], *Very Often* [3] A '*Not Applicable'* option is available, which should be selected if the item refers to an area that is not part of their life (e.g., they do not drive), as opposed to not experiencing impairment in that domain.	30	.93
The Affective Reactivity Index (ARI) [4]	7 items (6 symptom items, 1 impairment item)	3-point likert scale *Not True* [0], *Somewhat True* [1], *Certainly True* [2]	12	.86
The Mental Health Continuum-Short Form (MHC-SF) [5]	14 items (6 items for psychological wellbeing, 5 items for social wellbeing, 3 items for emotional wellbeing)	6-point likert scale *Never* [0], *Once or twice* [1], *About once a week* [2], *About 2 or 3 times a week* [3], *Almost every day* [4], *Every day* [5]	70	.92

Supplementary Table S2. Details of the constraints applied to the 3 models used to test measurement invariance

|	Loadings	Thresholds	Item residual variances	Factor variance	Factor mean
Configural	Free to vary in both groups (one factor loading fixed at 1 for scaling purposes)	Free to vary in both groups	Fixed at 1	Free to vary in both groups	Fixed at 0 (for identification purposes)
Metric	Equal across groups	Free (first threshold of each item is held equal across groups, and second threshold of the item used to set the metric of the factor is held equal across groups)	Fixed at 1 in first group and free in the other	Free to vary in both groups	Fixed at 0 in first group and free in the other
Scalar	Equal across groups	Equal across groups	Fixed at 1 in first group and free in the other	Free to vary in both groups	Fixed at 0 in first group and free in the other

Supplementary Table S3. Mean scores (SD) for the study subscales stratified by sex and self-reported ADHD diagnostic status, comparing males to females, and those without ADHD to those with ADHD

	Whole sample (*n*=1379-1484)	Females (*n*=984-1059)	Males (*n*=395-425)	Males vs Female		ADHD (*n*=198)	No ADHD (*n*=1180-1181)	No ADHD vs ADHD	
	M (SD)	M (SD)	M (SD)	*p*	Cohen's d (95% CI)	M (SD)	M (SD)	*p*	Cohen's d (95% CI)
MEWS	17.16 (9.21)	16.57 (9.11)	18.65 (9.29)	**.001**	.23 (.11, .34)	25.75 (7.32)	15.77 (8.68)	**<.001**	-1.17 (-1.33, -1.02)
MW-S	18.96 (5.66)	18.61 (5.75)	19.84 (5.34)	**.002**	.23 (.10, .33)	23.44 (4.18)	18.24 (5.49)	**<.001**	-.98 (-1.13, -.82)
MW-D	17.75 (5.88)	17.25 (5.87)	17.95 (5.87)	**.004**	.12 (.01, .23)	17.25 (6.62)	17.65 (5.69)	1.0	.07 (-.08, .22)
INN	10.84 (6.97)	9.97 (6.71)	12.98 (7.12)	**<.001**	.44 (.33, .55)	18.92 (5.10)	9.49 (6.30)	**<.001**	-1.54 (-1.70, -1.37)
HI	9.08 (5.86)	8.66 (5.70)	10.15 (6.10)	**<.001**	.26 (.14, .37)	15.46 (5.94)	8.04 (5.09)	**<.001**	-1.42 (-1.58, -1.26)
EL	3.00 (2.93)	2.93 (2.86)	3.19 (3.10)	.17	.09 (-.02, .20)	4.04 (3.08)	2.75 (2.82)	**<.001**	-.45 (-.60, -.30)
IMP	1.06 (0.79)	0.99 (0.77)	1.25 (0.79)	**<.001**	.34 (.22, .45)	1.95 (0.60)	0.92 (0.72)	**<.001**	-1.47 (-1.63, -1.30)
WB	49.61 (14.32)	50.61 (14.31)	47.12 (14.04)	**<.001**	-.25 (-.36, -.13)	45.40 (13.42)	50.32 (14.35)	**<.001**	.35 (.19, .50)

Note. MEWS = Mind Excessively Wandering Scale; MW-S = Mind Wandering Spontaneous; MW-D = Mind Wandering Deliberate; INN = inattention; HI = hyperactivity/impulsivity; EL = emotional lability; IMP = impairment; WB = wellbeing.

Statistical analysis adjusted for age.

Statistically significant findings are presented in bold.
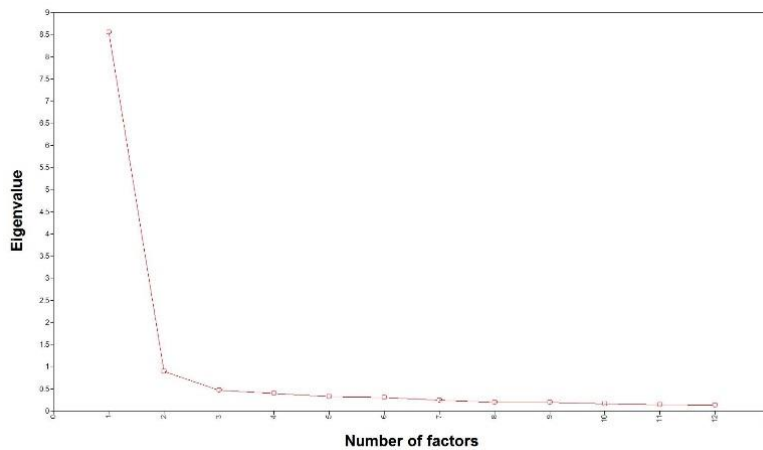
Supplementary Fig S1. Scree plot for EFA

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