Chapter 1

Review and Methodology: Genetic and Environmental Epidemiology of Attention-Deficit Hyperactivity Disorder In Young Australian Adults

Abstract

Attention-deficit hyperactivity disorder has long been recognised as a syndrome in children that is neurological in origin. The diagnostic criteria for ADHD have changed over time possibly reflecting the neuropsychological and behavioural heterogeneity that is characteristic of ADHD. The interviews and scales used to measure symptoms have reasonable reliability but convergent validity is low, reducing the comparability of research findings. ADHD may best be represented by categorical and dimensional measurement of symptoms to provide alternative perspectives of symptom expression, increasing our understanding of the variation in symptoms found across age and sex. Children and adults exposed to environmental adversity, for example family conflict, physical and emotional neglect, low socio-economic status, are frequently found to have a higher prevalence of ADHD. There have also been several genes consistently associated with this diagnosis: *COMT*, *DRD1*, *DRD2*, *DRD4*, *DRD5*, *MAOA*, *SLC6A2*, *SLC6A3*, *SLC6A4*, *SLC9A9* and *SNAP25*. These environmental and genetic factors are reviewed along with their possible involvement in the aetiology of ADHD. Additionally, the latent class analyses, classical twin studies and genome-wide association studies used to examine the environmental and genetic epidemiology of ADHD in Australian adults are presented and discussed.

1.1. Introduction to Attention Deficit Hyperactivity Disorder

Attention-deficit/hyperactivity disorder (ADHD) describes a syndrome comprising inattentive, hyperactive and impulsive behaviours that start in early childhood (see Table 1.1). These symptoms occur together more frequently than chance and people affected by ADHD, experience lower levels of academic achievement; deficits in cognitive, social and family functioning; more accidents while driving (Barkley, Murphy, Dupaul & Bush, 2002); impaired work performance (De Graaf et al., 2008) and increased unemployment. A moderate to high percentage of children, adolescents and adults with this syndrome experience comorbid disorders: 53% oppositional defiant disorder, 33% conduct disorder, 36% alcohol dependence, 42% multiple anxiety disorders, 40% overanxious disorder, 20% generalized anxiety disorder, 33% social phobia and 22% suffer from enuresis (Biederman, Faraone, Spencer & Wilens, 1993; Kessler et al., 2006). Despite these findings controversy still occurs in relation to the validity and aetiology of this diagnosis (Barkley, Cook, et al., 2002; Thapar, Cooper, Eyre & Langley, 2013). There is however no better indication of the validity of a disorder than people with symptoms across cultures and ages reliably reporting that these behaviours make their lives more difficult across multiple domains (De Graaf et al., 2008; Polanczyk & Rohde, 2007).

Table 1.1

Diagnostic Criteria for Attention-Deficit/Hyperactivity Disorder (ADHD)

Inattention	Hyperactivity-impulsivity
1-often fails to give close attention to details or makes careless mistakes in schoolwork, work or other activities	1-often fidgets with hands or feet or squirms in seat
2 -often has difficulty sustaining attention in tasks or play activities	2-often leaves seat in classroom or in other situations in which remaining seated is expected
3-often does not seem to listen when spoken to directly	3-often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)
4-often does not follow through on instructions and fails to finish school-work chores, or duties in the work-place (not due to oppositional defiance or a failure to understand instructions)	4-often has difficulty playing or engaging in leisure activities quietly
5-often has difficulty organizing tasks and activities	5-is often “on the go” or often acts as if “driven by a motor”
6-often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as school-work or home-work)	6-often talks excessively
7-often loses things necessary for tasks or activities (e.g. toys, school assignments, pencils, books, or tools)	Impulsivity
8-is often easily distracted by extraneous stimuli	7-often blurts out answers before questions have been completed
9-is often forgetful in daily activities	8-often has difficulty awaiting turn
	9-often interrupts or intrudes on others (e.g. butts into conversations or games)

Note: Full diagnostic criteria for the Diagnostic and Statistical Manual of Mental Disorders (4th edition) : *(A)* six inattentive and/or hyperactive-impulsive symptoms; *(B)* symptom onset by the age of 7 years; *(C)* experienced within two life domains; *(D)* problems resulted from ADHD symptoms; and *(E)* exclusion of autism and Asperger’s.

1.2. Medical Recognition of ADHD Symptoms

1.2.1. History of ADHD

The syndrome of ADHD was first described around 200 years ago. In 1798 Alexander Crichton a Scottish physician differentiated two forms of inattention: the first was described as an unnatural nervous over-activity that left affected individuals unable to focus on any one thing. The second form was said to result from depletion in attention associated with either tiredness or injury; i.e. head injury, poor nutrition, epilepsy, or brain tumour (Lange, Reichl, Lange, Tucha & Tucha, 2010; Palmer & Finger, 2001). From a different perspective, in 1851 Heinrich Hoffman a German psychiatrist wrote a children's book describing problematic inattentive and hyperactive-impulsive behaviour via the characters *fidgety Phil* and *Johnny Look-in-the-air* (Thome & Jacobs, 2004), indicating the cross-cultural and problematic symptoms of ADHD. In London during 1902, lectures by the paediatrician George Still were directed toward several conditions in children that appeared to encompass inattention, hyperactivity-impulsivity, conduct problems and autism (Lange et al., 2010; Still, 2006), a group of disorders that are often comorbid (Diamantopoulou, Verhulst & van der Ende, 2010; Ronald, Simonoff, Kuntsi, Asherson & Plomin, 2008).

Both Crichton and Still recognized ADHD symptoms could occur following or in the absence of disease or injury and were neurological in origin. This led to a change in the conceptualization of ADHD from minimal brain damage to minimal brain dysfunction, due to the observation that ADHD symptoms were evident when trauma was not (Lange et al., 2010). The differentiation of ADHD symptoms resulting from varied aetiological factors remains a necessary distinction in diagnosis.

1.2.2. Diagnostic Criteria for ADHD

The Diagnostic and Statistical Manual of Mental Disorders (DSM; American Psychiatric Association, 2000) was developed as a system to facilitate hypothesis free assessment of psychiatric disorder. Diagnostic criteria for ADHD were included in the second edition (II) of the DSM in 1968 and initially described as *hyperkinetic reaction of childhood* (Lazar & Frank, 1998). In the DSM-III (American Psychiatric Association, 1980) a pure inattentive subtype was recognized with a change in the diagnostic label to *attention-deficit disorder with and without hyperactivity*.

Symptoms were redefined again in the DSM-III text revision (TR: American Psychiatric Association, 1987), into an overarching label – *attention-deficit/ hyperactivity disorder* and the diagnosis of the inattentive subtype changed to *undifferentiated attention-deficit disorder*. In the 1994 edition of the DSM (IV) three ADHD subtypes were recognised: *inattention, hyperactivity-impulsivity and combined type*. These subtypes remained unchanged in the DSM-IV text revision (American Psychiatric Association, 2000). The numerous changes in diagnostic criteria may reflect the heterogeneity that is characteristic of ADHD, and indicate the ambiguity associated with the definition of subtypes and aetiology of symptoms.

Until recently there had been no differentiation between diagnostic criteria for children and adults (Lahey, Applegate, McBurnett & Biederman, 1994) and field studies of ADHD had previously included only participants under the age of 17. The duration of the syndrome into adulthood was recognized via wording of symptom criterion A.1 – *often fails to give close attention to detail or makes careless mistakes in schoolwork, **work** or other activities* and criterion C – *some impairment from the symptoms is present in two or more settings (e.g., at school [**or work**] and at home)* only (American Psychiatric Association, 2000, p. 92). There are an increasing number of studies providing data on adults (De Graaf et al., 2008; Fayyad et al., 2007; Kessler, Adler, Ames, Demler, et al., 2005; Kooij, Boonstra, Swinkels, et al., 2008). Based on this work, proposed changes in diagnostic criteria for adults for the DSM-5 include a drop in symptom criterion A from six to five symptoms and an increase in the age of onset from 7 to 12 (American Psychiatric Association, 2013). Examples of behaviours likely to be exhibited by adults with ADHD are also provided to increase diagnostic accuracy.

As an alternative to the DSM, the International Statistical Classification of Diseases and Related Health Problems 10th edition (ICD-10; World Health Organization, 1992), classifies ADHD within chapter 5 – *Mental and behavioural disorders* under the classification hyperkinetic disorders: Disturbance of activity and attention. The ICD-10 is used most prominently for resource allocation and the development of health systems in contrast to the primarily clinical use of the DSM. Within this body of work ADHD is diagnosed according to criteria outlined in the DSM-IV and DSM-IV-TR.

1.3. International Prevalence Rates for Adult ADHD

ADHD appears to be most prevalent from mid to late childhood showing a decline into adulthood. A recent meta-analysis of ADHD prevalence rates found 10.5% (8.9% - 12.5%) of children aged from 3 to 5 met DSM-IV-TR diagnostic criteria. Estimates were 11.4% (9.8% - 13.3%) for the age range 6 to 12 and 8.0% (4.4% - 14.3%) for ages 13 to 18. The rate for participants 19-years and older dropped to 5.0% (4.1% - 6.2%; Willcutt, 2012) indicating the persistence of the syndrome was approximately 44%. Table 1.2 presents international unadjusted rates for adults by study adapted from Willcutt (2012), notably none were conducted in Australia.

Table 1.2

International Prevalence of DSM-IV ADHD in Adulthood

Location	No. of Studies	Age Range	Prev. %	Author
Italy	1	17-35	1.0	DuPaul (2001)
NZ	1	17-51	2.7	DuPaul (2001)
USA	7	17-49	3.4	DuPaul (2001)
		>18	2.6	Faraone (2005)
		17-46	4.0	Heiligenstein (1998)
		18-44	4.4	Kessler (2006)
		16-22	7.5	McKee (2008)
		17-84	7.4	Murphy (1996)
		18-29	7.7	Ramtekkar (2010)
		18-75	6.9	Sprafkin (2007)

Note: DSM-IV diagnostic criteria were used to define ADHD in each of these studies

The estimates supplied by DuPaul (2001), Heiligenstein, Conyers, Berns and Miller (1998) and McKee (2008) were calculated within samples of college students. People affected by ADHD have a reduced likelihood of attaining a college education (De Graaf et al., 2008) suggesting that the estimates found within these studies are conservative.

Broadly defined prevalence estimates of ADHD are sometimes used in adult samples because of possible variation in the expression of symptoms (Das, Cherbuin, Butterworth, Anstey & Easteal, 2012; Kooij et al., 2005). The study conducted by Faraone and Biederman (2005) with data from 966 randomly selected adults provided two estimates – the first, listed in Table 1.2 (2.6%) was calculated using full diagnostic criteria. A second broad estimate indicated 16.4% of adults within the sample were adversely affected by symptoms, but did not meet DSM-IV diagnostic criteria. Prevalence rates provided in Table 1.2 were based on childhood DSM-IV

diagnostic criteria and may not provide a representative measure of ADHD within an adult population (Kessler et al., 2006).

In childhood the male to female ratio for positive diagnoses is 9:1 (American Psychiatric Association, 2000) and young females more often present with symptoms of inattention. In a US sample of adults within the age range 18 to 44, the male to female ratio dropped to 1.7:1. Within a Dutch sample females aged from 18 to 75 were found to have more symptoms of ADHD than men (2.5:1) when using a four-symptom threshold (Kooij et al., 2005) and for these women hyperactive-impulsive symptoms predicted the poorest outcome.

Prevalence estimates vary with the diagnostic criteria used to define clinical significance (Mannuzza, Klein & Moulton, 2003) and with sex. The most appropriate symptoms criteria for adults may differ from those most problematic during childhood (Barkley & Murphy, 2006). In support of this, past research has indicated that adults with four symptoms of either inattention or hyperactivity-impulsivity were significantly more functionally impaired than adults with fewer symptoms (Das et al., 2012; Kooij et al., 2005). Even though a proposal has been made to reduce the symptom criterion for adults within the DSM-5 to 5 (American Psychiatric Association, 2013), impairment may still be evident for those who fall below this diagnostic threshold and if symptoms vary from the 18-items relevant during childhood and adolescence.

1.4. Measurement of Symptoms

ADHD is measured using standardized questionnaires and/or clinical interviews that contain direct correspondence to the 18-symptom criteria listed in the three most recent DSMs. The purpose of data collection across research and clinical settings varies as do the people providing the data. So there are important considerations involved in the selection of appropriate samples and measures for research. For example does the test adequately measure ADHD? Was test standardization done using a population similar to the one under study and of adequate size? Are questionnaire items relevant and unambiguous? How long is the test and will presentation of items produce biased responding? Are the reliability coefficients above the .7 considered adequate for research purposes? And will the test allow me to directly answer my research question? ADHD questionnaires vary in their method of scoring and the range of behaviours addressed beyond the 18-symptom criteria for ADHD. There is also variation in ratings of ADHD with the informant that need to be considered.

1.4.1. Rater Effects

In childhood, data on the incidence of ADHD symptoms is generally collected from parents, teachers or trained interviewers. During adolescence collecting self-reported ADHD becomes more feasible, providing an additional perspective on ADHD expression in addition to teacher, parent and clinician report of symptoms. Adult ADHD data are most often self-reported.

1.4.1.1. Rater Effects on the Prevalence of ADHD

Research examining the effect of behavioural informant on ADHD prevalence rates (Barkley, Fischer, Smallish & Fletcher, 2002; Bartels et al., 2003; Derks, Hudziak, Dolan, Ferdinand & Boomsma, 2006) have shown prevalence rates of parent and teacher report of ADHD in children of school age are approximately equal. For the inattentive subtype prevalence for parent and teacher report of symptoms were respectively 3.9% and 4.7%, for hyperactivity-impulsivity corresponding estimates were 1.1% and 0.3% and for combined symptoms both parent and teacher rated ADHD indicated a prevalence rate of 2.2% (Burns, Walsh & Gomez, 2003). However, agreement between parent and teacher report is often found to be low (Malhi, Singhi & Sidhu, 2008; McLoughlin, Ronald, Kuntsi, Asherson & Plomin, 2007).

In adulthood teachers no longer report on symptoms and the prevalence of ADHD in young adults has been found to differ between parent and self-reported behaviours; within this study probands reported on their current symptoms and parents provided a retrospective report of behaviours. However, prevalence estimates for self-reported symptoms were 1.2% and 4.6% for males and females respectively and corresponding estimates calculated using parent report data were 5.6% and 1.6% (Dong Hun, Oakland, Jackson & Glutting, 2008). Generally agreement between investigator, partner, proband and clinican ratings of ADHD are also low for adults (Adler et al., 2008; Kooij, Boonstra, Swinkels, et al., 2008).

1.4.1.2. Rater Effects on the Heritability of ADHD

Heritability estimates also vary with rater. Estimates for parent, teacher and self-reported symptoms in a sample of adolescents were .82 (.80-.83), .60 (.58-.63) and .48 (.21-.74) respectively (Merwood et al., 2013). The heritability of ADHD in adults is typically lower than for children and this difference is confounded with the move from parental to self-report of symptoms (Kan

et al., 2012). The decline in heritability estimates of ADHD for adults could be due to the increased influence of environmental factors in symptom moderation. For example adults are more able to select environments in which their symptoms are not problematic. This decline could also be due to increased error variance when two rather than one person is reporting on behaviours of twins within a pair, but no work has directly addressed this.

1.4.2. Scales and Interviews

1.4.2.1. Interviews

Two interviews appear prominently in research, the Diagnostic Interview Schedule (DIS; Robins, Helzer, Croughan & Ratcliff, 1981) and the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA; Bucholz, Cadoret, Cloninger & Dinwiddie, 1994).

1.4.2.1.1. The Diagnostic Interview Schedule. The DIS is a fully-structured interview that was designed for an epidemiological study by the National Institutes of Mental Health permitting administration by untrained people. The normative sample included 216 children and adolescents (Robins, Helzer, Croughan & Ratcliff, 1981). Questions directed to respondents are closed ended and responses are coded as either yes or no. The DIS covers a range of psychiatric disorders including ADHD, updated to the current DSM (Miller, 2010). The interview takes approximately 90-minutes to 150-minutes to administer and includes retrospective assessment of childhood ADHD and a question asking participants whether or not symptoms have continued into adulthood so does not directly address the current manifestation of adult symptoms.

1.4.2.1.2. The Semi-Structured Assessment for the Genetics of Alcoholism. The SSAGA is a psychiatric interview developed for assessment of physical, psychosocial and psychiatric presentations of alcohol abuse and dependence and includes an assessment of adult ADHD based on DSM-III-R and DSM-IV diagnostic criteria and the ICD-10. The SSAGA is highly structured and as such can be administered by lay people. This interview has been translated into seven language, is widely used and reliabilities and test validity have been established in several studies (Bucholz et al., 1994; Hesselbrock, Easton, Bucholz, Schuckit & Hesselbrock, 1999). The strength of this interview is the poly-diagnostic criteria – this allows comparability of measures across studies.

1.4.2.2. Scales

Scales are a less expensive alternative to interviews, the Conner's Adult ADHD rating Scale (CAARS), the ADHD rating scale (ADRS) and the Strengths and Weaknesses of ADHD and Normal Behaviour Scale (SWAN) are used in community-based samples to measure ADHD symptoms. Questionnaire items correspond to the symptom criteria of the DSM-IV. Responses are coded as either binary *yes*/*no* response, as 4-point severity scores ranging from *no symptom* to *often experiences symptom* or as a dimensional trait that allows both positive and negative symptom expression.

1.4.2.2.1. The Conner's Adult ADHD Rating Scale. The CAARS (Conners, Erhardt & Sparrow, 1999) uses a severity score and has long and shortened versions written for both self and informant report. The standardization sample included approximately 1000 adults aged from 18 to 80 drawn randomly from the population of the United States (US). The domains measured by the 66-items within this questionnaire include inattention/memory problems, hyperactivity/ restlessness, impulsivity/emotional lability and problems with self-concept, measuring additional aspects of ADHD related behaviours.

1.4.2.2.2. The ADHD Rating Scale. The ADRS (DuPaul et al., 2001) is also based on a severity score. The ADRS includes 18-items referring directly to the 18-symptom criteria for diagnosis of ADHD from the DSM-IV and is often used for adults. This scale was standardized within a sample greater than 4500 but only included children and adolescents. The value of the ADRS is the adherence to the 18-symptom criteria of the DSM-IV-TR which at this time are equivalent for children and adults, but may not accurately address symptoms in adults.

1.4.2.2.3. The Strengths and Weaknesses of ADHD and Normal Behaviour Scale. The SWAN (Swanson et al., 2005) is an 18-item scale and measures high levels of attention and appropriate activity in addition to the behaviours symptomatic of ADHD. The SWAN was designed to avoid the truncation of scores at '0' and over identification of symptoms that occur when they are recorded as absent, or present to varying degrees. This scale correspondingly increases the power of analyses because of additional information collected about the range of ADHD related

behaviours within a sample. The SWAN was standardized using a sample of 857 school aged children so still does not adequately capture how symptoms may vary for adults.

Convergent validity of the CAARS, the ADRS and the DIS inattentive and hyperactive-impulsive subscales has been tested and these measures were found to address the same ADHD DSM-IV criteria (Kooij, Boonstra, Swinkels, et al., 2008). However, reliabilities were low ranging from .09 to .34 indicating a high degree of error variance across scales. The error across measures of ADHD limits the generalizability of research findings.

Table 1.3

Reliability of Measures for Adult ADHD

Questionnaire	Test-retest (period)	Interrater (period)	Cronbach's Alpha	Reference
WRAADDS	.96	.76	.78	(Marchant et al., 2013)
	(1-2 weeks)	(1-week)		
DIS	.79	.31-.43	.76	(Shaffer, Fisher, Lucas, Dulcan & Schwab-Stone, 2000)
	(1-year)	np		
SSAGA	.75	.70	np	(Bucholz et al., 1994; Schermerhorn et al., 2012)
	np			
CAARS	.87	.44-.61	.77	(Hirsch, Hauschild, Schmidt, Baum & Christiansen, 2013)
	np	np		(Franke et al., 2008)
ADRS	.86	.38-.42	.75	(DuPaul et al., 2001)
	np	np		(Franke et al., 2008)
SWAN	.67	.34	.82	(Arnett et al., 2011)
	(1-year)	(~256-days)		

Note: np = not provided. The range of the interrater reliability represents the range of coefficients across sub- scales. Cronbach's alpha represents the mean values for inattentive and hyperactive- impulsive sub-scales. Acceptable test-retest reliability estimates for clinical use and research are .9 and .7 respectively. Interrater reliability for the SSAGA is based on assessment of anti-social personality disorder.

1.4.3. Categorical and Dimensional Representation of ADHD Symptoms

The DSM was designed to identify people with psychiatric disorders and as such groups people according to whether or not they meet diagnostic criteria. The categorization of people with specific clusters of symptoms is important clinically and in research, but it also creates arbitrary distinctions between groups of people who do and do not receive a clinical diagnosis. Research indicates that ADHD is polygenic in nature and represents the cumulative effect of multiple genetic and environmental risk and protective factors (Gottesman & Shields, 1967; Thapar, Langley, Asherson & Gill, 2007). This implies there will be intermediate quantitative phenotypes that more closely reflect the effects of these factors and do not directly correspond with a clinical diagnosis.

There has been support for inclusion of dimensional measures of psychopathology in the DSM-5, to account for variance not identified using categorical definitions of psychiatric disorder (Derks, Dolan, Hudziak, Neale & Boomsma, 2007). The use of a defining threshold could provide a limited perspective of symptom aetiology and exclude people disadvantaged by ADHD due to variation in symptom expression across age and sex in unanticipated ways. ADHD in adults may not be accurately represented by our current measures (Barkley, Murphy & Fischer, 2010) and there appear to be sex specific effects in prevalence rates (American Psychiatric Association, 2000) and in genetic studies of ADHD (Biederman et al., 2008b). For example, the *T* allele of rs3785143 on *SLC6A2* had an association with ADHD in females ($p = .006$) and not males ($p > .05$), the val108/Met158 allele of *COMT* was found to be over expressed in males ($p = .003$) and rs3027399 on *MAOA* showed an association with ADHD in females ($p = .02$) but not males ($p > .05$). Both categorical and dimensional measurement of symptoms may provide the most precise system of measurement in research and clinical settings for complex disorders influenced by multiple environmental and genetic effects such as ADHD that also may vary by sex.

1.5. The Aetiology of ADHD

1.5.1. Environmental Risk Factors

A broad range of environmental factors have been implicated in the aetiology of ADHD. These include exposure to environmental toxins, for example lead, manganese, polychlorinated biphenyl (Banerjee, Middleton & Faraone, 2007; Byun et al., 2013; Polanska, Jurewicz & Hanke, 2013; Sioen et al., 2013), complications in pregnancy, for example preeclampsia, eclampsia, poor maternal health, postmature birth, long labour, low birth weight, antepartum haemorrhage, alcohol consumption, smoking, (Langley, Holmans, Van Den Bree & Thapar, 2007; Mill & Petronis, 2008) and psychosocial adversity (Biederman, Faraone & Monuteaux, 2002a; Laucht et al., 2007). The focus of this work will be on psychosocial adversity, including a range of environmental factors associated with poor outcomes such as emotional and physical neglect, family conflict, low socioeconomic status, parental alcohol abuse, and childhood sexual assault. Confounding factors exist between these variables, both men and women from low socioeconomic status are more likely to smoke (Hiscock, Bauld, Amos, Fidler & Munafo, 2012) and drink (May et al., 2013) increasing the probability of foetal exposure to nicotine and alcohol, two risk factors for ADHD.

1.5.1.1. Family Conflict

Family conflict is one environmental factor which in combination with others leads to higher levels of ADHD related impairment in a quantitative fashion, and this effect has been found across several studies (Biederman, Faraone, et al., 2002a; Martel, 2013; Mohammadi et al., 2012; Sugaya et al., 2012). Family conflict has been shown to endow a greater risk for ADHD than either low-socioeconomic status or paternal anti-social behaviour (Biederman, Faraone, et al., 2002a). Although the experience of dealing with a child with difficult behaviours is associated with higher levels of marital conflict (Wymbs & Pelham, 2010), this effect does not appear to influence ADHD in children (Knopik et al., 2006). This suggests that the relationship between ADHD and family conflict may be genetically driven and represent a gene-environment correlation (Rutter, Moffitt & Caspi, 2006). Additionally, sex has been found to moderate the relationship between ADHD related impairment and family conflict (Biederman, Faraone, et al., 2002a), with boys at higher risk for developing learning disorders and cognitive impairment than girls. These effects have not been examined in adults.

1.5.1.2. Physical and Emotional Neglect

Physical and emotional neglect are strong predictors for a range of psychiatric disorders including ADHD (Buschgens et al., 1996; Famularo, Kinscherff & Fenton, 1992; Sesar, Šimić & Barišić, 2010). For example, differential parental treatment in the form of harsh discipline and negative feeling is associated with symptoms of hyperactivity-impulsivity in 4-year old MZ twins (Asbury, Dunn, Pike & Plomin, 2003). Similarly, adults with ADHD are more likely to report physical abuse during childhood (Sugaya et al., 2012). Notably, higher levels of dysfunction have been found in parents of children with ADHD (Bornovalova, Blazei, Malone, McGue & Iacono, 2012) and alcohol dependence in mothers has been linked to higher levels of ADHD in girls (Hill, Tessner & McDermott, 2011). This indicates the intimate relationship between genes and environments – a parent with a psychiatric disorder may provide a less nurturing family environment for a child, and the genes that predispose them to ADHD.

1.5.1.3. Low Socioeconomic Status

Low socioeconomic status has been associated with ADHD as one of a combination of risk factors that leads to increased risk for diagnosis (Martel, 2013) however the direction of this

effect remains unclear. Adults with ADHD generally have a lower income than adults without ADHD and these adults also transmit ADHD risk genes to their children. A study of monozygotic twin differences in ADHD symptoms and parental socio-economic status indicated twins concordant for high levels of ADHD were more likely to be from a lower socio-economic background (Lehn et al., 2007). But within this study genetic effects and environmental experience are confounded. However, low family income is associated with a number of other environmental risk factors for example parental psychopathology, smoking behaviours (Hiscock et al., 2012) and higher probability of exposure to environmental pollutants. Socioeconomic status does not appear to affect the persistence of symptoms in boys (Biederman, Mick, et al., 2002). But boys have been found to experience more impairing symptoms of ADHD when they are from a low socioeconomic background in combination with additional environmental risk factors than girls with ADHD.

1.5.2. Gene-Environment Interactions

There is an interplay between genetic and environmental factors leading to higher or lower levels of ADHD symptom expression (Thapar, Langley, Asherson, et al., 2007). For example not all children exposed to environmental adversity develop symptoms of ADHD and, conversely not all children with diagnosed ADHD have been exposed to environmental adversity, gene-environment interactions may account for this. A polymorphism of *SLC6A1* has been found to moderate the effect of maternal warmth on the development of conduct problems for adolescents with ADHD (Sonuga-Barke et al., 2008). Similarly, girls with a 10-repeat *SLC6A3* polymorphism who reported maltreatment were found to have more symptoms of ADHD than boys or girls without the 10-repeat polymorphism or than those with this polymorphism who had not been exposed to maltreatment (Li & Lee, 2012). These studies explicate the way genes and environments may interact but neither of these results has been replicated.

1.5.3. Genetic Risk Factors

Twin studies have consistently shown the broad-sense heritability of ADHD in children ranges around 70% (Derks et al., 2007; Hay, Bennett, McStephen, Rooney & Levy, 2004). Estimates drop in adulthood (Boomsma et al., 2010; Larsson et al., 2013) to a range of 30% to 50% but reasons for this are not clear. Complex disorders appear to be influenced by multiple genes

each with relatively low effect size and penetrance (Hindorff et al., 2009; Hirschhorn & Daly, 2005) in contrast to the single highly penetrant polymorphism found for Mendelian disorders, and these are likely to differ across age groups. Genes in the dopaminergic, noradrenergic and serotonergic systems have been the focus of genetic studies of ADHD due to the mechanisms of action for ADHD medication (Biederman, 2005) and evidence for their involvement in symptoms (Solanto, 1998). Following are several summaries describing genes that have shown associations with diagnosed ADHD over time, using candidate gene, family-based association tests and genome-wide association studies. Odds-ratios are provided whenever these are available.

1.5.3.1. Catechol-O-methyltransferase (COMT)

COMT is involved in the degradation of dopamine, adrenalin and noradrenalin and is conceptualized to cause the executive function deficits associated with ADHD (Sergeant, Geurts, Huijbregts, Scheres & Oosterlaan, 2003). Research indicates the val108/158Met *COMT* polymorphism is over-expressed in ADHD probands (Biederman et al., 2008b; Carpentier et al., 2013; Michaelovsky et al., 2008; Palmason et al., 2010) and has been associated with ADHD related cognitive deficits (Matthews et al., 2012), but findings are mixed (Cheuk & Wong, 2006). **A** meta-analysis (Gizer, Ficks & Waldman, 2009b) including 16 candidate gene studies of *COMT* failed to find an effect for the val allele [OR = 0.99 (0.91, 1.08)].

1.5.3.2. Dopamine Receptor D1 (DRD1)

The D1 receptor encoded by the *DRD1* gene is found in the central nervous system and is the most abundant throughout this region. D1 is involved in the regulation of neuronal growth and development. This receptor has been linked to maternal orienting behavior in animal studies (Mileva-Seitz et al., 2012) and regulates *DRD2* action. There have been nominal associations between *DRD1* haplotypes and ADHD in several family-based association tests [(Misener et al., 2004), OR = 1.23 (1.03, 1.46); (Oades et al., 2008); (Ribases et al., 2012), OR = 1.50 (1.18, 1.90)] .

1.5.3.3. Dopamine Receptor D2 Isoform (DRD2)

The *DRD2* gene encodes the D2 dopamine receptor that appears to be involved in reward mediating circuits located in the mesocorticolimbic system (Neville, Johnstone & Walton, 2004). The Taq1A allele on *DRD2* has been associated with symptoms of impulsivity (Esposito-

Smythers, Spirito, Rizzo, McGeary & Knopik, 2009), however authors have noted that this marker lies in the exon of a neighbouring gene (Lucht & Rosskopf, 2008) and may be involved in *DRD2* expression levels (Laakso et al., 2005). Candidate gene studies have suggested an interaction between *DRD2* and val158Met related to working memory (Kollins et al., 2008; Xu et al., 2007). Nyman and colleagues (2007) found male specific effects for rs1079727 [OR = 1.89 (1.03, 3.45)], rs1079595 [OR = 1.99 (1.07, 3.69)], rs1124491 [OR = 2.08 (1.14, 3.80)] and rs1800497 [OR = 1.93 (1.05, 3.55)] on *DRD2*.

1.5.3.4. Dopamine Receptor D4 (DRD4)

DRD4 receptors are located in the frontal cortex, midbrain, amygdala and cardiovascular system. They regulate neuronal signaling in the mesolimbic system. The 48bp 7-repeat allele has been consistently associated with symptoms of ADHD in candidate gene and two genome-wide association studies (Faraone, Doyle, Mick & Biederman, 2001; Gizer et al., 2009b; Kustanovich et al., 2003; Lasky-Su et al., 2008). The meta-analysis conducted by Gizer and colleagues showed an odds-ratio of 1.33 (1.15, 1.54) indicating the increased probability of ADHD probands possessing this allele. The same allele has been implicated in symptoms of conduct and antisocial personality disorders (Beaver et al., 2007) two conditions often comorbid with ADHD. In the presence of *DRD2*, the 7-repeat allele on *DRD4* has been found more frequently in people reporting with history of conduct problems ($z = 3.00$, $p = 0.003$).

1.5.3.5. Dopamine Receptor D5 (DRD5)

DRD5 receptors as with *DRD4* receptors are restricted to the limbic region of the brain in contrast to the wide distribution of the D1 receptor. Interestingly it is genes encoding these receptors that have the most consistent associations to ADHD as the limbic system supports the regulation of emotion, memory, motivation and behavior (Kolb & Whishaw, 2009). Two meta-analyses have shown similar effect sizes for risk conferred by the 148bp allele on *DRD5* [OR = 1.34 (1.21, 1.50) (Li, Sham, Owen & He, 2006); OR = 1.23 (1.06, 1.43) (Gizer et al., 2009b)]. Li and colleagues (Li et al.) also found the 136bp allele on this gene had a weak protective effect [OR = 0.57 (0.34, 0.96)] against symptoms of ADHD.

1.5.3.6. Monoamine Oxidase (MAOA)

MAOA encodes mitochondrial enzymes, these catalyze the oxidative deamination of dopamine, norepinephrine and serotonin – the neurotransmitters that appear to be involved in ADHD (Solanto, 1998). In addition to impulsivity (Manuck, Flory, Ferrell, Mann & Muldoon, 2000), *MAOA* has been associated with depression (Priess-Groben & Hyde, 2012), panic disorder (Reif et al., 2012) and aggression (Volavka, Bilder & Nolan, 2006; Ziermans et al., 2012) showing possible pleiotropic effects and one possible mechanism for the high level of comorbidity found with ADHD. *MAOA* is found on the X-chromosome possibly accounting for sex specific effects that have been found, i.e. reduced visuo-spatial working memory capacity in girls and performance on a continuous adaptation motor task in boys (Ziermans et al., 2012). A meta-analysis conducted by Gizer and colleagues (2012) indicated the alleles on *MAOA* associated with ADHD have varied across studies resulting in a non-significant odds-ratio [OR = 1.02 (0.72, 1.43)].

1.5.3.7. Solute Carrier Family 6 Noradrenalin Transporter (SLC6A2)

The *SLC6A2* gene encodes for a member of the sodium neurotransmitter family involved in norepinephrine, dopamine and epinephrine reuptake and norepinephrine homeostasis. Two candidate genes studies conducted in Korean and Caucasian samples respectively, have shown associations between ADHD and the rs28386840 polymorphism on this gene [(Joung et al., 2010), OR = 1.50 (1.08, 2.34) ; (Kim et al., 2006), OR = 2.00 (1.19, 3.37)]. The rs3785143 SNP has previously shown a nominal association with ADHD [(Brookes, Xu, Chen, Zhou, Neale, Lowe, Aneey, et al., 2006), OR = 1.31] and sex specific effects have been found for this variant (Biederman et al., 2008a) but findings have been mixed [(Gizer et al., 2009b), OR = 1.02 (0.72, 1.43); (Renner et al., 2011), OR = 0.91].

1.5.3.8. Solute Carrier Family 6 Dopamine Transporter (SLC6A3)

The role of *SLC6A3* is dopamine reuptake. *SLC6A3* transporters are found in the striatum and substantia nigra showing broad distribution within the brains dopaminergic system. Studies examining the association between *SLC6A3* (also known as *DAT1*) and ADHD vary in their perspective. For example *SLC6A3:* shows an association with ADHD in children and adolescents with Tourette's syndrome (Comings, 2001); has been associated with methylphenidate response

[OR = 3.80 (1.00, 15.20); (Kooij, Boonstra, Vermeulen, et al., 2008)]; attentional asymmetry in children and adults (Bellgrove, Hawi, Kirley, Gill & Robertson, 2005; Newman, O'Connell, Nathan & Bellgrove, 2012) and is associated with smoking behavior for adults reporting childhood ADHD (McClernon, Fuemmeler, Kollins, Kail & Ashley-Koch, 2008). But, both direct effects (Brown et al., 2011; Hoogman et al., 2012) and null results (Langley et al., 2009; Niederhofer et al., 2008) have been found in candidate gene studies. The strongest replications for SNPs on this gene have been for rs40184 [(Brookes, Xu, Chen, Zhou, Neale, Lowe, Anney, et al., 2006), OR = 1.26], rs27072 [(Gizer, Ficks & Waldman, 2009a), OR = 1.20 (1.04, 1.38)] and rs2652511 (Genro et al., 2008).

1.5.3.9. Solute Carrier Family 6 Serotonin Transporter (SLC6A4)

The *SLC6A4* gene encodes a transporter responsible for reuptake and regulation of serotonin to other serotonin receptors. A 44bp insert/deletion on *SL6A4* has shown a strong association with symptoms of ADHD [(Kopeckova et al., 2008), OR = 2.70; (Faraone et al., 2005), OR = 1.31 (1.09, 1.59)]. *SLC6A4* has been implicated in the aetiology of depression (Dong, Wong & Licinio, 2009) and alcohol dependence [(Feinn, Nellissery & Kranzler, 2005), OR = 1.34 (1.11, 1.63)]. A novel gene x environment interaction has also been found between *SLC6A4* rs2020939 variant and maternal warmth that was suggested to moderate the conduct problems comorbid to ADHD (Sonuga-Barke et al., 2008).

1.5.3.10. Solute Carrier Family 9 Subfamily A (SLC9A9)

The *SLC9A9* gene encodes a protein essential for synaptic transmission and plasticity. Polymorphisms of *SLC9A9* have been associated with ADHD and autism (Chapman et al., 2011; Lasky-Su et al., 2008) and are implicated in the time to onset of ADHD within a genome-wide association study (Lasky-Su, Anney, et al., 2008) and to age specific effects of inattention and hyperactive-impulsive like symptoms in an animal model (Zhang-James, DasBanerjee, Sagvolden, Middleton & Faraone, 2011). There have been no replications across studies for SNPs found on this gene.

1.5.3.11. Synaptosomal Associated Protein (SNAP25)

The *SNAP25* gene encodes a protein in presynaptic plasma membrane that regulates neurotransmitter release synaptic vesicle membrane fusion and docking. More generally this protein has a role in synaptic function for uncertain neuronal systems and has shown consistent associations with ADHD over time (Barr et al., 2000; Kim et al., 2007; Mill et al., 2002) and across cultures (Sarkar et al., 2012). There have been replications for SNPs on *SNAP25*: rs362987 [(Feng et al., 2005), $Z = 1.98 – 2.65$, $p < 0.05$] and rs8636 (Sarkar et al., 2012), family-based and candidate gene studies respectively.

1.5.4. Summary of ADHD Genes

The list of genes associated with ADHD provided above is not exhaustive but indicates the most frequently found genetic associations and their possible role in symptoms of ADHD. Each of these genes account for a relatively small proportion of the ADHD phenotype, indicating the multifactorial aetiology and complexity of this syndrome.

1.6. Methodology

Several statistical methods are used to investigate the relationships between ADHD, environments and genes within this series of studies: regression, principal components analysis, survival analysis, latent class analysis, structural equation modeling (used in classical twin methodology) and genome-wide association studies. Although several statistical methods are used in this work (regression, principal components and survival analyses), I focus on a description of latent class analysis, classical twin modeling and genome-wide association studies, the analyses used to answer my primary research questions. I also discuss the principles on which these methods are based.

1.6.1. Latent Class Analysis

Latent class analysis provides an alternative to the linear data reduction method of principal components analysis. Latent class analysis has proven useful for analyzing categorical data when observing the relationship between affected cases that may include a number of confounding factors. These factors are often based on responses to questionnaire items that may cluster in particular ways and can be studied in various ways. Within this work, latent class

analysis will be used simply to differentiate ADHD symptoms according to the cluster of symptoms reported by each participant. The assumption underlying this choice is that variation in genetic and environmental factors influencing ADHD cannot be accurately differentiated using the inattentive and hyperactive-impulsive subtypes outlined in the DSM-IV and found as linear dimensions in principal components analysis. The *undifferentiated* subtypes are considered to account for the heterogeneity found in symptom expression and aetiological studies of ADHD (Banaschewski, Becker, Scherag, Franke & Coghill, 2010b; Castellanos et al., 2005). This method may also capture innate differences in the expression of ADHD between adults and children and across sex. The model used is defined below and forms the basis of the R package poLCA (Linzer & Lewis, 2007) that is used to run the latent class analyses.

Within this modeling technique, each of the ADHD items ($J = 1…18$) is assumed to be a categorical variable with K_j possible responses for individuals ($i = 1…N$) as defined by the coding of ADHD scale items. An individual's positive response to the Jth item (Y_{ijk}) is coded as 1 and all other response possibilities on that item coded as 0. The number of classes (R) estimated in the model is tested using the Bayesian information criterion and is set prior to estimation. The class-conditional probability that an observation in class $r = 1…R$ is the Kth response to the Jth symptom is represented as π_{jrk}. So within each class $\sum_{k=1}^{k_j} \pi_{jrk} = 1$, the sum of the probability of each possible response. The class mixing proportions (p_r) represent the weighted sum of the $class \times item \times response$ contingency tables $\sum_r p_r = 1$ and the equation used to calculate the probability that individual i in class r reports a particular cluster of symptoms is shown in equation 1.1:

$$f(Y_i; \pi_r) = \prod_{j=1}^{j} \prod_{k=1}^{k_j} (\pi_{jrk})^{Y_{ijk}} \quad (1.1)$$

The probability density function representing the probability a symptom is reported by participants within a particular class is shown in equation 1.2:

$$\mathrm{P}(Y_i|\pi, p) = \sum_{r=1}^{R} p_r \prod_{j=1}^{j} \prod_{k=1}^{k_j} (\pi_{jrk})^{Y_{ijk}} \quad (1.2)$$

The latent class model is estimated by maximizing the log-likelihood function, which follows in equation 1.3 using the expectation maximization algorithm:

$$\log L = \sum_{i=1}^{N} \ln \sum_{r=1}^{R} p_r \prod_{j=1}^{j} \prod_{k=1}^{k_j} (\pi_{jrk})^{Y_{ijk}} \quad (1.3)$$

Latent class analysis has previously been used to increase the specificity of ADHD measurement. The classes found appear to be replicable and can differentiate ADHD according to subtype and comorbidity (Acosta et al., 2008). Several studies indicate separate continuous dimensions of inattention and hyperactivity-impulsivity (Hudziak et al., 1998; Lubke, Hudziak, Derks, van Bijsterveldt & Boomsma, 2009; Neuman et al., 1999) for example few symptoms and from mild to severe classes for both inattention and combined symptoms with only a severe hyperactive-impulsive class for adolescent males (Rasmussen et al., 2002). Within mixed sex samples talkative-impulsive and inattentive-impulsive latent classes (Rasmussen et al., 2004) have been identified. For a sample of adults, classes including few symptoms, mild inattentive, mild combined, moderate combined, talkative-hyperactive, severe combined and severe inattentive classes were found (Acosta et al., 2008). These classes similarly reflected distinctions of severity with some qualitative variation in the associations with impulsive symptoms (i.e. either hyperactivity or inattention). Classes appear to be familial (Neuman et al., 1999; Rasmussen et al., 2004) and this suggests genetic distinctions across levels of severity in light of the relative contribution of genes and environments found in twin studies of ADHD (Derks, Hudziak, Beijsterveldt, Dolan & Boomsma, 2004; Knopik et al., 2006).

1.6.2. Biometrical Genetics

Biometrical genetics provides a mathematical technique to decompose the ADHD phenotype into genetic and environmental components. This technique is usually based on estimation of variance components, and the interpretation of these components is related back to basic laws of inheritance and genetic relationship. These methods provide the foundation for classical twin studies and for regression analyses estimating the direct effect of genes. The basic principles of genetics are described below.

1.6.2.1. Transmission Genetics

Transmission genetics incorporates three Mendelian principles to describe the process by which genes are transmitted from parent to offspring; from meiotic division to the formation of a

new organism with a unique genetic identity: (1) the first principle *the law of inheritance* states that genetic identity is controlled by paired unit factors within each organism – describing two alleles at a genetic locus one inherited from the father and the other coming from the mother; (2) the second principle describes *dominance* and *recessiveness;* when paired alleles responsible for a single trait are unalike, one may dominate the other, respectively said to be dominant and recessive. This principle can be extended to include the co-dominance of factors; (3) the third principle describes *genetic segregation* – the random segregation of alleles so a gamete will receive on or the other of a pair with equal likelihood (Klug, Cummings, Spencer & Palladino, 2013). These principles form the base of biometrical genetics. Our increased understanding of genetic effects such as linkage-disequilibrium and mutation for example, can be accounted for statistically. The bioinformatics approach also provides a framework for decomposing the phenotypic variance into genetic and environmental components; $P = G + E$, where P represents the phenotype, G the genetic effects and E represents variance due to environmental factors. The genetic component can be estimated for variation in relationship, for example from a difference between monozygotic and dizygotic twins.

1.6.2.2. Hardy-Weinberg Equilibrium

Hardy-Weinberg (HW) equilibrium is based on the transmission genetics statistically showing within an infinitely large population in which there is no genetic mutation, selection or migration and mating is random – allele and genotype frequencies remain constant. The HW law predicts the frequency of genotypes at a single locus, given the allele frequencies at that locus. This can be illustrated simply using one pair of alleles (*A* and *a*) at a single locus, where p and q represent the frequency of germ cells carrying *A* and *a* respectively. Resulting genotype frequencies at equilibrium are p^2 (*AA*), 2pq (*Aa*) and q^2 (*aa*). Figure 1 represents the phenotypic difference between *AA* and *aa* genotypes. Assuming additive genetic effects (*d*) only, the heterozygote (*Aa*) falls midway between the two homozygotes but in Figure 1 non-additive effects (*h*) are evident in the deviation of the heterozygote from the midpoint (*0*).

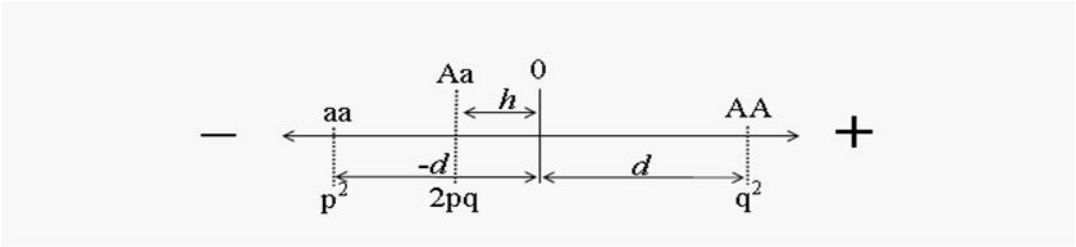

Figure 1.1 Representation of the phenotypic deviation between genotypes for an allelic pair at one locus. 0 represents the mean of the two homozygotes and the position of the heterozygote assuming only additive genetic effects: *h* represents the phenotypic deviation due to non-additive genetic effects similarly illustrated in Neale and Cardon (1992) and Mather and Jinks (1971).

1.6.2.3. Calculating Genetic Effects Influencing a Phenotype

Genotypic frequencies within the system illustrated in Figure 1.1 are $\frac{1}{4}$ for *aa*, $\frac{1}{2}$ for *Aa* and $\frac{1}{4}$ for *AA* in a population in Hardy-Weinberg equilibrium for a locus with an allele frequency of 0.5. If the genotypic values (or effects) are represented as $-d, h, d$ respectively, then the population mean at a single locus can be calculated summing over genotypes at one locus the product of the frequencies and genotypic effects (Neale & Cardon, 1992). The mean genotypic effect at each locus including additive (*d*) and non-additive (*h*) effects is summed across loci (*k*) for an individual (*i*) and together with interactions between loci (due to epistatic effects) represent the total genetic value of an individual. In the population, these genetic values will follow a continuous distribution based on the central limit theory. These genetic values are often indicated as liability in accord with the polygenic theory of psychiatric disorders (Gottesman & Shields, 1967). Calculations for the genotypic mean (μ) and variance ($\pm^2$) across multiple loci are presented in Equations 1.4 and 1.5 respectively where *V* represents variance component:

$$\mu = \frac{1}{2}\sum_{i=1}^{k} h_i \tag{1.4}$$

$$\begin{aligned}\sigma^2 &= \frac{1}{2}\sum_{i=1}^{k} d_i^2 + \frac{1}{4}\sum_{i=1}^{k} h_i^2 \\ &= V_{additive} + V_{non-additive}\end{aligned} \tag{1.5}$$

1.6.3. Twin Methodology

Biometrical genetics provides the foundation by which indirect genetic and environmental effects contributing to variation in ADHD symptoms can be decomposed into genetic and environmental variance components using data collected from monozygotic (MZ)

and dizygotic (DZ) twins and their family members. Twin studies provide additional information about which aspects of the environment account for variation in ADHD. MZ twins share 100% of their genes and DZ twins share an average of 50% (standard deviation 3%; Visscher, Thompson & Haley, 1996) . In the classical twin design, we need to assume that familial environmental factors act to the same extent in both MZ and DZ families, while for twins reared apart we assume there is no correlation in familial environment in the households of each twin.

The difference between MZ twins within a pair provides an estimate of the degree to which unique environmental factors (*E*) contribute to variation within a trait, represented as 1-MZ correlation (*r*). Common environmental effects (*C*) are shown in the degree to which the DZ*r* exceeds half the size of the MZ correlation, *C* = 2DZ*r* - .5MZ*r*. Conversely dominant genetic effects (*D*) are revealed in the degree to which the DZ*r* is less than .5MZ*r*, *D* = .5MZ*r* – DZ*r*. The power to detect additive genetic effects is greater in twin modeling thus this genetic effect is assumed to represent the greater degree of genetic variance. Simple additive genetic effects are indicated when the DZ*r* is approximately half the size of the MZ*r*. These variance components can be estimated using the principles of path analysis within a univariate model (shown in equation 1.6 and Figure 1.2), with twin 1 and twin 2 respective phenotypes represented as follows (Neale & Cardon, 1992):

$$P_1 = a_1A + c_1C + e_1E$$
$$P_2 = a_2A + c_2C + e_2E \qquad (1.6)$$

It is assumed that phenotype means and variances will be equal within a twin pair so *e, c* and *a* paths are set to be equal. Figure 1.2 shows the model for estimation the *A, C* (or *D*) and *E* variance using structural equations.

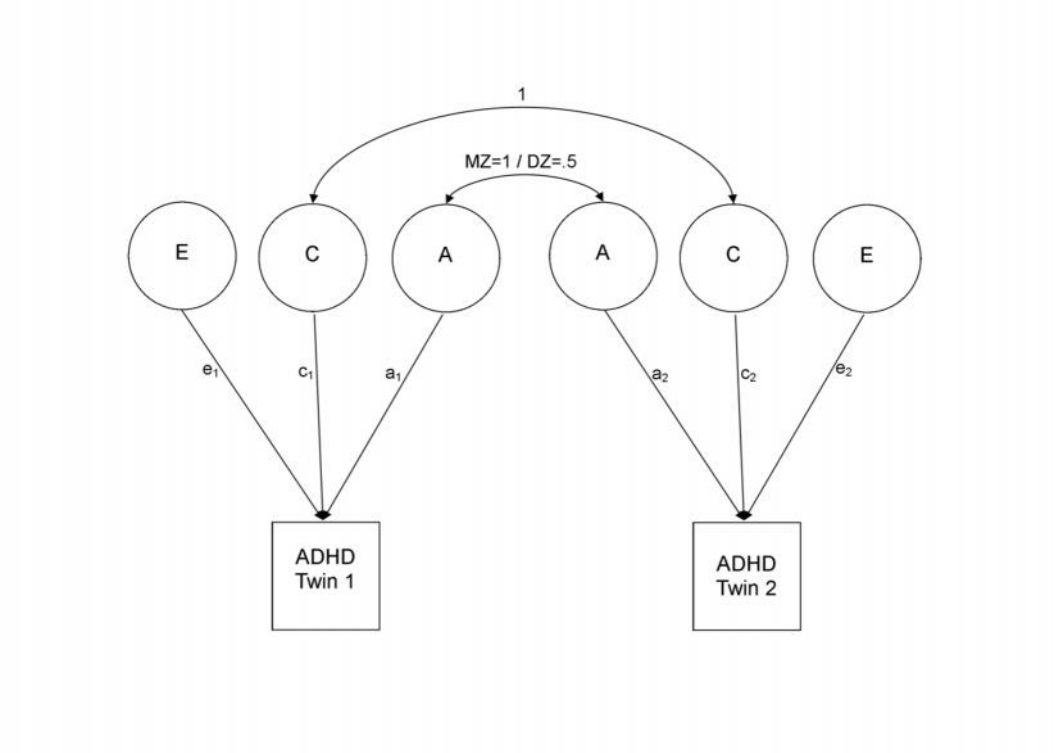

Figure 1.2. Univariate twin model for estimating additive genetic effects (*A*), shared environmental effects (*C*) and unique environmental effects (*E*) accounting for variation in ADHD symptoms.

MZ and DZ covariances are jointly analysed using maximum likelihood estimation (equation 1.9). Following on from the biometrical genetics equation 1.7, under the classical twin model the variance and covariance of MZ and DZ twins are parameterized as follows in equation 1.7:

$$\begin{bmatrix} a^2 + c^2 + e^2 & a^2 + c^2 \\ a^2 + c^2 & a^2 + c^2 + e^2 \end{bmatrix} \quad \text{for MZ twins, and}$$

$$\begin{bmatrix} a^2 + c^2 + e^2 & .5a^2 + c^2 \\ .5a^2 + c^2 & a^2 + c^2 + e^2 \end{bmatrix} \quad \text{for DZ twins.} \qquad (1.7)$$

The probability density function for each observation is calculated using the above covariance matrices ($\sum$) the variable vectors (x) means (μ_1), the determinant ($|\sum|$) and inverse ($\sum^{-1}$) of the covariance matrices as shown in equation 1.8:

$$|2\pi\Sigma|^{-n/2}\exp(-\frac{1}{2}(x_1-\mu_1)'\Sigma^{-1}(x_1-\mu_1)) \qquad (1.8)$$

The fit function for *k* observed variables is shown in equation 1.9:

$$-k\log(2\pi) + \log|\Sigma| + (x_1 - \mu_1)'\Sigma^{-1}(x_1 - \mu_1) \quad (1.9)$$

It is possible to extend twin models to estimate rater-bias effects, sex-specific genetic and environmental effects and inter-twin phenotypic interactions (for example contrast effects) by testing effects on total trait variance for MZ and DZ pairs.

1.6.4. Genome-Wide Association Studies

Genome-wide association studies have become possible because of advances in genotyping technology over the last 10 years. This method provides a hypothesis free approach to testing whether the variation in human DNA is related to disease risk within a sample (Hindorff et al., 2009). The power to detect causal variants is greatest when the genetic variation is lowest, corresponding to more common allele frequencies within the sample under study (Pe'er et al., 2006). The power of analysis is also dependent on the ability of an array to capture low frequency alleles. Investigators set thresholds for allele frequencies to include in analyses in relation to these considerations. The basic linear regression model presented in equation 1.10 is used to estimate the effect (β) a SNP (x_i) and covariates have on the measure of ADHD (Y);

$$\hat{Y} = \beta_i x_i + \beta_{age} Age + \beta_{sex} Sex + \beta_{age^2} Age^2 + \beta_{age\,x\,sex} Age \times Sex \quad (1.10)$$

The complexity of these analyses is not due to the statistical model but is due to the computational complexity resulting from the number of SNPs being analysed. Significance levels are set according to the SNPs included in analyses and the correlational structure of these across the genome (Dudbridge & Gusnanto, 2008). Typically, for genome-wide association studies a significance threshold of 5×10^{-8} is adopted representing the number of independent SNPs across the genome.

1.7. Summary and Objectives of the Thesis

The disadvantage experienced by people with ADHD is well documented and this syndrome affects approximately 5% of adults in the US and European countries. However the diagnostic criteria for ADHD may not be appropriate for adults, and result in an underestimate of the difficulties experienced by adults with subthreshold symptoms. There appears to be additional variation in symptoms by sex that has not been clearly defined. This could be due to the variation across measurement of symptoms and differences in the manifestation and aetiology of symptoms across age and sex. Additionally, work is needed to clarify the genetic and environmental aetiology of ADHD internationally, and more particularly for adults within the Australian population. The following series of studies addresses these gaps in our current understanding. The first study examines the prevalence and persistence of ADHD in Australian adults using three methods of classifying clinically relevant symptoms. The disadvantage experienced by these adults is measured in the domains of health, career and exposure to environmental adversity. The second study conducts similar analyses using latent classes to redefine the specific symptoms associated with disadvantage and whether or not these vary from the defined inattentive and hyperactive-impulsive symptoms outlined in the DSM-IV. The third study includes an estimate of the relative contribution of genes and environments to symptom aetiology and how these variance components may differ by sex and with behavioural informant. This study also addresses the difference in heritability estimates of ADHD in children and adults. The fourth study is a genome-wide association test of ADHD using a dimensional measure of symptoms as an alternative to a severity score or categorical representation of symptoms.

Chapter 2

Attention Deficit Hyperactivity Disorder in Australian Adults: Prevalence, Persistence, Conduct Problems and Disadvantage

Abstract

The prevalence and persistence of ADHD have not been described in young Australian adults and few studies have examined how conduct problems (CP) are associated with ADHD for this age group. We estimate lifetime and adult prevalence and persistence rates across three categories of ADHD for 3795 Australian adults, and indicate how career, health and childhood risk factors differ for people with ADHD symptoms and ADHD symptoms plus CP. Trained interviewers collected participant experience of ADHD, CP, education, employment, childhood experience, relationship and health variables. Three diagnostic definitions of ADHD used were: *(i)* full DSM-IV criteria; *(ii)* excluding the age 7 onset criterion (*no age criterion*); *(iii)* participant experienced difficulties due to ADHD symptoms (*problem symptoms*). Prevalence rates in adulthood were 1.1%, 2.3% and 2.7% for each categorization respectively. Persistence of ADHD from childhood averaged across sex was 55.3% for full criteria, 50.3% with no age criterion and 40.2% for problem symptoms. ADHD symptoms were associated with parental conflict, poor health, being sexually assaulted during childhood, lower education, income loss and higher unemployment. The lifetime prevalence of conduct problems for adults with ADHD was 57.8% and 6.9% for adults without ADHD. The greatest disadvantage was experienced by participants with ADHD plus CP. The persistence of ADHD into adulthood was greatest for participants meeting full diagnostic criteria and inattention was associated with the greatest loss of income and disadvantage. The disadvantage associated with conduct problems differed in severity and was relevant for a high proportion of adults with ADHD. Women but not men with ADHD reported more childhood adversity, possibly indicating varied etiology and treatment needs. The impact and treatment needs of adults with ADHD and CP and the report of sexual assault during childhood by women and men with ADHD also deserve further study.

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Chapter 3

Latent Classes of Attention-Deficit/Hyperactivity Disorder in Adults Vary With Sex and Environmental Adversity

Abstract

We describe adult reported ADHD controlling for sex, comorbid conduct problems (CP) and exposure to environmental adversity. Interviewers collected ADHD, CP and sociodemographic data from 3793 twins and their siblings aged 22 to 49 (*M* = 32.6). We estimate linear weighting of symptoms within ADHD subtypes and CP. Latent class analysis and regression describe associations between measured variables. Odds-ratios for twin concordance within latent-classes provided an estimate of genetic effects on class membership and we estimate the clinical relevance of each class. Five classes were found for women and men; few symptoms, hyperactive-impulsive, CP, inattentive and combined symptoms with CP. There was systematic variation in ADHD symptoms by sex, with CP and environmental adversity. Women within the inattentive class reported more symptoms and were more disadvantaged than men in the same class. Monozygotic twin concordance was higher for two symptomatic classes but not for diagnosed ADHD or conduct disorder.

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Chapter 4

Effects of Sex and Maternal versus Self-Report on Heritability Estimates of Attention-Deficit Hyperactivity Disorder

Abstract

The heritability of attention-deficit/ hyperactivity disorder in childhood ranges from 70% to 90%, and this figure drops to 30% to 54% in adults. It is unclear how much of this is due to a transition in reporting from parent-based to self-report measurement, or due to an increase in importance of environmental factors in symptom variation. Additionally, sex difference in genetic and environmental aetiology of ADHD has previously been suggested. In childhood males more often present with ADHD particularly hyperactivity-impulsivity, girls present less frequently but more often with symptoms of inattention. Presentation appears to become more equal in adults and women have reported more symptoms of hyperactivity-impulsivity. Genetic and environmental factors contributing to variance in mother and self-report of inattentive, hyperactive and impulsive behaviours are individually tested for sex difference and for aetiological variation. ADHD data were collected from both informants using the Strengths and Weaknesses of ADHD and Normal Behaviour Scale (SWAN): 3236 twins and siblings (mean age 21.2, *SD* = 6.3) have ADHD provided by their mothers. An additional 953 twins and their siblings (mean age 25.5, *SD* = 3.2) have provided self-report data. There were 633 family members who participated in both studies. Sex difference was evident in the unique environmental factors contributing to symptom variation. Heritability estimates for adults using maternal report of symptoms were .74, .82 and .80 and similar to what has been found for maternal report of childhood symptoms. Similarly self-reported symptoms corresponded to heritability estimates previously found for adults reporting on their own ADHD symptoms - .50, .33 and .43 for inattention, hyperactivity-impulsivity and combined symptoms. There was a rater contrast evident in maternal report of ADHD and rater differences appear to be due to genetic factors contributing to variance of mothers' report of symptoms while specific environmental factors influenced self-report.

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Chapter 5

Genome-Wide Association Study of Inattention And Hyperactivity-Impulsivity Measured As Quantitative Traits

Abstract

Genome-wide association studies (GWAS) of attention-deficit/hyperactivity disorder (ADHD) offer the benefit of a hypothesis free approach to measuring the quantitative effect of genetic variants on affection status. Generally the findings of GWAS relying on ADHD status have been non-significant, but the one study using quantitative measures of symptoms found SLC9A9 and SLC6A1 were associated with inattention and hyperactivity-impulsivity. Accordingly we performed a GWAS using quantitative measures of each ADHD subtype measured with the Strengths and Weaknesses of ADHD and Normal Behaviour (SWAN) scale in two community-based samples. This scale captures the full range of attention and kinetic behaviour; from high levels of attention and appropriate activity to the inattention and hyperactivity-impulsivity associated with ADHD within two community-based samples. Our discovery sample comprised 1851 participants [mean age = 22.8 (4.8); 50.6% female] while our replication sample comprised 155 participants [mean age = 26.3 (3.1); 68.4% females]. Age, sex, age x sex and age^2 were included as covariates and the results from each sample were combined using meta-analysis, then analyzed with a gene-based test to estimate the combined effect of markers within genes. We compare our results to markers that have previously been found to have a strong association with ADHD symptoms. Neither the GWAS nor subsequent meta-analyses yielded genome-wide significant results, the strongest effect was observed at rs2110267 for symptoms of hyperactivity-impulsivity (4.62×10^{-7}). The strongest effect in the gene-based test was for *GPR139* on symptoms of inattention (6.40×10^{-5}). Replication of this study with larger samples will add to our understanding of the genetic aetiology of ADHD.

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Chapter 6

General Discussion and Conclusion

6.1. Review

This thesis had two aims; the first was to clarify the pattern of ADHD symptom expression in young Australian adults and to assess causes and effects of these symptoms, environmental and genetic. The prevalence, persistence and relative disadvantage for adults reporting these symptoms was estimated in chapters 2 and 3, using logistic regression and latent class regression respectively. This was to determine the relative disadvantage experienced by adults who did experience difficulties from ADHD but whose symptoms may have fallen below the DSM-IV-TR diagnostic criteria, or whose symptoms varied from the inattentive, hyperactive-impulsive and combined subtypes. Chapter 4 estimated the indirect effect of genes and environments on ADHD. This chapter also addressed the drop in ADHD heritability in adulthood in relation to the change of behavioural informant from parent to self. The fifth chapter described a GWAS in which direct genetic effects were estimated for ADHD using a dimensional measure of symptoms. The methods used throughout this thesis address gaps in our current understanding of ADHD in adults; specifically the heterogeneity in aetiological studies and the variation in symptom count, prevalence rates and heritability estimates that appear across sex and age.

I follow with an outline of the primary findings of this work discussing how each chapter is related and the unique perspective offered by comparing the measures that were used.

6.2. Prevalence and Persistence of ADHD in Australian Adults

Estimation of the prevalence and persistence of ADHD within several classifications and latent classes allowed some speculation on the number of adults who did not meet DSM-IV-TR diagnostic criteria but did report disadvantage across several life domains solely due to ADHD symptoms. A comparison of the prevalence and persistence of these varied classifications follows.

6.2.1. DSM-IV Diagnostic Criteria

Data from the Study of Cannabis Use and Mental Health described in chapter 2 included diagnostic criteria *A, B, C, D*. However data from the Melanocytic Naevi and Nineteen-Up studies analysed in chapters 4 and 5 included only criterion *A*, so it was not possible to compare DSM based

prevalence and persistence rates across all studies. But, the persistence of ADHD into adulthood was estimated for three DSM-IV-TR based diagnostic categories defined within the Cannabis Study; a broad category representing adults who reported ADHD symptoms created problems in their lives, all DSM criteria excluding the age of onset and full diagnostic criteria. Persistence appeared to be related to the severity of symptoms and the persistence of symptoms within each diagnostic category did not differ for women and men. The prevalence of symptoms was higher for men than women as has previously been found for children (American Psychiatric Association, 2000) and some adult samples (Faraone & Biederman, 2005). Symptom count appeared to be most indicative of the disadvantage associated with ADHD in a quantitative manner. Australian adults who met the full diagnostic criteria had the most severe expression of symptoms and can be considered as the most disadvantaged.

6.2.2. Prevalence of Latent Classes Compared to DSM-IV-TR criteria

The prevalence of DSM-IV-TR latent classes is largely provided in Table 3.2 of chapter 3. This table shows a large difference in the prevalence of people meeting criteria for DSM based categorisation and those falling within corresponding latent classes. This pattern could indicate that for a proportion of participants – inattentive, hyperactive-impulsive and combined symptom clusters did not create problems in their lives. It could also indicate that these participants did not meet diagnostic criteria for ADHD, but did experience difficulties. The mean symptom count in the hyperactivity-impulsivity latent class was 3.5 this was 4.5 for adults in the inattentive class and 11.2 for the combined symptoms class. Adults with at least 4-symptoms have previously reported consequent disadvantage.

6.2.3. Prevalence of ADHD Latent Classes

Latent class analyses were conducted within two studies using four samples. The first sample was self-reported ADHD data collected in the Study of Cannabis Use and Mental Health using the SSAGA. Conduct disorder items were also collected in this study and were included in the latent class analysis, differing to the other studies in this regard. Two samples comprised maternal report of symptoms collected in the Study of Melanocytic Naevi using the SWAN. These two samples represented median division by age cohort – those below 19 and those 19 and older. The fourth sample was self-reported ADHD collected in the Nineteen-Up study also using the

SWAN. The classes that were found for each sample and corresponding prevalence rates are presented in Table 6.1.

Table 6.1

Prevalence of Latent Classes Across four Samples

Classes	Cannabis Study	MN adolescents	MN adults	NU adults
No/few symptoms	.65	.86	.90	.66
Hyperactivity-impulsivity	.14	--	.03	.18
Inattention	.17	.04	.04	.11
Conduct problems	.17	--	--	--
Mild combined	--	.07	--	--
Severe combined	.05	.02	.02	.05

Five latent classes best described the pattern of ADHD symptoms reported by adult participants in the Cannabis Study and four classes best described each of the remaining samples. Prevalence rates for class membership were quite similar for adults reporting on their own symptoms in the Cannabis and Nineteen-Up studies. Class prevalence rates were also similar when mothers reported on symptom as seen in the adolescent and adult cohorts of the Melanocytic Naevi study. There is comparability between these classes and what has previously been found for adolescents and adults (Acosta et al., 2008; Althoff et al., 2006; Neuman et al., 1999). However there are also clear differences and substantial work would be needed to provide detail about how and in what way classes might differ across samples and studies.

Interestingly, classes estimated using self-reported data have quite similar prevalence rates even though scales differed. Items in the Cannabis Study were coded as binary response and included negative wording, in contrast to the positive wording and 5-point dimensional scale used in the Nineteen-Up study. Corresponding prevalence rates for symptomatic latent classes calculated with maternal-report of symptoms were lower even though this scale was most similar to self-reported data in the Nineteen-Up study. This could be due to the extended 7-point scale of the SWAN ADHD data collected in the study of Melanocytic Naevi, providing respondents with an additional response option that also reduced the relative severity of reported symptoms. Surprisingly this is in contrast to the discussion in chapter 4 speculating maternal report of symptoms accounts for the increased severity of symptoms that has previously been reported (Kooij, Boonstra, Swinkels, et al., 2008).

6.3. Environmental Correlates of ADHD in Australian Adults

6.3.1. Environmental Associations for Inattentive and Hyperactive-Impulsive Subtypes

The analyses examining environmental associations of ADHD were not directional so causation cannot be inferred. The first two studies (chapters 2 and 3) examined the environmental factors predicting or predicted by ADHD (risk factors and disadvantage respectively). As previously found, participants reporting more symptoms of inattention and hyperactivity-impulsivity also reported more conflict with their parents, more tension between their parents and less consistent parental rules during their childhood years than adults with fewer symptoms. These people were more often sick and reported poor physical and emotional health, a reduced chance of achieving a degree, lower grades in primary and high school and were more often unemployed than participants with few or no ADHD symptoms. Chapter 4 defined environmental factors according to whether or not these experiences were shared by family members. This analysis supported what has consistently been shown for ADHD; environmental experiences not shared by family members account for approximately one-third of the differences we see in the manifestation of this syndrome. However in this thesis a shared environmental factor accounted for differences in ADHD expression in women but not in men, in contrast to previous findings.

6.3.2. Environmental Associations for ADHD Latent Classes

The use of latent class regression provided an alternate perspective of the disadvantage associated with varied clusters of ADHD symptoms. This study showed sex differences in the environmental factors influencing symptoms. Women but not men with combined symptoms were less often raised by both biological parents and more often reported an alcohol problem. Women with inattentive symptoms more often reported poor emotional health while men with these symptoms did not. Women experiencing inattention may be more disadvantaged or inattention could differ qualitatively for women and men. These findings require further study – for example, examination of genetic expression between groups of people who have and have not been exposed to environmental adversity and whether sex by ADHD group interactions are evident for specific biological pathways.

6.3.3. Environmental Effects in Twin Study

The following discussion relates to ADHD symptoms measured as dimensional traits using the SWAN, thus including high and low levels of attention and activity so I use the terms *attention, activity* and *combined behaviours* to describe ADHD the measured behaviours.

6.3.3.1. Environmental Effects in Sex-Limited Analysis

The results of sex-limited analyses supported the findings of studies outlined in chapters 2 and 3. In these studies, women reporting greater exposure to environmental adversity during childhood also reported more ADHD symptoms than women without similar exposure. Men reporting ADHD symptoms did not have greater exposure to adverse environments than men reporting few or no symptoms. The sex-limited analyses showed a common environmental factor influencing levels of hyperactivity-impulsivity for women not found for men. The specific environmental factors contributing to variation in combined ADHD symptoms were consistently higher for men than women. This shows there is greater variance in this environmental component accounting for ADHD symptoms in men. In contrast the specific environmental variance associated with ADHD in women has a smaller magnitude showing higher covariance for MZ female twins and possibly a reduced range of factors accounting for differences in ADHD related behaviours in women.

6.3.3.2. Environmental Effects in Rater Measurement Model

Environmental factors shared by family members were not found in the comparison of mother or self-reported symptoms. Self-reported ADHD data did show a higher specific environmental component than maternal-report and this accounted for difference in raters' report of attention, activity and combined behaviours. This variance component also includes measurement error so may reflect greater error resulting from two rather than one person reporting on behaviours within a twin pair.

6.4. Genetic Aetiology of ADHD in Australian Adults

6.4.1. Genetic Effects in Twin Study

6.4.1.1. Genetic Effects in Sex-Limited Analyses

Genetic effects in the sex-limited analyses supported the suggestion of sex effects in a previous study (Kan et al., 2012). A non-additive genetic effect accounting for sex-differences in attention was found in the maternal-report data and when attention was self-reported. The additive genetic effect accounting for variation in combined behaviours differed for women and men in both samples. There were male specific additive genetic effects for attention, activity and combined behaviours when ADHD was reported by mothers, implicated only in combined behaviours reported by self.

Broad-sense heritability estimates for maternal-report data were approximately equal for women and men indicating the genetic source but not magnitude of effect differed across sex. These findings are novel and require replication. However sex differences have been found for ADHD related behaviours in association with *SLC6A4*, *MAOA, SLC6A2* and *COMT* (Biederman et al., 2008b) variants in childhood. Additional sex effects have been found in animal studies examining behaviours associated with ADHD candidate genes (Gogos et al., 1998).

6.4.1.2. Genetic Effects in Rater Measurement Model

Approximately one-third of the variance in maternal and self-reported attention was shared by raters and accounted for by non-additive genetic effects. A similar pattern was evident for combined behaviours. Additive genetic effects were common to maternal and self-reported activity, again accounting for approximately one-third of the variance in these behaviours. There was a genetic effect specific to mother's report of behaviour that was not evident when behaviour was self-reported. Initially this effect was thought to be due to a severity rating in maternal-report, upon reflection latent class prevalence rates do not support this theory. However these analyses do indicate the difference in heritability estimated of ADHD between children and adults appears to be due to genetic effects evident in mother's but not self-reported behaviours.

6.4.2. Results of Genome-Wide Association Study

The most significant SNPs found in the genome-wide association did not correspond to the SNPs that have previously been associated with ADHD [and] as listed in the opening chapter.

Neither was there evidence for association between attention, activity or combined behaviours with known candidate genes. We did however find suggested replication for SNPs on *FOXP1* and *PPP2R5*, with a previous study using a quantitative measure of ADHD. These genes are novel candidates for ADHD. Candidate SNPs listed in chapter 1, found on *COMT*, *DRD1*, *DRD2*, *DRD3*, *SLC6A2*, *SLC6A3*, *SLC6A4* and *SNAP25* were included in our GWAS, however the *p*-values achieved for associations with ADHD subtypes did not fall below .1.

6.5. General Limitations

One limitation of this study was the strictly continuous representation of the SWAN scale. A study using categorical measurement to compare the genetic and environmental aetiology of the SWAN at both extremes of the distribution could have clarified whether genetic and environmental variation in ADHD related behaviours were the same at both extremes of the distribution. There were also differences in the wording used to ask participants about their ADHD related behaviours and this will naturally introduce a level of bias into the measures. Additionally the difference in scale length in SWAN measures between the study of Melanocytic Naevi and Nineteen-Up studies created bias, even though these scores were standardized within sample prior to comparing results. Inclusion of questions addressing DSM diagnostic criteria *B*, *C*, *D* and *E* in each of the SWAN scales would have allowed greater comparability of ADHD across samples and within latent class categories.

6.6 Conclusions and Future Directions

Evidence suggests latent classes capture subthreshold cases of ADHD and the symptom count for these classes falls within the range of what has previously led to disadvantaged for adults (Das et al., 2012; Kooij et al., 2005) across populations. Additionally, latent class analysis provided a valuable method for comparing the pattern of symptoms between women and men and across DSM based categories. Genetic analyses using latent class representation could provide refined detail about how the genetic aetiology of ADHD symptoms varies across sex and diagnostic categories. Genetic analysis of the extremes of the SWAN distribution will also provide important information about risk and protective factors for ADHD.

Surprisingly, different measures were most comparable across samples when the informant was the same, and did not appear to be related to the scale used or manner in which questionnaire

items were posed. However these effects need to be tested systematically and would provide a valuable reference for ongoing studies of ADHD.

Pleiotropic effects have recently been reported for psychiatric disorders (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013) and transcript abundance could be differentiated to represent the expression of one of those pathways at a particular point in time. This could also provide a quantitative phenotype intermediate to gene and environment. Although the tissue of analysis most often used for gene-expression studies is blood – which may seem irrelevant for a neurological disorder – the correlation between blood and brain expression has been found to average to $r = 0.6$ (Sullivan, Fan & Perou, 2006). Additionally, a recent study has shown an association between the major histocompatability complex and schizophrenia (de Jong et al., 2012). This study warrants replication in participants with and without ADHD, and could implicated physiological variation between people with and without this syndrome. Additionally, gene-expression may vary for people exposed to specific environments and in this way provide direct information about sex differences that were found in this series of studies.

Chapter 7
Thesis Revisions

Thankyou reviewers for your valuable comments, I have made some changes in text to address concerns and suggestions that were raised for each thesis chapter. I follow with an overview of these changes:

7.1. Chapter 1

A sentence has been added to the second paragraph of chapter 1 *1.2.2.* to indicate how ADHD diagnostic criteria have been modified in the DSM-5. Additionally, each summary within section *1.5.3.* has been refined and odds-ratios as a measure of effect added whenever these were available. Two sentences have been added to *1.6.1.* to highlight differences between the analytic methods of principal components and latent class analysis.

7.2. Chapter 2

Wording in the methods section of chapter 2 (*2.2.2.1.*) has been changed to indicate *alcohol problems* were defined by health professionals. Additionally the false discovery rate was calculated for each group of regression analyses to describe the effect of multiple testing within this study and a sentence describing these results was provided at the end of *2.4.2., 2.4.3.* and *2.4.4.* Reference is also made at the end of *2.4.3.* to the relevance of sex specific analyses provided in the Appendix, this was to highlight sex differences. Two sentences have been added to the limitations discussion of Chapter 2 (2.5) to indicate that qualitative measures may in some cases provide more accurate measurement of environmental variables.

7.3. Chapter 3

Three sentences have been added to the introduction of chapter 3 (3.1). The first describes sex difference in symptom expression (based on results of the previous chapter), providing support for sex specific analyses. The second is in section *3.1.1.,* indicating how comorbidity, specifically conduct problems may account for heterogeneity in ADHD symptom expression. This is used to provide justification for the inclusion of conduct problems in latent class analyses. The third is in

3.1.2. and provides a contrast between latent class and principal components analysis. In the methods section (*3.2.3.4.*), wording is changed to indicate *alcohol problems* are diagnosed by a health professional. Within this chapter the effect of multiple testing was also described with the false discovery rate (FDR; added to the end of *3.3.2.*). The FDR values calculated for regression analyses for each group of sociodemographic variables were provided at the end of sections *3.4.5.* and *3.4.6.* of the results. Previous wording in results section *3.4.2.* (p71.) has been removed and this information has been provided in Table 3.2.

7.4. Chapter 4

Within chapter 4 there was one change; a clause was added to discussion of the limitations in *4.4.*. This briefly describes how class entropy can affect heritability estimates.

7.5. Chapter 5

Within chapter 5, detail has been added to section *5.2.4.2.* of the methods to indicate that our data (MN and NU studies) had not been included in the meta-analysis of Neale and colleagues (2010). There was also detail added to reflect the characteristics of the SNPs most strongly associated with ADHD in section *5.3.3.*.

7.6. Chapter 6

A reference has been added to 6.6. of chapter 6 indicating that the average correlation between blood and brain expression is 0.6.

I hope these revisions address the concerns raised by each reviewer. I again thank you for your comments, both suggested improvements and for the favourable acknowledgement of this series of studies, it has been a pleasure.

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Appendix A

Table A1

Career Related Variables Predicting ADHD Subtypes

Career Related Variables	Frequency (*n*)	Odds-Ratio ADHD		Odds-Ratio ADHD & CP	
		Inattention	*Hyperactive Impulsivity*	*Inattention*	*Hyperactivity-impulsivity*
Education					
Full Sample					
Up to year 12	960	(1)	(1)	(1)	(1)
Further study	2910	0.63*	0.86	0.49***	0.65*
Women		(0.41-0.97)	(0.54-1.27)	(0.32-0.74)	(0.43-0.97)
Up to year 12	574	(1)	(1)	(1)	(1)
Further study	1883	0.58	0.78	0.46*	0.64
Men		(0.33-1.03)	(0.45-1.37)	(0.27-0.80	(0.38-1.09)
Up to year 12	386	(1)	(1)	(1)	(1)
Further study	1025	0.70	0.89	0.54	0.67
		(0.36-1.37)	(0.46-1.71)	(0.29-1.01)	(0.36-1.25)
Grades PS					
Full Sample					
Below Average	174	(1)	(1)	(1)	(1)
Average & above	3614	0.11***	0.39**	0.10***	0.31***
Women		(0.06-0.21)	(0.20-0.76)	(0.05-0.17)	(0.16-0.59)
Below Average	83	(1)	(1)	(1)	(1)
Average & above	2336	0.09***	0.38	0.08***	0.32*
Men		(0.04-0.21)	(0.14-1.01)	(0.04-0.18)	(0.12-0.83)
Below Average	90	(1)	(1)	(1)	(1)
Average & above	1277	0.46***	0.41	0.12***	0.33*
		(0.06-0.32)	(0.16-1.05)	(0.05-0.27)	(0.13-0.80)
Grades HS					
Full Sample					
Below Average	226	(1)	(1)	(1)	(1)
Average & above	3565	0.18***	0.54	0.12***	0.32***
Women		(0.10-0.32)	(0.29-1.01)	(0.07-0.20)	(0.18-0.57)
Below Average	109	(1)	(1)	(1)	(1)
Average & above	2310	0.14***	0.53	0.09***	0.32*
Men		(0.06-0.30)	(0.21-1.32)	(0.04-0.20)	(0.14-0.75)
Below Average	90	(1)	(1)	(1)	(1)
Average & above	1277	0.24***	0.56	0.16***	0.33*
		(0.10-0.54)	(0.23-1.34)	(0.07-0.34)	(0.15-0.75)
Income					
Full Sample					
< $770 per week	1687	(1)	(1)	(1)	(1)
$770 or more	2151	0.58*	0.85	0.58*	0.85
Women		(0.38-0.87)	(0.58-1.25)	(0.39-0.87)	(0.58-1.23)
< $770 per week	1388	(1)	(1)	(1)	(1)
$770 or more	1046	0.60	0.94	0.54*	0.85
Men		(0.34-1.07)	(0.56-1.56)	(0.31-0.95)	(0.51-1.39)
< $770 per week	298	(1)	(1)	(1)	(1)
$770 or more	1104	0.44*	0.71	0.37**	0.58
		(0.23-0.87)	(0.36-1.41)	(0.20-0.71)	(0.30-1.12)
Employed					
Full Sample					
Not on benefit	3769	(1)	(1)	(1)	(1)
Receiving benefit	101	3.36*	1.70	4.75***	2.53*
Women		(1.40-8.03)	(0.65-4.45)	(2.09-10.81)	(1.02-6.28)
Not on benefit	2405	(1)	(1)	(1)	(1)
Receiving benefit	52	4.57*	1.34	5.65**	1.84
Men		(1.44-14.50)	(0.30-5.92)	(1.86-17.17)	(0.45-7.50)
Not on benefit	1362	(1)	(1)	(1)	(1)
Receiving benefit	49	2.44	2.09	3.69*	3.20
		(0.67-8.93)	(0.57-7.59)	(1.09-12.53)	(0.94-10.82)

*Note: * p≤ .05, Note: ** p≤ .01, *** p≤ .001, n = 3876*

Table A2

Family Variables Predicting ADHD Subtypes

Family Related Variables	Frequency (*n*)	Odds-Ratio ADHD only		Odds-Ratio ADHD & CP	
		Inattention	*Hyperactivity-Impulsivity*	*Inattention*	*Hyperactivity-impulsivity*
Childhood SES					
Full Sample					
Below average	519	(1)	(1)	(1)	(1)
Average & above	3347	0.68	0.74	0.58*	0.64
Women		(0.40-1.15)	(0.45-1.22)	(0.35-0.95)	(0.40-1.04)
Below average	345	(1)	(1)	(1)	(1)
Average & above	2107	0.57	0.63	0.49*	0.57
Men		(0.30-1.09)	(0.34-1.18)	(0.26-0.91)	(0.31-1.05)
Below average	172	(1)	(1)	(1)	(1)
Average & above	1240	0.89	1.00	0.72	0.78
		(0.37-2.14)	(0.42-2.37)	(0.31-1.68)	(0.34-1.79
Parents to 16					
Full Sample					
No	684	(1)	(1)	(1)	(1)
Yes	3188	0.87	0.64	0.68	0.54*
Women		(0.53-1.53)	(0.41-1.01)	(0.43-1.10)	(0.35-0.83)
No	463	(1)	(1)	(1)	(1)
Yes	1994	0.75	0.55*	0.57	0.46**
Men		(0.40-1.41)	(0.31-0.96)	(0.32-1.04)	(0.27-0.78)
No	220	(1)	(1)	(1)	(1)
Yes	1193	1.13	0.89	0.87	0.71
		(0.48-2.65)	(0.41-1.94)	(0.38-1.95)	(0.34-1.49)
Conflict w Mother					
Full Sample					
Never or rarely	2432	(1)	(1)	(1)	(1)
Sometimes or often	1438	1.57*	1.55*	1.98***	1.89***
Women		(1.04-2.38)	(1.06-2.29)	(1.33-2.93)	(1.30-2.74)
Never or rarely	1498	(1)	(1)	(1)	(1)
Sometimes or often	959	1.77*	1.65	2.21**	1.94*
Men		(1.03-3.05)	(0.99-2.73)	(1.31-3.73)	(1.19-3.16)
Never or rarely	933	(1)	(1)	(1)	(1)
Sometimes or often	478	1.34	1.43	1.80	1.88*
		(0.70-2.56)	(0.77-2.66)	(0.97-3.32)	(1.05-3.39)
Conflict w Father					
Full Sample					
Never or rarely	2664	(1)	(1)	(1)	(1)
Sometimes or often	1206	1.53*	1.27	1.86**	1.55*
Women		(1.01-2.31)	(0.85-1.89)	(1.24-2.78)	(1.06-2.28)
Never or rarely	1725	(1)	(1)	(1)	(1)
Sometimes or often	732	1.77*	1.29	2.14*	1.54
Men		(1.03-3.05)	(0.76-2.17)	(1.26-3.62)	(0.94-2.55)
Never or rarely	938	(1)	(1)	(1)	(1)
Sometimes or often	473	1.24	1.25	1.51	1.55
		(0.65-2.36)	(0.67-2.33)	(0.82-2.80)	(0.85-2.81)
Parents argued					
Full Sample					
Never or rarely	2570	(1)	(1)	(1)	(1)
Sometimes or often	1287	1.52*	1.37	1.67*	1.48*
Women		(1.01-2.30)	(0.92-2.02)	(1.12-2.50)	(1.01-2.16)
Never or rarely	1532	(1)	(1)	(1)	(1)
Sometimes or often	914	1.91*	1.38	2.18**	1.54
Men		(1.11-3.29)	(0.84-2.28)	(1.29-3.70)	(0.94-2.52)
Never or rarely	1037	(1)	(1)	(1)	(1)
Sometimes or often	372	1.08	1.35	1.27	1.56
Parental Tension		(0.54-2.15)	(0.71-2.58)	(0.65-2.46)	(0.84-2.91)
Full Sample					
Never or rarely	2822	(1)	(1)	(1)	(1)
Sometimes or often	1048	1.73*	1.32	1.97***	1.48
Women		(1.13-2.63)	(0.87-1.98)	(1.31-2.95)	(1.00-2.20)
Never or rarely	1690	(1)	(1)	(1)	(1)
Sometimes or often	765	2.20**	1.41	2.60***	1.63
Men		(1.28-3.78)	(0.84-2.35)	(1.54-4.40)	(0.99-2.68)
Never or rarely	1131	(1)	(1)	(1)	(1)
Sometimes or often	282	1.45	1.43	1.45	1.43
Mother's Rules		(0.72-2.91)	(0.73-2.83)	(0.72-2.91)	(0.73-2.83)

Family Related Variables	Frequency (*n*)	Odds-Ratio ADHD only		Odds-Ratio ADHD & CP	
		Inattention	*Hyperactivity-Impulsivity*	*Inattention*	*Hyperactivity-impulsivity*
Full Sample					
Inconsistent	366	(1)	(1)	(1)	(1)
Consistent	3494	0.54*	0.75	0.44**	0.60
Women		(0.31-0.96)	(0.42-1.35)	(0.26-0.75)	(0.35-1.05)
Inconsistent	239	(1)	(1)	(1)	(1)
Consistent	2209	0.38*	0.74	0.33***	0.61
Men		(0.19-0.76)	(0.35-1.55)	(0.17-0.63)	(0.30-1.24)
Inconsistent	127	(1)	(1)	(1)	(1)
Consistent	1283	1.03	0.77	0.73	0.58
		(0.37-2.86)	(0.30-1.97)	(0.28-1.91)	(0.24-1.40)
Father's Rules					
Full Sample					
Inconsistent	711	(1)	(1)	(1)	(1)
Consistent	3151	0.57*	0.64	0.45***	0.53**
Women		(0.36-0.89)	(0.41-1.00)	(0.29-0.70)	(0.35-0.81)
Inconsistent	484	(1)	(1)	(1)	(1)
Consistent	1968	0.52*	0.62	0.40***	0.51*
Men		(0.29-0.94)	(0.35-1.09)	(0.23-0.70)	(0.30-0.87)
Inconsistent	227	(1)	(1)	(1)	(1)
Consistent	1181	0.65	0.66	0.52	0.54
		(0.31-1.37)	(0.32-1.37)	(0.26-1.07)	(0.27-1.07)
Mother's Drinking					
Full Sample					
Never or rarely	2608	(1)	(1)	(1)	(1)
Sometimes or often	1260	0.81	0.97	0.81	0.97
Women		(0.52-1.25)	(0.65-1.44)	(0.52-1.25)	(0.65-1.44)
Never or rarely	1697	(1)	(1)	(1)	(1)
Sometimes or often	759	0.77	0.90	0.72	0.86
Men		(0.42-1.41)	(0.52-1.55)	(0.40-1.31)	(0.50-1.48)
Never or rarely	910	(1)	(1)	(1)	(1)
Sometimes or often	500	0.93	1.14	0.89	1.11
		(0.48-1.79)	(0.61-2.12)	(0.47-1.69)	(0.61-2.01)
Father's Drinking					
Full Sample					
Never or rarely	1396	(1)	(1)	(1)	(1)
Sometimes or often	2474	0.80	0.79	0.80	0.79
Women		(0.54-1.20)	(0.54-1.16)	(0.54-1.20)	(0.54-1.16)
Never or rarely	884	(1)	(1)	(1)	(1)
Sometimes or often	1573	0.75	0.75	0.75	0.76
Men		(0.43-1.28)	(0.45-1.25)	(0.44-1.26)	(0.46-1.25)
Never or rarely	511	(1)	(1)	(1)	(1)
Sometimes or often	900	0.90	0.82	0.90	0.85
		(0.47-1.71)	(0.44-1.52)	(0.48-1.67)	(0.47-1.54)

Note: * $p \leq .05$, *Note:* ** $p \leq .01$, *** $p \leq .001$, $n = 3876$

Table A3

Health Variables Predicting ADHD Subtypes

Health Related Variables	Frequency (n)	Odds-Ratio ADHD		Odds-Ratio ADHD & CP	
		Inattention	*Hyperactive Impulsivity*	*Inattention*	*Hyperactive Impulsivity*
Days Ill year [a]					
Full Sample					
< 31 days	2607	(1)	(1)	(1)	(1)
>30 days	71	3.74*	1.63	4.43**	2.00
Women		(1.29-10.90)	(0.48-5.49)	(1.60-12.26)	(0.62-6.42)
< 31 days	1690	(1)	(1)	(1)	(1)
>30 days	51	5.94**	2.02	6.61***	2.52
Men		(1.79-19.67)	(0.52-7.86)	(2.12-20.61)	(0.69-9.27)
< 31 days	917	(1)	(1)	(1)	(1)
>30 days	20	0.86	0.73	1.21	1.02
Birth Weight (g)		(0.05-14.42)	(0.04-12.20)	(0.08-18.21)	(0.07-15.42)
Full sample					
< 2501g	658	(1)	(1)	(1)	(1)
> 2500g	1012	0.73	0.79	0.77	0.84
Women		(0.37-1.43)	(0.44-1.43)	(0.40-1.50)	(0.47-1.49)
< 2501g	501	(1)	(1)	(1)	(1)
> 2500g	661	0.62	0.79	0.66	0.81
Men		(0.27-1.42)	(0.38-1.66)	(0.29-1.46)	(0.39-1.67)
< 2501g	157	(1)	(1)	(1)	(1)
> 2500g	351	1.13	0.72	1.10	0.76
Physical health		(0.30-4.18)	(0.26-1.98)	(0.31-3.96)	(0.29-2.01)
Full Sample					
Poor – Fair	778	(1)	(1)	(1)	(1)
Good – excellent	3090	0.47***	0.63*	0.41***	0.55*
Female		(0.30-0.73)	(0.41-0.97)	(0.27-0.62)	(0.36-0.83)
Poor – Fair	505	(1)	(1)	(1)	(1)
Good – excellent	1951	0.39***	0.53*	0.34***	0.46**
Male		(0.22-0.69)	(0.31-0.92)	(0.20-0.58)	(0.27-0.77)
Poor – Fair	273	(1)	(1)	(1)	(1)
Good – excellent	1137	0.60	0.85	0.53	0.72
Emotional health		(0.30-1.23)	(0.41-1.75)	(0.27-1.04)	(0.36-1.44)
Full Sample					
Poor – Fair	674	(1)	(1)	(1)	(1)
Good – excellent	3194	0.20***	0.36***	0.18***	0.32***
Female		(0.13-0.31)	(0.24-0.55)	(0.12-0.28)	(0.22-0.49)
Poor – Fair	438	(1)	(1)	(1)	(1)
Good – excellent	2018	0.18***	0.35***	0.16***	0.31***
Male		(0.10-0.31)	(0.20-0.59)	(0.10-0.28)	(0.18-0.51)
Poor – Fair	235	(1)	(1)	(1)	(1)
Good – excellent	1175	0.23***	0.39*	0.20***	0.34***
Close friends		(0.12-0.45)	(0.20-0.78)	(0.11-0.39)	(0.18-0.66)
Full Sample					
No	132	(1)	(1)	(1)	(1)
Yes	3736	0.46	0.51	0.38*	0.45
Female		(0.20-1.07)	(0.22-1.19)	(0.17-0.85)	(0.20-1.00)
No	64	(1)	(1)	(1)	(1)
Yes	2393	0.41	0.36	0.35	0.34
Male		(0.12-1.41)	(0.12-1.13)	(0.11-1.15)	(0.11-1.04)
No	68	(1)	(1)	(1)	(1)
Yes	1341	0.50	0.70	0.44	0.63
Marital status		(0.15-1.61)	(0.21-2.39)	(0.14-1.36)	(0.19-2.05)
Full Sample					
Not Married	1800	(1)	(1)	(1)	(1)
Married	2074	0.70	0.67*	0.60*	0.59*
Female		(0.46-1.05)	(0.46-0.99)	(0.40-0.89)	(0.40-0.86)
Not married	994	(1)	(1)	(1)	(1)
Married	1376	0.72	0.67	0.62	0.61*
Male		(0.41-1.24)	(0.40-1.11)	(0.37-1.06)	(0.37-1.00)
Not Married	717	(1)	(1)	(1)	(1)
Married	697	0.67	0.69	0.57	0.60
Sexual assault		(0.35-1.26)	(0.37-1.29)	(0.30-1.05)	(0.33-1.09)
Full Sample					
Never	3463	(1)	(1)	(1)	(1)
Once or more	327	2.38**	2.00*	3.25***	2.60***
Female		(1.38-4.09)	(1.17-3.44)	(1.94-5.44)	(1.55-4.38)
Never	2139	(1)	(1)	(1)	(1)
Once or more	279	2.55*	2.10*	4.06***	3.06***

Health Related Variables	Frequency (n)	Odds-Ratio ADHD		Odds-Ratio ADHD & CP	
		Inattention	*Hyperactive Impulsivity*	*Inattention*	*Hyperactive Impulsivity*
Male		(1.33-4.90)	(1.11-3.99)	(2.24-7.36)	(1.70-5.50)
Never	1322	(1)	(1)	(1)	(1)
Once or more	48	2.34	2.16	2.67	2.32
Alcohol problem		(0.65-8.41)	(0.57-8.16)	(0.78-9.09)	(0.65-8.28)
Full Sample					
No	2607	(1)	(1)	(1)	(1)
Yes	74	0.93	1.46	2.31	3.03*
Female		(0.26-3.31)	(0.48-4.44)	(0.72-7.38)	(1.09-8.46)
No	1708	(1)	(1)	(1)	(1)
Yes	36	1.06	1.35	2.62	2.70
Male		(0.17-6.74)	(0.24-7.68)	(0.51-13.53)	(0.57-12.77)
No	899	(1)	(1)	(1)	(1)
Yes	38	0.85	1.51	1.95	3.20
		(0.14-5.08)	(0.34-6.66)	(0.38-10.17)	(0.81-12.68)

Note: * $p \leq .05$, ** $p \leq .001$, CP = conduct problems, Alc=alcohol, CSA=child sexual assault, Phys=physical, Emot=emotional and $n = 3876$, [a]$n = 2678$.

Appendix B

Table B1

Sex-Limited Analysis with Contrast Effect for Maternal-report ADHD Subtypes and Latent Class Membership – Raw Unstandardised Paths

					Male Variance					*Female variance*			
Model	-2LL	df	*p*-value	*contrast*	*a*	*c*	*d*	*e*	*Male a*	*a*	*c*	*d*	*e*
Inattention													
ACE	8415.52	3124	--	.12 (.07,.17)	.20 (.04,.36)	.00 (-.21,.21)	--	.59 (.54,.66)	.81 (.73,.89)	.69 (.58,.78)	.00 (-.23,.23)	--	.62 (.55,.70)
ADE	8409.29	3124	--	.12 (.07,.17)	.10 (-.39,.39)	--	.31 (-.25,.65)	.59 (.53,.66)	.77 (.53,.88)	.40 (-.67,.67)	--	.60 (.27,.78)	.58 (.52,.65)
Drop contrast	8433.00	3125	<.001	--	.10 (-.19,.80)	--	.61 (.18,.85)	.51 (.46,.57)	.65 (.30,.87)	.69 (.43,.86)	--	.44 (-.68,.70)	.51 (.46,.56)
Drop male A	8419.39	3125	.001	.08 (.05,.12)	.26 (-.13,.64)	--	.80 (.54,.89)	.55 (.50,.62)	--	.46 (.08,.74)	--	.60 (.49,.62)	.55 (.50,.62)
Equal A	8410.58	3125	.26	.13 (.08,.18)	.06 (-.44,.44)	--	.33 (-.20,.56)	.59 (.53,.66)	.77 (.62, .87)	.06 (-.44,.44)	--	.72 (.56,.79)	.58 (.52,.65)
Equal AD	8423.10	3126	<.001	.11 (.07,.15)	.00 (-.38,.38)	--	.70 (.55,.77)	.56 (.51,.62)	.50 (.35,.62)	.00 (-.38,.38)	--	.70 (.55,.77)	.59 (.53,.67)
Equal AE	**8410.69**	**3126**	**.75**	**.13 (.08,.18)**	**.06 (-.44,.44)**	**--**	**.33 (-.20,.67)**	**.58 (.54,.63)**	**.77 (.62,.87)**	**.06 (-.44,.44)**	**--**	**.71 (.56,.78)**	**.58 (.54,.63)**
Hyperactivity-impulsivity													
ADE	8083.97	3124	--	.08 (.04,.12)	.65 (.51,.79)	--	.00 (-.52,.52)	.52 (.47,.58)	.57 (,.24,.68)	.84 (.71,.89)	--	.00 (-.42,.42)	.41 (.37,.46)
ACE	8083.73	3124	--	.08 (.04,.12)	.63 (.43, .82)	.11 (-.35,.35)	--	.52 (.47,.58)	.59 (.32,.72)	.82 (.74,.89)	.17 (-.38,.38)	--	.41 (.37,.46)
Drop contrast	8098.83	3125	<.001	--	.82 (.48,.97)	.00 (-.38,.31)	--	.48 (.43,.53)	.41 (-.73,.73)	.83 (.75,.90)	.33 (-.48,.48)	--	.38 (.35,.42)
Drop male A	8089.62	3125	.02	.05 (.02,.09)	.87 (.78,.94)	.14 (.04,.33)	--	.52 (.46,.58)	--	.82 (.74,.88)	.26 (.05,.42)	--	.41 (.37,.45)
Equal A	**8087.45**	**3125**	**.05**	**.06 (.03,.10)**	**.80 (.73,.87)**	**.03 (-.27,.16)**	**--**	**.51 (.46,.57)**	**.38 (-.53,.53)**	**.80 (.73,.87)**	**.27 (.06,.42)**	**--**	**.41 (.37,.46)**
Equal AC	8092.17	3126	.03	.07 (.03,.11)	.83 (.77,.88)	.00 (-23,.23)	--	.51 (.46,.57)	.36 (.16,.49)	.83 (.77,.88)	.00 (-.23,.23)	--	.42 (.38,.46)
Equal AE	8096.19	3126	<.001	.07 (.03,.11)	.76 (.68,.83)	.05 (-.18,.22)	--	.47 (.43,.51)	.50 (.36,.61)	.76 (.68,.83)	.30 (-.45,.45)	--	.47 (.43,.51)
Combined Symptoms													
ACE	8180.57	3124	--	.11 (.07,.16)	.47 (.31,.60)	.00 (-.26,.26)	--	.53 (.47,.58)	.73 (.62,.82)	.80 (.73,.86)	.00 (-.27,.27)	--	.47 (.42,.53)
ADE	8179.48	3124	--	.12 (.07,.16)	.44 (.25,.62)	--	.22 (-.57,.57)	.52 (.47,.58)	.71 (.52,.81)	.72 (.51,.85)	--	.36 (-.61,.61)	.46 (.42,.52)
Drop contrast	8205.85	3125	<.001	--	.55 (.37,.78)	--	.34 (-.67,.67)	.46 (.42,.52)	.66 (-.83,.83)	.88 (.75,.92)	--	.00 (-.44,.44)	.41 (.37,.45)
Drop male A	8189.31	3125	.002	.08 (.04,.12)	.66 (.35,.82)	--	.56 (.30,.79)	.51 (.45,.57)	--	.76 (.59,.87)	--	.34 (-.34,.56)	.45 (.40,.50)
Equal A	8183.90	3125	.04	.12 (.07,.16)	.57 (.40,.72)	--	.15 (-.39,.49)	.53 (.47,.59)	.63 (.49,.73)	.57 (.40,.72)	--	.55 (.38,.69)	.46 (.41,.51)
Equal D	8179.79	3125	.58	.11 (.07,.16)	.43 (.25,.59)	--	.30 (-.54,.54)	.52 (.47,.58)	.69 (.53,.81)	.75 (.58,.86)	--	.30 (-.54,.54)	.46 (.42,.52)
Equal DE	**8182.50**	**3126**	**.10**	**.12 (.07,.16)**	**.44 (.26,.60)**	**--**	**.27 (-.53,.53)**	**.49 (.46,.54)**	**.71 (.56,.83)**	**.73 (.57,.84)**	**--**	**.27 (-.53,.53)**	**.49 (.46,.54)**
Latent Classes													
ADE	3087.63	3170	--	-.05 (-.15,.04)	.79 (.43,.94)	--	.42 (.00,.78)	.44 (.33,.60)	.00 (-.66,.66)	.90 (.55,.96)	--	.15 (.00,.73)	.42 (.00,.78)
ACE	3087.86	3170	--	-.06 (-.20,.03)	.88 (.40,.94)	.11 (.00,.44)	--	.45 (.32,.61)	.08 (-.74,.74)	.84 (.53,.96)	.36 (.00,.71)	--	.40 (.27,.58)
Drop contrast	3091.99	3171	.04	--	.88 (.22,.92)	.11 (.00,.47)	--	.45 (.37,.68)	.08 (-.72,.78)	.84 (.52,.96)	.36 (.00,.74)	--	.40 (.30,.65)
Drop male A	3087.86	3171	1.0	-.07 (-.16,.03)	.89 (.75,.94)	.11 (.00,.41)	--	.45 (.33,.61)	--	.84 (.53,.96)	.36 (.00,.71)	--	.40 (.28,.58)
Equal A	3087.98	3172	.73	-.06 (-.16,.03)	.89 (.75,.94)	.08 (.00,.41)	--	.46 (.34,.61)	--	.89 (.75,.94)	.24 (.00,.51)	--	.40 (.28,.55)
Equal AC	3088.54	3173	.45	-.06 (-.15,.03)	.90 (.78,.94)	.00 (.00,.41)	--	.43 (.33,.56)	--	.90 (.78,.94)	.00 (.00,.41)	--	.43 (.33,.56)
Equal ACE	**3088.54**	**3174**	**1.0**	**-.06 (-.15,.03)**	**.90 (.78,.94)**	**.00 (.00,.41)**	**--**	**.43 (.33,.56)**	**--**	**.90 (.78,.94)**	**.00 (.00,.41)**	**--**	**.43 (.33,.56)**

Note: -2LL = -2 x log-likelihood; AIC = Akaike Information Criterion; df = degrees-of-freedom; Best fitting models are bolded and selected according to the least amount of change in -2LL when parameters are dropped from the model.

Table B2

Sex-Limited Analysis with Contrast Effects for Self-reported ADHD Subtypes and Latent Class Membership – Raw Unstandardised Paths

Model	-2LL	df	*p*-value	*contrast*	*Male Variance*					*Female variance*			
					a	*c*	*d*	*e*	*Male a*	*a*	*c*	*d*	*e*
Inattention													
ACE	2585.43	922	--	-.10 (-.21,.00)	.61 (.00,.82)	.00 (-.59,.59)	--	.79 (.62,.96)	.00 (-.63,.63)	.85 (.62,.97)	.00 (-.53,.53)	--	.57 (.46,.70)
ADE	2585.06	922	--	-.09 (-.20,.01)	.49 (-.81,.81)	--	.39 (-.76,.76)	.77 (.61,.96)	.00 (-.62,.62)	.75 (-.96,.96)	--	.40 (-.89,89)	.57 (.47,.70)
Drop contrast	2588.09	923	.08	--	.27 (-.64,.64)	--	.39 (-.69,.69)	.86 (.72,1.0)	.00 (-.57,.57)	.54 (-.86,.86)	--	.56 (-.87,.87)	.63 (.54,.75)
Drop male A	2588.08	924	.22	--	.27 (-.64,.64)	--	.39 (-.69,.69)	.86 (.72,1.0)	--	.54 (-.86,.86)	--	.56 (-.87,.87)	.63 (.54,.75)
Equal A	**2588.50**	**925**	**.34**	**--**	**.36 (-.64,.64)**	**--**	**.32 (-.42,.69)**	**.86 (.72,.99)**	**--**	**.36 (-.64,.64)**	**--**	**.68 (.34,.89)**	**.63 (.54,.74)**
Equal AD	2594.14	926	.02	--	.33 (-.72,.72)	--	.60 (-.79,.79)	.75 (.66,.86)	--	.33 (-.72,.72)	--	.60 (-.78,.78)	.69 (.59,.79)
Equal AE	2594.96	926	.01	--	.30 (-.70,.70)	--	.57 (-.56,.78)	.73 (.64,.83)	--	.30 (-.70,.70)	--	.62 (-.61,.81)	.73 (.64,.83)
Hyperactivity-impulsivity													
ACE	2605.21	922	--	-.07 (-.19,.06)	.49 (-.27,.78)	.00 (-.65,.65)	--	.79 (.63,.97)	.30 (-.66,.66)	.73 (-.42,.89)	.00 (-.47,.47)	--	.71 (.57,.88)
ADE	2603.86	922	--	-.04 (-.17,.06)	.32 (-.77,.77)	--	.45 (-.74,.74)	.80 (.65,.97)	.00 (-.64,.64)	.33 (-.86,.86)	--	.64 (-.85,.85)	.71 (.58,.86)
Drop contrast	2604.40	923	.46	--	.00 (-.64,.64)	--	.49 (-.68,.68)	.84 (.71,.98)	.00 (-.74,.74)	.00 (-.74,.74)	--	.67 (-.79,.79)	.74 (.65,.87)
Drop male A	2604.40	924	1.00	--	.00 (-.64,.64)	--	.49 (-.68,.68)	.84 (.71,.98)	--	.00 (-.74,.74)	--	.67 (-.79,.79)	.74 (.65,.87)
Equal A	2604.40	925	1.00	--	.00 (-.60,.60)	--	.49 (-.51,.68)	.84 (.71,.98)	--	.00 (-.60,.60)	--	.67 (-.69,.79)	.84 (.71,.98)
Equal AD	2606.38	926	.16	--	.00 (-.64,.64)	--	.60 (-.71,.71)	.78 (.69,.89)	--	.00 (-.64,.64)	--	.60 (-.71,.71)	.60 (-.71,.71)
Equal ADE	**2606.39**	**927**	**.92**	**--**	**.00 (-.64,.64)**	**--**	**.60 (-.71,.71)**	**.79 (.71,.88)**	**--**	**.00 (-.64,.64)**	**--**	**.60 (-.71,.71)**	**.79 (.71,.88)**
Combined Symptoms													
ADE	2585.25	922	--	-.10 (-.21,.01)	.51 (-.11,.77)	--	.28 (-.70,.70)	.77 (.62,.93)	.00 (-.56,.56)	.75 (-.96,.96)	--	.36 (-.88,.88)	.61 (.50,.75)
ACE	2584.41	922	--	-.10 (-.22,.00)	.58 (.03,.78)	.00 (-.57,.57)	--	.77 (.62,.93)	.00 (-.56,.56)	.84 (.58,.96)	.00 (-.55,.55)	--	.61 (.50,.75)
Drop contrast	2587.99	923	.06	--	.39 (-.13,.59)	.00 (-.44,.44)	--	.88 (.76,.99)	.00 (-.52,.52)	.73 (.45,.85)	.00 (-.50,.50)	--	.70 (.60,.81)
Drop male A	2587.99	924	1.0	--	.39 (-.13,.59)	.00 (-.44,.44)	--	.88 (.76,.99)	--	.73 (.45,.85)	.00 (-.50,.50)	--	.70 (.60,.81)
Equal A	2592.21	925	.04	--	.49 (-.66,.66)	.06 (-.22,.35)	--	.83 (.72,.95)	--	.49 (-.66,.66)	.42 (-.63,.63)	--	.76 (.67,.87)
Equal C	**2587.99**	**925**	**1.0**	**--**	**.39 (-.12,.59)**	**.00 (-.39,.39)**	**--**	**.88 (.76,.99)**	**--**	**.73 (.53,.85)**	**.00 (-.39,.39)**	**--**	**.70 (.60,.81)**
Equal CE	2592.54	926	.03	--	.51 (.14,.66)	.00 (-.39,.39)	--	.79 (.71,.87)	--	.64 (.40,.76)	.00 (-.39,.39)	--	.79 (.71,.87)
Latent Classes													
ADE	1747.99	917	--	-.09 (-.24,.05)	.73 (.27,.99)	--	.00 (.00,.69)	.67 (.46,.97)	.00 (-.61,.61)	.83 (.59,.92)	--	.00 (.00,.74)	.56 (.39,.81)
ACE	1745.77	917	--	-.17 (-.39,.01)	.52 (.00,.90)	.55 (.00,.89)	--	.63 (.41,.94)	.00 (-.62,.62)	.65 (.00,.90)	.55 (.00,.82)	--	.52 (.33,.80)
Drop contrast	1749.08	918	.06	--	.47 (.00,.88)	.38 (.00,.76)	--	.81 (.60,1.0)	.00 (-.61,.61)	.59 (.00,.86)	.40 (.00,.75)	--	.70 (.50,.89)
Drop male A	1749.08	919	1.0	--	.47 (.00,.88)	.38 (.00,.76)	--	.81 (.60,1.0)	--	.59 (.00,.86)	.40 (.00,.75)	--	.70 (.50,.89)
Equal A	1749.31	920	.63	--	.51 (.00,.82)	.36 (.00,.75)	--	.80 (.60,1.0)	--	.51 (.00,.82)	.46 (.00,.75)	--	.72 (.55,.90)
Equal AC	1749.55	921	.62	--	.53 (.00,.82)	.41 (.00,.70)	--	.81 (.60,1.0)	--	.53 (.00,.82)	.41 (.00,.70)	--	.74 (.57,.89)
Equal ACE	**1749.84**	**922**	**.59**	**--**	**.50 (.00,.78)**	**.41 (.00,.67)**	**--**	**.76 (.62,.89)**	**--**	**.50 (.00,.78)**	**.41 (.00,.67)**	**--**	**.76 (.62,.89)**

Note: -2LL = -2 x log-likelihood; AIC = Akaike Information Criterion; df = degrees-of-freedom; Best fitting models are bolded and selected according to the least amount of change in -2LL when parameters are dropped from the model.

Appendix C

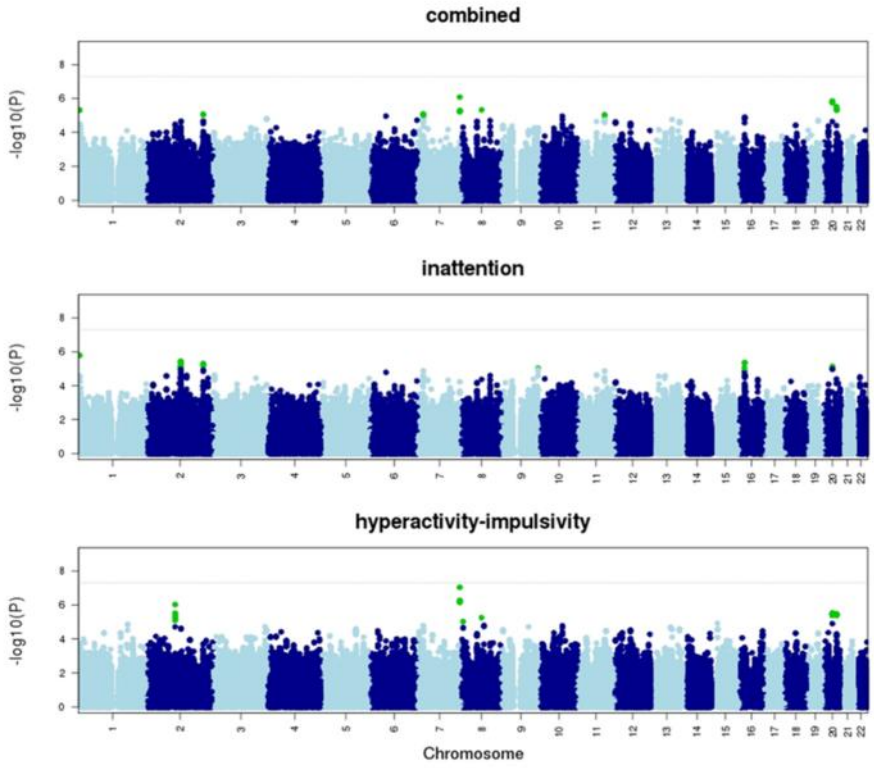

Figure C1 Manhattan plot of GWAS results for Melanocytic Naevi maternal-report SWAN ADHD data showing strength of genetic associations.

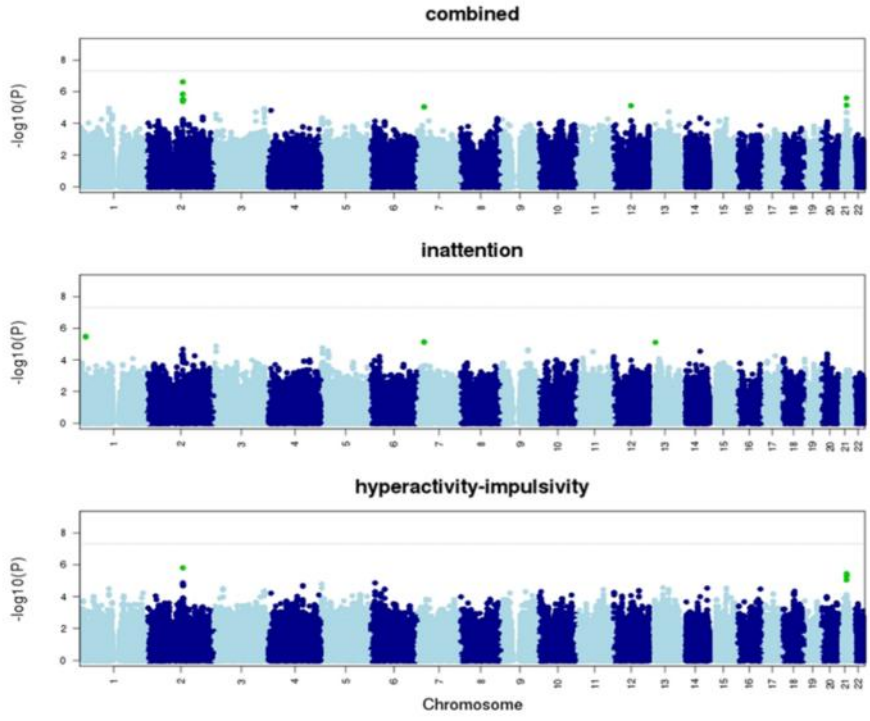

Figure C2. Manhattan plot of GWAS results for Nineteen-Up self-reported SWAN data showing strength of genetic associations.

Table C1

Descriptive Statistics for GWAS Indicating Strongest 25 SNP Associations with SWAN Measured ADHD Subtypes in Study of Melanocytic Naevi

Ch	Marker	Freq	effect	SE	h^2	P-value	Ch	Marker	Freq	effect	SE	h^2	P-value	Ch	Marker	Freq	effect	SE	h^2	P-value
	Combined							*Inattention*							*Hyp-imp*					
7	rs2110267	0.75	0.29	0.06	2.40	8.48e-07	1	rs11579593	0.94	-0.62	0.13	2.96	1.61e-06	7	rs2192271	0.78	0.27	0.05	1.90	5.39e-07
20	rs6057648	0.02	-0.80	0.17	2.07	1.48e-06	2	rs2419987	0.31	-0.22	0.05	1.40	3.66e-06	7	rs6947495	0.78	0.27	0.05	1.88	5.57e-07
20	rs6119285	0.98	0.80	0.17	2.08	1.51e-06	2	rs4848873	0.31	-0.22	0.05	1.41	3.70e-06	7	rs12671878	0.22	-0.27	0.05	1.77	7.14e-07
20	rs6057652	0.98	0.79	0.17	2.00	1.55e-06	2	rs6742416	0.31	-0.22	0.05	1.39	3.78e-06	2	rs6758152	0.10	-0.34	0.07	1.60	9.49e-07
20	rs6057651	0.02	-0.79	0.17	2.01	1.55e-06	2	rs4848871	0.69	0.22	0.05	1.39	3.79e-06	20	rs6057652	0.98	0.80	0.17	1.92	3.04e-06
20	rs7270085	0.02	-0.79	0.17	2.00	1.56e-06	2	rs4848872	0.69	0.22	0.05	1.39	3.81e-06	20	rs7270085	0.02	-0.80	0.17	1.92	3.05e-06
20	rs6119286	0.02	-0.79	0.17	2.03	1.75e-06	2	rs2670610	0.31	-0.22	0.05	1.39	3.94e-06	20	rs6057651	0.02	-0.80	0.17	1.92	3.06e-06
20	rs6057659	0.02	-0.80	0.17	2.01	1.76e-06	2	rs2256248	0.31	-0.22	0.05	1.39	3.96e-06	2	rs11903187	0.16	-0.28	0.06	1.57	3.16e-06
20	rs8123073	0.98	0.80	0.17	2.01	1.77e-06	2	rs2670605	0.69	0.22	0.05	1.40	3.97e-06	2	rs10193430	0.16	-0.28	0.06	1.56	3.23e-06
20	rs17123726	0.98	0.80	0.17	2.01	1.78e-06	2	rs2419979	0.69	0.22	0.05	1.38	4.08e-06	20	rs910191	0.70	0.22	0.05	1.55	3.23e-06
20	rs910191	0.70	0.22	0.05	1.56	3.13e-06	16	rs12596252	0.24	-0.28	0.06	1.90	4.32e-06	2	rs12613775	0.84	0.28	0.06	1.54	3.24e-06
20	rs4458264	0.71	0.21	0.05	1.44	4.46e-06	16	rs1902813	0.24	-0.28	0.06	1.88	4.43e-06	2	rs1036736	0.16	-0.28	0.06	1.54	3.24e-06
20	rs4402823	0.29	-0.21	0.05	1.44	4.49e-06	16	rs12926725	0.76	0.28	0.06	1.87	4.51e-06	20	rs6057659	0.02	-0.81	0.17	1.93	3.46e-06
20	rs4810796	0.29	-0.21	0.05	1.43	4.74e-06	2	rs2707549	0.32	-0.22	0.05	1.36	4.74e-06	20	rs8123073	0.98	0.81	0.17	1.92	3.49e-06
8	rs11994034	0.99	-1.01	0.22	2.14	4.82e-06	2	rs11681930	0.21	-0.25	0.06	1.38	4.86e-06	2	rs2119507	0.87	0.29	0.06	1.48	3.49e-06
1	rs11579593	0.94	-0.54	0.12	2.66	4.91e-06	2	rs10153620	0.21	-0.25	0.06	1.36	5.64e-06	20	rs17123726	0.98	0.81	0.17	1.92	3.51e-06
20	rs13043694	0.29	-0.21	0.05	1.43	4.99e-06	2	rs11891025	0.16	-0.27	0.06	1.30	6.25e-06	20	rs6119285	0.98	0.79	0.17	1.96	3.58e-06
7	rs2192271	0.78	0.24	0.05	1.57	5.20e-06	2	rs11892551	0.16	-0.27	0.06	1.30	6.26e-06	20	rs6057648	0.02	-0.79	0.17	1.94	3.59e-06
7	rs6947495	0.78	0.24	0.05	1.56	5.32e-06	2	rs11901919	0.84	0.27	0.06	1.30	6.27e-06	20	rs4458264	0.71	0.22	0.05	1.46	3.74e-06
7	rs12671878	0.22	-0.24	0.05	1.47	6.27e-06	2	rs12612808	0.67	0.21	0.05	1.34	6.35e-06	20	rs4402823	0.29	-0.22	0.05	1.46	3.76e-06
7	rs10257873	0.83	0.24	0.05	1.26	8.04e-06	2	rs10496613	0.65	0.22	0.05	1.39	6.38e-06	20	rs4810796	0.29	-0.22	0.05	1.45	3.95e-06
2	rs11681930	0.21	-0.23	0.05	1.30	8.39e-06	2	rs7561456	0.67	0.21	0.05	1.33	6.55e-06	20	rs13043694	0.29	-0.22	0.05	1.45	4.16e-06
2	rs10153620	0.21	-0.22	0.05	1.29	9.55e-06	2	rs6541914	0.67	0.21	0.05	1.33	6.65e-06	20	rs6119286	0.02	-0.79	0.17	1.91	4.16e-06
11	rs10750131	0.12	0.39	0.09	2.46	9.70e-06	2	rs6756857	0.69	0.22	0.05	1.37	6.93e-06	2	rs12622900	0.86	0.28	0.06	1.41	5.39e-06
7	rs3807950	0.80	0.23	0.05	1.31	9.83e-06	20	rs6057648	0.02	-0.82	0.18	1.84	7.36e-06	2	rs17029462	0.14	-0.28	0.06	1.42	5.44e-06

***Note: Eff = effect size, Ch = chromosome number Freq = allele frequency, SE = standard error,* h^2 = proportion of variance accounted for**

Table C2

Descriptive Statistics for GWAS Indicating Strongest 25 SNP Associations with SWAN Measured ADHD Subtypes in Nineteen-Up Study

Ch	Marker	Freq	Eff.	SE	h^2	P-value	Ch	Marker	Freq	Eff.	SE	h^2	P-value	Ch	Marker	Freq	Eff.	SE	h^2	P-value
	Combined							*Inattention*							*Hyp-imp*					
2	rs13001970	0.82	-0.50	0.10	22.99	2.45e-07	1	rs10917006	0.93	-0.79	0.17	18.46	3.28e-06	2	rs13001970	0.82	-0.55	0.11	19.84	1.60e-06
2	rs11678590	0.82	-0.44	0.09	17.23	1.44e-e6	1	rs9662008	0.94	-0.79	0.17	17.32	3.51e-06	21	rs363518	0.21	-0.45	0.10	14.57	3.72e-06
21	rs363518	0.21	-0.39	0.08	15.06	2.58e-e6	7	rs1978122	0.14	0.55	0.12	16.87	7.38e-06	21	rs363517	0.77	0.41	0.09	12.88	4.74e-06
2	rs4641887	0.19	0.44	0.09	17.81	3.09e-06	7	rs17211952	0.14	0.54	0.12	16.84	7.56e-06	21	rs2226333	0.23	-0.41	0.09	12.82	4.91e-06
2	rs7573598	0.20	0.44	0.09	18.53	3.18e-06	13	rs7319068	0.28	-0.41	0.09	16.69	7.74e-06	21	rs363514	0.83	0.44	0.10	11.79	8.72e-06
2	rs1113307	0.19	0.44	0.09	17.70	3.22e-06	3	rs9814302	0.85	-0.52	0.12	17.31	1.32e-05	2	rs11678590	0.82	-0.46	0.11	14.04	1.34e-05
2	rs13027475	0.81	-0.43	0.09	17.39	4.22e-06	5	rs440485	0.13	0.46	0.11	11.58	1.77e-05	6	rs6913355	0.85	0.46	0.11	11.89	1.36e-05
21	rs363514	0.83	0.37	0.08	12.00	7.28e-06	5	rs585394	0.13	0.46	0.11	11.54	1.78e-05	5	rs1632064	0.13	0.55	0.13	15.57	1.61e-05
12	rs1252268	0.31	0.37	0.08	17.87	7.72e-06	2	rs13001970	0.82	-0.46	0.11	15.42	2.08e-05	2	rs7573598	0.20	0.47	0.11	15.69	1.79e-05
7	rs1978122	0.14	0.48	0.11	16.75	9.12e-06	9	rs10817736	0.72	-0.38	0.09	13.84	2.32e-05	2	rs4641887	0.19	0.47	0.11	14.92	1.94e-05
7	rs17211952	0.14	0.48	0.11	16.73	9.25e-06	9	rs17425177	0.72	-0.38	0.09	13.81	2.33e-05	2	rs1113307	0.19	0.47	0.11	14.83	2.01e-05
1	rs11184888	0.13	-0.48	0.11	16.22	1.13e-05	9	rs10982644	0.72	-0.38	0.09	13.94	2.39e-05	2	rs13027475	0.81	-0.47	0.11	14.90	2.04e-05
1	rs2991371	0.18	-0.39	0.09	13.72	1.26e-05	9	rs10982647	0.28	0.38	0.09	14.07	2.49e-05	4	rs17492080	0.89	-0.67	0.16	18.65	2.07e-05
3	rs9814216	0.23	0.41	0.10	18.29	1.27e-05	9	rs10817739	0.72	-0.38	0.09	14.18	2.59e-05	4	rs1368509	0.89	-0.67	0.16	18.55	2.10e-05
3	rs7641401	0.23	0.41	0.10	18.29	1.27e-05	5	rs3846559	0.44	-0.32	0.08	12.50	2.63e-05	4	rs17007553	0.11	0.67	0.16	18.54	2.10e-05
3	rs7641467	0.23	0.41	0.10	18.29	1.27e-05	14	rs2238247	0.79	-0.39	0.09	11.97	2.80e-05	8	rs2084803	0.22	-0.66	0.16	32.93	2.46e-05
3	rs4859146	0.23	0.41	0.10	18.29	1.27e-05	3	rs9843022	0.14	0.51	0.12	15.00	2.87e-05	13	rs11618779	0.26	0.39	0.09	12.99	2.75e-05
3	rs6443838	0.23	0.41	0.10	18.29	1.27e-05	11	rs7925016	0.21	-0.39	0.09	11.95	2.99e-05	15	rs7177131	0.90	0.65	0.16	16.81	2.88e-05
3	rs4859260	0.77	-0.41	0.10	18.28	1.27e-05	5	rs424336	0.89	-0.60	0.14	16.61	3.42e-05	14	rs857060	0.74	-0.40	0.10	13.86	2.88e-05
3	rs2055762	0.23	0.41	0.10	18.43	1.30e-05	5	rs372208	0.90	-0.59	0.14	14.99	3.70e-05	5	rs369488	0.14	0.50	0.12	13.43	2.93e-05
3	rs1509229	0.77	-0.41	0.10	18.24	1.34e-05	5	rs436704	0.10	0.59	0.14	14.95	3.74e-05	3	rs6762182	0.17	-0.52	0.12	16.26	3.18e-05
3	rs9878775	0.77	-0.41	0.10	18.25	1.34e-05	5	rs26426	0.90	-0.59	0.14	14.95	3.99e-02	1	rs2991371	0.18	-0.44	0.11	12.45	3.19e-05
4	rs4077958	0.25	-0.41	0.09	19.29	1.53e-05	5	rs26424	0.10	0.59	0.14	14.92	8.22e-02	3	rs7650219	0.17	-0.52	0.12	16.26	3.21e-05
13	rs1326684	0.13	0.46	0.11	14.38	1.86e-05	5	rs153267	0.90	-0.59	0.14	14.88	3.86e-05	3	rs9864339	0.83	0.52	0.12	16.25	3.21e-05
3	rs7622233	0.84	-0.45	0.11	16.24	1.96e-05	2	rs11678590	0.82	-0.42	0.10	12.32	4.08e-05	16	rs4843469	0.37	-0.39	0.09	15.22	3.29e-05

***Note: Eff = effect size, Ch = chromosome number Freq = allele frequency, SE = standard error,* h^2 = proportion of variance accounted for**