# The environmental and genetic aetiology of the severity and presence of attention and hyperactivity related disorders in a population from South Africa

Jade Mansfield

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Supervisor: Ms Z. Odendaal

Co-supervisor: Mrs S-R. Schneider

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# List of abbreviations

| | |
|---|---|
| 5-HIAA | 5-hydroxy-indolacetic acid |
| 5-HT | 5-Hydroxytryptamine, serotonin |
| 5-HTP | 5-hydroxytryptophan |
| *5-HTT* | Serotonin transporter |
| *5-HTT*LPR | Serotonin-transporter-linked polymorphic region |
| A | Adenine |
| AADC | L-amino acid decarboxylase |
| AAISRS | Adult ADHD Investigator Symptom Rating Scale |
| ADD | Attention Deficit Disorder |
| ADD-DF | Brown ADD Diagnostic Form |
| ADD-H | Attention Deficit Disorder with Hyperactive characteristics |
| ADHD | Attention-Deficit Hyperactivity Disorder |
| ADHD-C | Attention-Deficit Hyperactivity Disorder Combined type |
| ADHD-HI | Attention-Deficit Hyperactivity Disorder Predominantly Hyperactive/Impulsive |
| ADHD-I | Attention-Deficit Hyperactivity Disorder Predominantly Inattentive |
| ADHD-RS-IV | ADHD Rating Scale-IV |
| AI | Adult Interview |
| ASRS | Adult ADHD Self-report Scale |
| bp | Base pairs |
| BPD | Bipolar disorder |
| Brown ADD-RS | Brown ADD Rating Scale |
| BSA | Bovine Serum Albumin |
| C | Cytocine |
| CAADID | Conners' Adult ADHD Diagnostic Interview for DSM-IV |
| CAARS | Conners Adult ADHD Rating Scales |
| CADDRA | Canadian Attention-Deficit Hyperactivity Disorder Resource Alliance |
| CD | Conduct disorder |
| CHRNA4 | Nicotinic acetylcholine receptor alpha 4 subunit |
| ChSS-SRF | Childhood Symptom Scale – Self Report Form |
| $Cl^-$ | Chlorine ion |
| CSS-SR | Current Symptoms Scale Self-report |
| CSV | Comma-separated values |
| DAT | Dopamine transporter |
| DIVA | Diagnostic Interview for Adults with ADHD |
| DMSO | Dimethyl sulfoxide |
| DNA | Deoxyribonucleic acid |
| dNTP | Nucleotide triphosphates containing deoxyribose |
| DRD4 | Dopamine receptor D4 |
| DSM | Diagnostic and Statistical Manual of Mental Disorders |
| EDTA | Ethylenediaminetetraacetic acid |
| EtOH | Ethanol hydroxide |
| FAS/FAE | Foetal alcohol syndrome/Fetal alcohol exposure |
| FDA | US Food and Drug Administration |
| $Fe^+$ | Iron ion |
| fMRI | Functional magnetic resonance imaging scans |
| g | Gravitational force |
| G | Guanine |
| GEC | Gene-Environment Correlation |
| GEI | Gene-Environment Interaction |
| Hg | Mercury |

| | |
|---|---|
| *HTR1B* | Hydroxytryptamine (Serotonin) receptor 1B |
| *HTR2A* | Hydroxytryptamine (Serotonin) receptor 2A |
| HWE | Hardy-Weinberg Equilibrium |
| IBM® SPSS | International Business Machines Corporation Statistical package for the Social Sciences |
| IQ | Intelligence quotient |
| kg | Kilogram |
| L | Litre |
| L allele | Long allele |
| LD | Learning Disorder |
| MAO | Monoamine oxidase |
| MAO-A | Monoamine oxidase A |
| MAO-B | Monoamine oxidase B |
| MBD | Minimal Brain Dysfunction |
| $Mg^{2+}$ | Magnesium ion |
| $MgCl_2$ | Magnesium chloride |
| ml | Millilitres |
| mM | Micro molar |
| Mn | Manganese |
| MRI | Magnetic resonance imaging |
| n | Number of individuals |
| $NA^{+}$ | Sodium ion |
| $NAD^{+}$ | Nicotinamide adenine dinucleotide |
| NET | Norepinephrine transporter |
| ng | Nanograms |
| OCT | Organic cation transporter |
| OCD | Obsessive Compulsive Disorder |
| ODD | Oppositional Defiant Disorder |
| Pb | Lead |
| PCBs | Polychlorinated biphenyls |
| PCR | Polymerase chain reaction |
| PET | Positron emission technology |
| PMAT | Plasma membrane monoamine transporter |
| S allele | Short allele |
| *SERT* | Serotonin transporter |
| *SLC6A4* | Solute carrier 6 A4 (Serotonin transporter gene) |
| SNP | Single-nucleotide polymorphism |
| SBP | Serotonin-binding protein |
| T | Thymine |
| Tm | Melting temperature |
| U | Units |
| ug | Microgram |
| VNTR | Variable number of tandem repeats |
| WFIRS-P | Weiss Functional Impairment Rating Scale – Parent report |
| WFIRS-S | Weiss Functional Impairment Rating Scale – Self Report |
| WRAADDS | Wender-Reimherr Adult Attention Deficit Disorder Scale |
| WURS | Wender Utah Rating Scale |
| µl | Microliters |

# Chapter 1

## General introduction, motivation, aims, and outline of the research

Referencing style used in this dissertation is the APA 6th Edition

## 1.1 Introduction: A brief overview of ADHD

Children are inherently energetic, impulsive, and unfocused. Therefore, drawing the line between a normal, happy, fun-loving child and abnormal behaviour can be problematic. Debates have also surrounded the suggestion that parents use Attention-Deficit Hyperactivity Disorder (ADHD) as an excuse for ineffective parenting methods (Wheeler, 2010). Thus, distinguishing children with serious attention and hyperactivity problems from children who display normal levels of these for their age becomes complicated (Singh, 2003; Tait, 2009). Attention-Deficit Hyperactivity Disorder is a neurodevelopmental disorder which occurs often in childhood and, in some instances, progresses into adulthood (Barkley, Murphy, & Fischer, 2008). The definition repeatedly provided in the literature does not cover the full extent of the nature of ADHD. This is a highly complex disorder which shares symptoms with many other psychological and behavioural conditions, such as oppositional defiant disorder, conduct disorder and bipolar disorder (A. Brown *et al.*, 2012; Ebejer *et al.*, 2012; Gadow & Nolan, 2002; Kessler *et al.*, 2006; Vance & Luk, 2001; van Goozen *et al.*, 2004). For this reason significant problems are experienced not only with the defining, but also the diagnosing of the disorder (Ferrer *et al.*, 2010; Hurtig *et al.*, 2007; Tamam, Karakus, & Ozpoyraz, 2008).

It is necessary to first define ADHD. As the name suggests, it is comprised of more than one identifying characteristic. There are three possible combinations of these characteristics. These make up the different types that fall under the umbrella of the disorder ADHD. Overall, ADHD occurs at a rate of approximately 7% in the population (Thomas, Sanders, Doust, Beller, & Glasziou, 2015). Type one is more commonly known as Attention Deficit Disorder or ADD and characteristically involves an inability to pay attention (ADHD-I). The prevalence of ADHD-I is approximately 6% of the population (El-Nemr, Badr, & Salem, 2015). A second type is

characteristically comprised of impulsivity and hyperactivity (ADHD-HI). The prevalence of ADHD-HI is the lowest, occurring in approximately 4% of the population (El-Nemr *et al.*, 2015; Faraone, Biederman, & Friedman, 2000). The third is a Combined type which includes a combination of all three characteristics (inattention, hyperactivity and impulsivity) (ADHD-C) (Barkley *et al.*, 2008) and occurs at a prevalence of approximately 9% of the population (El-Nemr *et al.*, 2015). As a whole ADHD persists into adulthood in approximately 30-80% of cases. Because adult ADHD has only recently been acknowledged, the diagnosis of the disorder has increased, thus causing large discrepancies in prevalence rates (Cheung *et al.*, 2015; Kessler, Adler, Barkley, *et al.*, 2005; Robison, Sclar, & Skaer, 2005). Unlike ADHD-I and ADHD-C which show progression into adulthood in a large proportion of cases, 60% and 32%, respectively (Cheung *et al.*, 2015), ADHD-HI appears to decrease with age (showing only about 8% progression) (Cheung *et al.*, 2015; Holbrook *et al.*, 2014).

A recent line of research has considered whether deficits in executive functioning are the underlying cause of ADHD symptoms and may predict the progression of ADHD into adulthood (McCabe *et al.*, 2010; Rinsky & Hinshaw, 2011; Mandell & Ward, 2011; Johnson, 2015; Ziereis & Jansen, 2015). Executive functioning, also known as higher order cognition or goal-directed behaviour, includes complex cognitive tasks such as working memory, self-regulation, shifting mental sets, goal maintenance, planning, maintaining behaviour and attention (Barkley, 1997b; Mandell & Ward, 2011; Rinsky & Hinshaw, 2011). Many of these tasks are also affected in individuals with ADHD, hence the interest in this line of work.

Attention and hyperactivity problems have become increasingly diagnosed since the turn of the century (Ebejer *et al.*, 2012; Holowenko & Pashute, 2000; Huss, Holling, Kurth, & Schlack, 2008; Ponizovsky, Marom, & Fitoussi, 2014; Robison *et al.*, 2005; Safer, Zito, & Fine,

1996; Thomas *et al.*, 2015; Visser *et al.*, 2014a) and because of this, the debate regarding the effectiveness of diagnosis has come into question (Simon, Czobor, Balint, Meszaros, & Bitter, 2009; Visser, Bitsko, Danielson, Perou, & Blumberg, 2010). Recently the DSM (Diagnostic and Statistical Manual for Mental Disorders) description for ADHD has been updated for the DSM-V to better characterise and illustrate the symptoms of ADHD, as well as to take into account the fact that ADHD may continue into adulthood (American Psychiatric Association, 2013).

## 1.2 Population statistics and prevalence

Issues with estimated prevalence rates occur due to varied methods of measurement (Hinshaw *et al.*, 2011; Lahey, Pelham, Loney, Lee, & Willcutt, 2005). Different researchers use different psychometric tests to confirm the presence or absence of a disorder and use different properties for the inclusion and exclusion of individuals in the group marked abnormal. Even self-report scales versus structured interviews cause discrepancies in the statistical prevalence of disorders (Magnusson, 2006). Also, the inclusion of multiple reports of a single individual's behaviour may cause the exclusion of that individual from a sample and thus lower the prevalence rates of certain disorders (Magnusson, 2006). Several affected individuals may be misdiagnosed or underdiagnosed, thus reinforcing the necessity for research into potential diagnostic markers.

Clinically diagnosed ADHD in children shows a prevalence of about 5% to 7% across various populations, including populations from Europe and North America (Huss *et al.*, 2008; Thomas *et al.*, 2015). In a population of Brazilian individuals aged 14 and older (adolescents and adults), Polanczyk *et al.* (2010) found a prevalence rate of 6%. De Zwaan *et al.* (2012) found a prevalence of 4.7% for adults in a large German population, and went so far as to make a distinction between the prevalence of ADHD in rural areas (12.1%) as compared to those in

urban areas (3.8%). They also noted age differences, with ADHD being more common in young adults (ages 18-24) than in older adults (ages 55-64). Contrary to the high prevalence rates suggested by other studies, Holowenko and Pashute (2000) found a prevalence rate of between 0.3% and 0.4% in a British school population. Ebejer *et al.* (2012) found a prevalence rate of between 1.1% and 2.7% for an Australian population. They also described rates of persistence into adulthood as occurring at about 24.6% to 63%. Inmates have been shown to display a prevalence of around 10.5%, as compared to the 2% to 5% prevalence found for the general population (Cahill *et al.*, 2012). Further, among female prisoners the prevalence is around 15.1%, as opposed to the 9.8% prevalence in male prisoners (Cahill *et al.*, 2012). Amongst incarcerated youths, prevalence rates are about 20% (Gordon & Moore, 2005). In terms of the prevalence of specific subtypes, the hyperactivity-impulsivity type occurs most often, followed by the prevalence for predominantly inattentive type, and finally the Combined subtype (Cahill *et al.*, 2012). Quite clearly statistical estimates of the prevalence of ADHD are difficult to interpret correctly, and should be used with great caution. It is important to consider that different populations may be influenced by different environmental components, as well as differences in allele frequencies. However, the general consensus for the prevalence of ADHD is about 3-6% of the population, and increases when ADHD predominantly inattentive type (ADHD-I) is included.

The diagnosis of ADHD has been irregular at best, with name and diagnostic criteria changes creating much uncertainty about the true prevalence. If medication use is any indication, then the prevalence of ADHD has risen hugely (Nigg, 2006). In the United States of America, the use of Methylphenidate as a treatment for ADHD doubled from 1981 to 1987 and then again from 1991 to 1995 (Nigg, 2006; Olfson, Gameroff, Marcus, & Jensen, 2003; Zito,

Safer, Gardner, Boles, & Lynch, 2000). This is a fourfold increase over a time frame of just fifteen years. During the 1990s the use of stimulant medication other than Methylphenidate has also doubled, whereas the diagnosis of ADHD by physicians has doubled in boys and tripled in girls (Garfield *et al.*, 2012; Hinshaw *et al.*, 2011; Nigg, 2006; Olfson *et al.*, 2003; Visser *et al.*, 2014a; Zito *et al.*, 2000). It is vital that clinicians refine their knowledge to make accurate diagnoses of individuals with ADHD. This can only be done by clinicians, scientists, educators and parents coming to consensus about what constitutes ADHD and to identify ADHD in each individual's own context.

## 1.3 Research motivation and outline

The fact that the prevalence of ADHD has increased so greatly in the last few years is the biggest mitigating factor for more research (Robison, Sclar, Skaer, & Galin, 1999; Visser *et al.*, 2010). As we have seen, the difficulty of diagnosing ADHD, especially in children, warrants the uncovering of more knowledge. Of even greater concern is the lax prescription of stimulant medication (Huang, Chu, Cheng, & Weng, 2014; Visser *et al.*, 2010), where in young children this could affect neural development (Kalia, 2008; Shanks *et al.*, 2015).

It can be deduced that ADHD in children is problematic due to an inability to function and succeed, especially in terms of education. However, less often considered is the problematic nature of ADHD in adults. Adults with ADHD have problems maintaining jobs due to constant distraction or difficulty in completing tasks (D. Das, Cherbuin, Butterworth, Anstey, & Easteal, 2012; Whalen, Jamner, Henker, Delfino, & Lozano, 2003). While research into the presence of ADHD in children is warranted, the progression of this condition into adulthood is, by no means, inconsequential. A further reason for studying adults is the variable nature and plasticity of children's brains (Kolb & Gibb, 2014). Before puberty the brain is still making and

terminating vital connections, thus it stands to reason that behaviour in children has not yet reached a point of stability and may be wildly variable, until the brain has completely developed (de Magalhães & Sandberg, 2005). This said, it may be more plausible to observe and study ADHD in adults in order to understand causation and then determine whether this is applicable in children with the disorder.

Many genetic studies have been performed, some successful in identifying genes associated with ADHD (Agranat-Meged *et al.*, 2008; Arias-Vásquez *et al.*, 2011; Baca-García *et al.*, 2005; Ballon *et al.*, 2007; Banerjee, Banerjee, Chatterjee, Sinha, & Nandagopal, 2012; Bellgrove & Mattingley, 2008; Bhaduri, Sarkar, Sinha, Chattopadhyay, & Mukhopadhyay, 2010; Bidwell *et al.*, 2011; Biederman *et al.*, 2008; Bobb *et al.*, 2005; Bralten *et al.*, 2013; Brookes *et al.*, 2006; Cao, LaRocque, & Li, 2013; Carrasco *et al.*, 2005; Caylak, 2012; Guimarães *et al.*, 2006, 2009; Laucht, Hohm, Esser, Schmidt, & Becker, 2007; Ribases *et al.*, 2007; Smoller *et al.*, 2006) and some not (Altink *et al.*, 2008; Ballon *et al.*, 2007; Bellgrove & Mattingley, 2008; Bobb *et al.*, 2005; Brookes *et al.*, 2006; Caylak, 2012; Ho *et al.*, 2012; Ribases *et al.*, 2007). In fact, the list of candidate genes and gene polymorphisms is extensive (Zhang *et al.*, 2012). What is less widely understood is exactly how these genes work together to produce what we phenotypically characterise as ADHD. What is widely debated in any genetic study of behaviour is the role of nature and nurture (Barkley, 1997a; Wender, 2000). There are many debates surrounding the extent to which environmental factors, such as exposure to smoking, diets high in sugar, and highly polluted environments influence the presence of ADHD (Altink *et al.*, 2009; Barkley, 1997a; Hurtig *et al.*, 2007; Kandel, 1998; Robison *et al.*, 1999; Rodriguez & Bohlin, 2004a; Wender, 2000). The extent to which lack of sleep, smoking, and exercise play on improving or worsening ADHD symptoms is questionable (Gapin, Labban, Bohall, Wooten,

& Chang, 2015; Laucht *et al.*, 2007; Roth & Zinsenheim, 2009). This all points to a lack of understanding of the mechanisms at work in creating and contributing to the phenotypic representation of ADHD.

The importance of this dissertation extends far beyond assimilating information on a recognised condition. Research into adult ADHD is important to help understand and manage childhood manifestations of the condition. While a lot of research has been done on children, it is difficult to know whether this research is applicable to ADHD manifestation itself, or rather to the stage of development of the child. Observing adult ADHD could eliminate the questions around childhood developmental phases and allow for an observation of ADHD characteristics in their purest form. Also of importance is to broaden understandings on ADHD which progresses into adults and the genetic mechanisms which could be at play in this progression. Little research has been done on ADHD in adults, as it has long been considered a condition of childhood, however, this research could provide grounds for the treatment and management of ADHD in adult individuals. Identifying the genetic components of the condition could be applicable in clinical settings, and may assist clinicians (doctors, psychologists and psychiatrists) in making accurate diagnoses, in both children and in adults. Being able to make accurate diagnoses will actively reduce the amount of medications (Ritalin in particular) prescribed to children unnecessarily. This research may also be valuable in motivating clinicians to use an environment-based treatment approach, rather than a purely medicinal one.

Taking all of this into account, this study will take the form of a retrospective comparative cohort study. It will make use of a sample of adult individuals, already diagnosed with ADHD, compared to a sample of individuals without ADHD. Quantitation will take place using two questionnaires, a self-report scale (the Adult ADHD Self-report Scale [ASRS] and the

Weiss Functional Impairment Rating Scale – Self Report [WFIRS-S]) and a semi-structured interview (Diagnostic Interview for Adults with ADHD [DIVA]) (CADDRA, 2011; Kessler, Adler, Ames, *et al.*, 2005; Kooij & Francken, 2010; Weiss, 2000). The self-report survey will also include a significant section pertaining to biographical and environmental data necessary for statistical analysis in this study (CADDRA, 2011). Studies on the success of self-report versus interview for the quantitation of ADHD for research purposes are very limited, thus a comparison will be made between the two assessment methods, with focus on a general discussion of each method in terms of the problems and pitfalls of each. It is important to note that these questionnaires will primarily be used to ensure continuity, simplicity, reliability and validity rather than for re-diagnosis of ADHD participants. This will be discussed in Chapter 3 of this dissertation.

Genetic material will be collected in order to analyse genes encoding for components in the serotonergic system, suspected of being integral in the modulation of ADHD. Gene regions to be analysed include two encoding for serotonin receptors and one encoding the serotonin transporter. Within these genes, four polymorphisms will be singled out for analysis based on previous associations, including three single-nucleotide polymorphisms (SNPs) and one variable number of tandem repeats (VNTR) (Guimarães *et al.*, 2006, 2009; Ribases *et al.*, 2007; Smoller *et al.*, 2006). This will be discussed in Chapter 4.

Basic descriptive statistics will be used to determine whether the population is truly representative and unbiased. The presence of ADHD-I, ADHD-HI or ADHD-C will be assessed with the aforementioned questionnaires and correlated with gene polymorphisms in the serotonergic pathway to uncover possible associations. Environmental factors such as exposure to smoking, exercise and sleep will also be assessed against polymorphisms and

ADHD diagnosis to determine possible links. Further statistical methods, such as regression analysis and decision tree analysis will be employed to affirm significant correlations between the specified gene polymorphisms and ADHD in the South African population. This will be covered in Chapter 5.

## 1.4 Research aims and hypotheses

Attention-Deficit Hyperactivity Disorder is a multifactorial disorder involving complex gene-gene and gene-environment interactions and correlations. These complex interactions and correlations make assessment and measurement of the disorder difficult. A structured interview may prove to be a more successful method of quantitation than a self-report scale, as the interviewer can, to an extent, control the environment in which the interview is taking place, thus eliminating distractions. In addition, vital information can be obtained from interviews just by observing the participant and how they interact. Once overcoming these assessment and measurement issues, genetic and environmental contributions to ADHD will be determined. A number of genetic and environmental combinations work together to cause ADHD, hence the reason for the vast number of studies which have failed to replicate associations. Serotonin appears to play an integral role in the manifestation of ADHD. Defects in the serotonin system bring about the phenotypic manifestation of ADHD. Research will allow for a basic profile to be constructed, including combinations of genes and environmental influences which bring about ADHD, to aid and improve the diagnosis of the disorder. Genetic testing will become a more viable and successful form of diagnosis for ADHD, once the genes that are instrumental in causing the disorder are determined.

The first aim of this study is to determine whether certain environmental factors show significant associations to the modulation and/or severity ADHD. Such deductions will be made

by assessing differences and similarities within the selected population of ADHD participants compared to the unaffected sample. This may clear up uncertainties on the development of ADHD. Second, this study aims to determine what type of assessment scales (interview or self-report) provide informative data for ADHD research. The third aim of this study is to determine whether the serotonergic system contributes to the way in which ADHD (all three types) manifests. This combination of genetic and environmental information may be used to draw up a profile which may provide a plausible method of accurate diagnosis for ADHD in the future. Findings from this study will contribute to the growing pool of scientific literature on ADHD, and especially ADHD which progresses into adulthood.

## 1.5 Dissertation format

This dissertation is written in article format and thus each chapter will contain its own introduction, body and concluding remarks. This initial chapter serves as a brief and general introduction to the following chapters, as well as a motivation for and expectation of the research. Chapter 2 will serve as a full literature review on the psychobiology of ADHD, including historical, psychological, developmental, etiological and biological aspects. Chapter 2 will discuss ADHD in detail, in relation to history, symptoms, biological and neurological factors. This chapter aims to create a full picture of the disorder and ultimately to create a well-rounded definition of ADHD based on the collective research described to date. A top-down approach will be used to describe ADHD, moving from the easily observed characteristics, through unobservable neurological aspects and to complications at the cellular level. Chapter 2 will be split up into 4 sections. First, the psychological factors of ADHD will be discussed, which will include issues regarding classification and diagnostics, the behavioural and emotional tolls of ADHD which make up its symptoms and the development of ADHD through childhood and into

adulthood. Second, the underlying neurological aspects which bring about these psychological manifestations will be discussed, with specific reference to the role the serotonin pathway plays in the manifestation of ADHD. Third, the biological reasons for these neurological functionalities will be detailed. Fourth and finally, concluding remarks will be made regarding all three of these factors taken as a whole. Chapter 3 will contain an in-depth analysis of environmental components assessed in this study, as well as the benefits and limitations of using self-report scales and interviews in the assessment of ADHD for research purposes. Molecular techniques, analysis and results will be fully described and discussed in Chapter 4. Finally, all combined analyses involving both survey data and molecular data will be discussed in Chapter 5.

# Chapter 2

# The psychobiology of Attention-Deficit Hyperactivity Disorder

## Abstract

Attention-Deficit Hyperactivity Disorder (ADHD) is a complex neurodevelopmental disorder of attention and hyperactivity. Attention-Deficit Hyperactivity Disorder has had a variable history with much controversy about the validity of the disorder as a whole, and its progression into adulthood. Symptoms of adult ADHD include inattention, hyperactivity and impulsivity, as well as depression, emotional instability, poor interpersonal relationships, disorganisation, cognitive deficits, and stress intolerance. Environmental influences include prenatal stress, smoking and hypoxia as causes, and comorbid conditions, familial environment, and physical exercise as severity regulators. Neurobiological studies have mapped ADHD to the frontal and parietal areas of the brain and noted reduced activation in these areas, as well as reduced size. This has led to the suggestion of serotonergic influence in ADHD. Polymorphisms in serotonin genes which regulate transporter expression and receptor function have been implicated as biological predictors. Upon reflection, ADHD appears to fit a unified theory of executive functioning. Cognitive, behavioural and neurological deficiencies, and genetic alterations common in ADHD share links with executive functioning. This review focuses on creating a comprehensive definition of ADHD in the context of both children and adults. It covers the controversial history of the disorder, psychological aspects, including characteristics in both children and adults, neurological and biological aspects focusing on the serotonergic system, and a discussion of a unifying theory based on executive functioning.

**Keywords:** Biological aspects, Genetics, Neurological aspects, Psychological aspects, Serotonin

## 2.1 Introduction: ADHD as a complex disorder

Attention-Deficit Hyperactivity Disorder (ADHD) (Figure 2.1) has been greatly misunderstood. Not only has the classification of this disorder constantly changed (American psychiatric association, 1968; American Psychiatric Association, 1985; American psychiatric association, 1994; American Psychiatric Association, 2013; Barkley, 1997a; James, 1950; Still, 2006), but so has the societal feeling about the validity and seriousness of the condition (Clarke, Heussler, & Kohn, 2005; Wheeler, 2010). Currently ADHD is being recognised as a serious neurodevelopmental condition (American Psychiatric Association, 2013; Tait, 2009). However, due to the complexity of the disorder, accurate diagnosis is difficult and is often made without proper investigation. These difficulties occur because of large overlaps between ADHD and other psychological and cognitive disorders, both in relation to symptomology and subsequent biological components (Cook, Stein, Ellison, Unis, & Leventhal, 1995; Eubig, Aguiar, & Schantz, 2010; Schettler, 2001; Wang *et al.*, 2008; Wender, 2000).

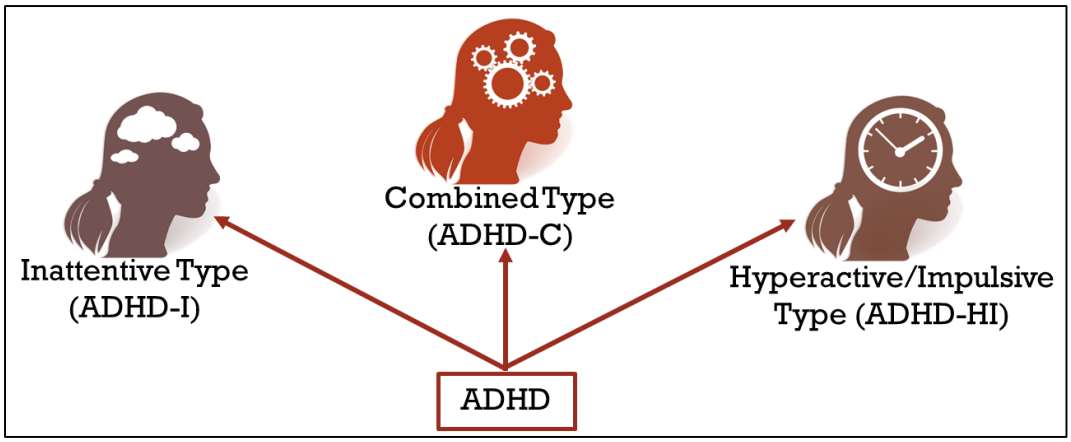


Figure 2.1: Three subtypes of the collective disorder Attention-Deficit Hyperactivity Disorder (ADHD).

Behavioural conditions are always accompanied by controversy about the contributions of nature and nurture (Coll, Bearer, & Lerner, 2014; Keller, 2010; Pigliucci, 2001; Pinker, 2004). The characteristics of ADHD caused by nature (caused by biology) include

inattention and distractibility, hyperactivity, impulsivity, restlessness, academic underachievement, mood instability, bossiness, temper outbursts and frustration (Barkley, 1997a; Caswell, Bond, Duka, & Morgan, 2015; Clarke et al., 2005; D. Das et al., 2012; Ferguson, 2000; Martin, 2014; Rapport et al., 2009; Sobanski et al., 2010; Teicher, Polcari, Fourligas, Vitaliano, & Navalta, 2012; Tsal, Shalev, & Mevorach, 2005; Tymms & Merrell, 2011; Wender, 1995, 2000; Whalen, Jamner, Henker, Delfino, et al., 2003). However, even before these symptoms manifest, studies have noted lower birth weight and delayed development, suggested to be an indication of environmental origins (Lehn *et al.*, 2007). Inattention in particular has been proposed to have strong genetic influences, and Hyperactivity has been found to have additive genetic effects (Nikolas & Burt, 2010; Pazvantoğlu *et al.*, 2013). These biological traits affect life experience and similarly life experiences affect the severity of biological traits (Retz & Rösler, 2009). Children with ADHD have been shown to have normal IQ, however, have difficulty learning and concentrating (Bridgett & Walker, 2006). This may lead to frustration from the child, parents and teachers, lowering self-esteem and enthusiasm and thereby amplifying ADHD symptoms (Eisenberg *et al.*, 2005; Joussemet, Koestner, Lekes, & Landry, 2005). Interpersonal relationships deteriorate with ADHD individuals appearing not to listen and having an apparent selfish approach (Nikolas & Burt, 2010; Wender, 2000). Studies on combined type versus inattentive type ADHD have found that ADHD-C is highly associated with aggression and comorbid behavioural disorders, as well as peer rejection, compared with ADHD-I (Nikolas & Burt, 2010). Home frustrations may be most demeaning due to difficulty for children to maintain focus (Wender, 2000). Frustration from parents may evolve into harsh discipline or parents blaming each other or themselves for the problems experienced (E. H. Arnold, O'Leary, & Edwards, 1997; Nikolas, Klump, & Burt, 2012). Household tensions may worsen behaviour as an attempt to draw attention towards the ADHD individual

(Mokrova, O'Brien, Calkins, & Keane, 2010; Nikolas *et al.*, 2012; Retz *et al.*, 2008; Wender, 2000). Nikolas *et al.* (2012) have suggested that ADHD individuals with high levels of self-blame show less concrete genetic influences for the condition.

Attention-Deficit Hyperactivity Disorder occurring in adulthood was not even considered until about the 1970s (Wood, Reimherr, Wender, & Johnson, 1976). Even today, not much is understood about the manifestation of ADHD in adults, as most studies have focused on ADHD in children (DosReis, Barksdale, Sherman, Maloney, & Charach, 2010; Faraone, Biederman, & Monuteaux, 2001; Fuchs, Birbaumer, Lutzenberger, Gruzelier, & Kaiser, 2003; Galland, Tripp, & Taylor, 2009; Kaiser, Schoemaker, Albaret, & Geuze, 2015; Karpinski, Scullin, & Montgomery-Downs, 2008; Lambert, 2005; Lycett, Mensah, Hiscock, & Sciberras, 2014; Nikolas *et al.*, 2012; Oades *et al.*, 2008; Pazvantoğlu *et al.*, 2013; Perrin & Last, 1996; Visser *et al.*, 2014b; Zito *et al.*, 2000). Due to this it is necessary to consider existing data on ADHD in children and learn about the similarities and differences with ADHD in adults. Understanding ADHD as a disorder requires an understanding of its development from childhood, through adolescence and into adulthood. However, to be able to understand biologically and neurologically what is occurring in an ADHD child, it is more plausible to begin by assessing the neurogenetic interactions in adults, as their brains have reached growth stability.

## 2.2 Psychological factors of ADHD

Psychiatry took an extensive time to arrive at the current classification of ADHD and its subtypes (Figure 2.2). The first recordings of ADHD in children were made in Shakespearean plays and German poetry in the mid-1800s (Barkley, 1997a). Later, William James described a disorder called "explosive will", similar in symptomology to ADHD (James, 1950). George Still

then described 20 children in his practice with "volitional inhibition" or a deficit in moral control (Barkley, 1997a; Still, 2006). In 1966, Stewart *et al.* began to describe ADHD as "the Hyperactive child syndrome". It was only later that the DSM included a form of ADHD.

The Diagnostic and Statistical Manual for Mental Disorders Version 2 (DSM-II) described the symptoms of ADHD and other disorders as a hyperkinetic reaction of childhood (American psychiatric association, 1968). This disorder was characterised by over activity, restlessness, distractibility and inattention occurring in childhood and declining in adolescence (Barkley, 1997a). The DSM-III initially separated ADD and grouped the other characteristics of ADHD under conduct disorder. This included a subtype, ADD-H, which included the Hyperactivity characteristics (Wender, 1995). This eliminated the definition of the disorder simply being a reaction of childhood and redefined it as being a cognitive and developmental disorder (Barkley, 1997a). Later, the revised version of the DSM-III (American Psychiatric Association, 1985) redefined ADD to ADHD under the collective category, disruptive behaviour disorder, along with conduct disorder (CD) and oppositional defiant disorder (ODD). The DSM-IV put ADHD under a new heading, Attention-Deficit and disruptive behaviour disorder (American psychiatric association, 1994). This divided the disorder into the three subtypes with two sets of characteristics, those for inattention and those for hyperactivity-impulsivity (American psychiatric association, 1994; Barkley, 1997a; Wender, 1995).

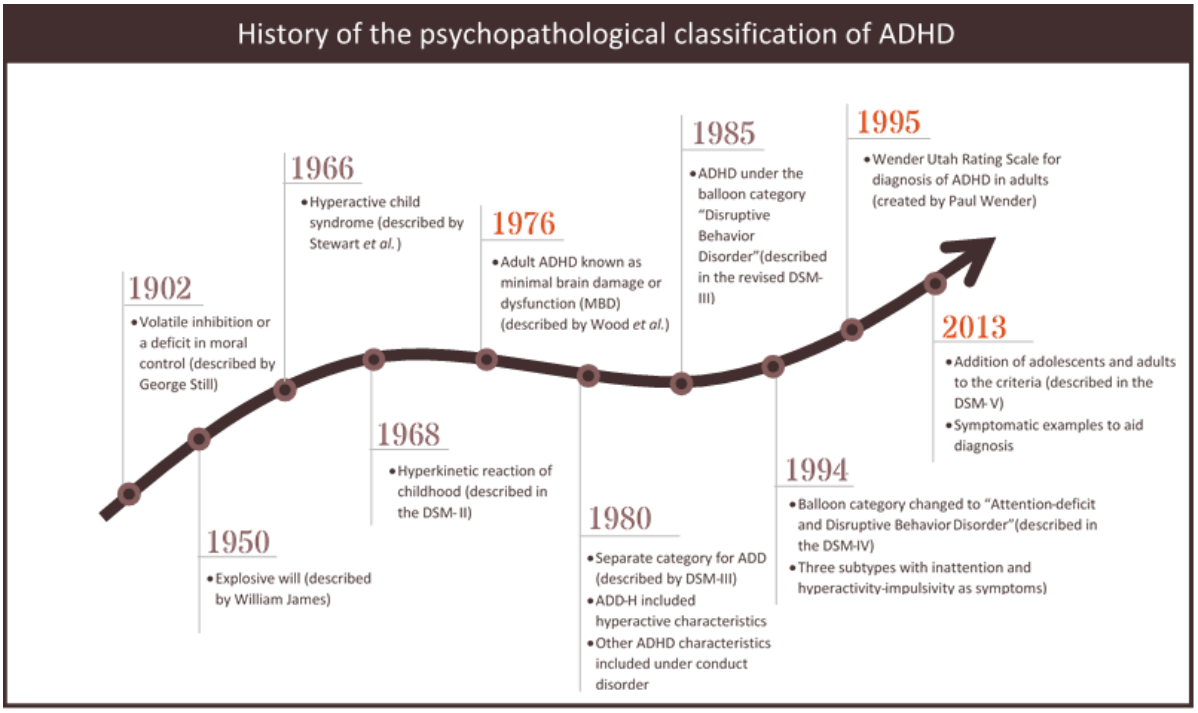


Figure 2.2: Summarising timeline depicting the evolution of the psychopathological classification of ADHD from the early 1900s to currently (Dates in orange text represent those where adult criteria were considered).

Much more recently the validity of the DSM-IV subtypes has come into question. Woo and Rey (2005) concluded that the DSM-IV was sufficient in diagnosing ADHD-C, but not ADHD-HI and ADHD-I. Further, they stated that the addition of ADHD-I to the criteria has significantly increased the prevalence rates of ADHD in recent years. They also debated on the validity of including ADHD-HI into the definition of ADHD, since inattention is central to the other two subtypes, but not this one. Woo and Rey (2005) suggest ADHD-HI is better suited to ODD (Woo & Rey, 2005). Lahey *et al.* (2005) also reported significant instability of the DSM-IV subtypes over time. Further, both Woo and Rey (2005), and Lahey *et al.* (2005) noted that children with ADHD-HI either outgrew their ADHD completely or transferred to another subtype in successive years. This further brings into question the reliability of the DSM-IV characterisation of ADHD. It is for this reason that the DSM-IV definition of ADHD has been revised. Vande Voort *et al.* (2014) commented on the results of the change of age-of-onset in the DSM-V from 7

years to 12 years. Other changes include the addition of adolescents and adults to the criteria who must present with at least 5 inattentive, hyperactive or impulsive symptoms. However, they noted that severity and comorbidity did not differ in children between ages 7 and 12. Also, symptomatic examples have been included to help clinicians in their diagnosis (American Psychiatric Association, 2013a, b). These changes resulted in the increase in the prevalence rates of ADHD.

Initially, ADHD in adults was not considered a possibility (Clarke *et al.*, 2005). It was only in the 1960s that the concept of adult ADHD was accepted (Barkley *et al.*, 2008). The reason for controversy may be that while some characteristics are carried over from childhood, it manifests somewhat differently in adults (Mendelson, Johnson, & Stewart, 1971). As with childhood ADHD, ADHD in adults has been subject to various name changes. Initially adult ADHD was considered different to childhood ADHD and termed minimal brain damage or dysfunction (MBD) (Wood *et al.*, 1976). This MBD was considered to be a combination of an error in cognition (Boydstun *et al.*, 1968; Quitkin & Klein, 1969; Singer, Stewart, & Pulaski, 1981) inherited from the parents prior to birth and unconventional child rearing practices (Keith & Erickson, 1978). To prove the progression of MBD into adulthood, Wood *et al.* (1976) treated patients with Methylphenidate (a stimulant medication also known as Ritalin) and observed positive benefits from taking the medication. Further evidence emerged that the symptoms of hyperactivity and impulsivity found in childhood ADHD sometimes progressed into adolescence (Morrison & Minkoff, 1975). The inheritance of symptoms from parents was also noted further supporting the hypothesis that ADHD could persist into adulthood (Morrison & Stewart, 1973; Wood *et al.*, 1976). The first psychometric test for adult ADHD was created by Paul Wender (Wender, 1995) called the Wender Utah Rating Scale. While this scale was

successful in including comorbid conditions such as oppositional defiant disorder, conduct disorder, mixed mood disorder and bipolar disorder, it failed to consider comorbidity between ADHD and major depression, psychosis and severe personality disorder (Barkley *et al.*, 2008). Despite many studies (Antai-Otong, 2008; Cahill *et al.*, 2012; de Zwaan *et al.*, 2012; Kessler *et al.*, 2006, 2007; Valero *et al.*, 2012; van de Glind *et al.*, 2013) there is still much debate about ADHD in adults (Barkley *et al.*, 2008; Clarke *et al.*, 2005). Literature concerning childhood ADHD is significantly more in comparison to ADHD progression into adulthood (American psychiatric association, 2013; DosReis *et al.*, 2010; Faraone *et al.*, 2001; Fuchs *et al.*, 2003; Galland *et al.*, 2009; Kaiser *et al.*, 2015; Karpinski *et al.*, 2008; Lambert, 2005; Lycett *et al.*, 2014; Nikolas *et al.*, 2012; Oades *et al.*, 2008; Pazvantoğlu *et al.*, 2013; Perrin & Last, 1996; Visser *et al.*, 2014b; Zito *et al.*, 2000).

Currently ADHD is understood to encompass a number of symptoms and cause significant life impairment. Inattention, impulsivity and hyperactivity are not the only characteristics of ADHD, however, they are the three main facets under which other characteristics fall (Crosbie, Pérusse, Barr, & Schachar, 2008; Doyle *et al.*, 2005; Rommelse, Geurts, Franke, Buitelaar, & Hartman, 2011) (Figure 2.3). These other characteristics may include aggressiveness, defiance, discipline resistance, emotionality, lawlessness, dishonesty, self-appeasement and defective moral standards in childhood (Barkley, 1997a; Ferguson, 2000; Kiive & Harro, 2013; Schroeder & Kelley, 2009; Sobanski *et al.*, 2010; Wender, 1995, 2000). In adulthood, however, characteristics such as forgetfulness, emotional instability, irritability, anxiety, self-depreciation and depression are more often experienced (Clarke et al., 2005; D. Das et al., 2012; Flory, Malone, & Lamis, 2011; Lambert, 2005; Rabiner, Anastopoulos, Costello, Hoyle, & Swartzwelder, 2008; Semeijn et al., 2015; Skirrow & Asherson, 2013;

Whalen, Jamner, Henker, Delfino, et al., 2003). It is considered essential that the ADHD symptoms impair at least two major life areas, including the workplace, education settings, social settings and/or relationships (American psychiatric association, 2013). Severe life dysfunctions may include difficulties with money management, driving, obeying the law, substance use and dependence, child rearing and running the household, maintenance of health and sexual functioning (Barkley et al., 2008; Clarke et al., 2005; D. Das et al., 2012; Ferguson, 2000; Flory et al., 2011; Lambert, 2005; Mokrova et al., 2010; Schroeder & Kelley, 2009; Whalen, Jamner, Henker, Delfino, et al., 2003). The characteristics for ADHD in children and adults thus shows some differences. To understand the full picture of ADHD, we must begin by understanding the psychological developmental factors through childhood and adulthood.

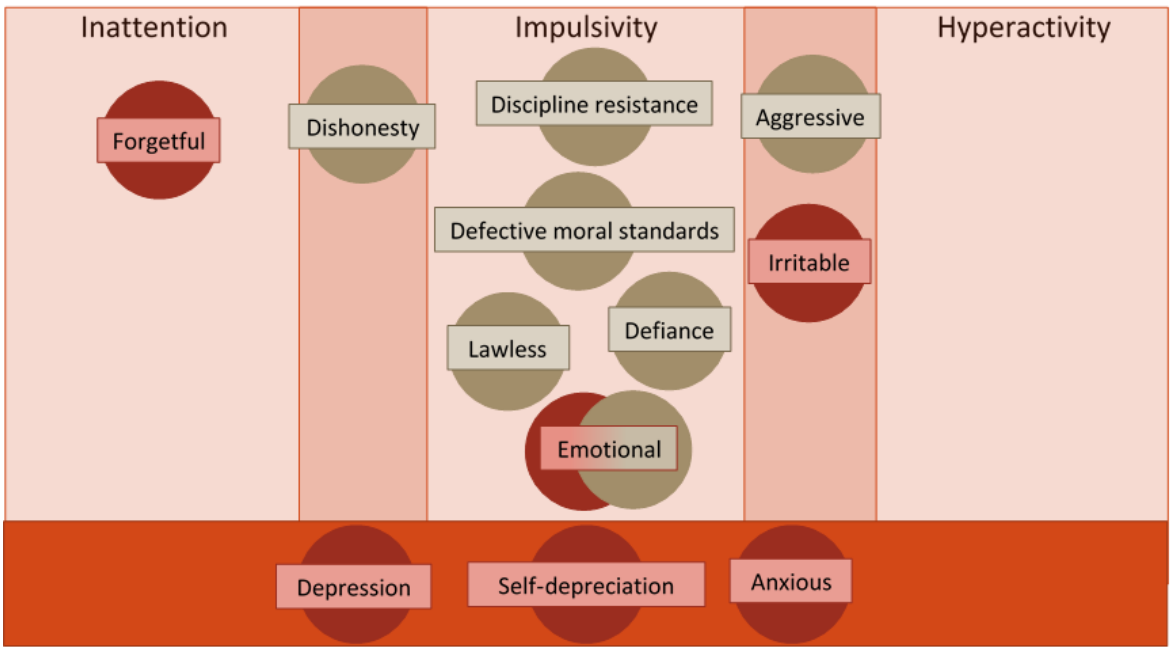


Figure 2.3: A Venn diagram displaying the overlap of characteristics in childhood (brown circles) and in adulthood (red circles), for each of the main symptoms of ADHD (inattention, impulsivity and hyperactivity), and the characteristics that occur across all three symptoms (in dark orange band).

### 2.2.1 Classification of ADHD in children

Pure childhood ADHD (without the presence of comorbid conditions) manifests itself as an inability to pay attention and a tendency to be easily distracted. Learning disabilities and other psychiatric conditions can occur comorbid with ADHD (Barkley, 1997a; Tsal *et al.*, 2005; Wender, 1995). Interestingly, the DSM-III originally described two different subtypes of inattention, namely distractibility and impulsivity in the hyperactive subset, and sluggish cognitive tempo (drowsiness, lethargy and reduced activity) in the inattentive subset (Milich, Balentine, & Lynam, 2001). Tsal *et al.* (2005) also suggested various attentional subsets, namely selective attention, sustained attention and orienting attention which are deficient in children with ADHD. Deficits in sustained attention manifest in children switching between activities often and appearing to be at a loss of things to do (Barkley, 1997a; Tsal *et al.*, 2005; Wender, 1995).

Most often, childhood ADHD is not recognised until the child begins to attend school (Faraone *et al.*, 2000) when teachers note daydreaming, difficulties with instructions, or tasks' incompletion (Figure 2.4) (Barkley, 1997a; Sushevska, Olumchev, Saveska, & Kadri, 2011; Wender, 1995). Most commonly inattention is mentioned by teachers as opposed to parents (Sushevska *et al.*, 2011). Inattention appears to be a significant factor in lower academic scorers (Rogers, Hwang, Toplak, Weiss, & Tannock, 2011). Mathematics and reading appears to be challenging in children with ADHD-I (Tymms & Merrell, 2011). Martin (2014) suggests that ADHD is a significant predictor of incomplete schoolwork, suspension and expulsion and changing schools. Parents, tend to pressure ADHD children to succeed academically, however, this often ends in reversion to previous behaviour (Rogers, Theule, Ryan, Adams, & Keating, 2009). This can further be worsened by comparisons with siblings (Pinhas, 2014). Parents may

view ADHD children as obstinate and indifferent, however, they do respond to social reinforcement, but this diminishes rapidly (Wender, 1995). Parents often do not provide consistent punishment and reward to shape the behaviour of the child in the correct manner (Mokrova *et al.*, 2010; Schroeder & Kelley, 2009; Wender, 1995). One-on-one attention may be successful in getting an ADHD child to focus optimally (Loe & Feldman, 2007). These children are often seen as capable, but uninterested (Rogers *et al.*, 2009). It is important to note that tasks which are found interesting, allow ADHD children to focus for extended periods of time (Barkley, 1997a; Wender, 1995).

Gross and fine motor Hyperactivity are common in children with ADHD. Manifestations all generally translate into an inability to sit still (Figure 2.4) (Barkley, 1997a; Rapport *et al.*, 2009; Wender, 1995). Where inattention is reported by teachers, Hyperactivity is predominantly reported by parents (Sushevska *et al.*, 2011). Mothers have even reported vigorous kicking even *in utero* (Barkley, 1997a; Wender, 1995). Rapport *et al.* (2009) described high movement rates during both visual-spatial, and phonological tasks. Further, they found that activity level in ADHD children was more elevated than in controls, even when performing complex cognitive tasks. Other manifestations of Hyperactivity include talkativeness, impaired coordination (issues with balance or hand-eye coordination), untidy handwriting, trouble colouring within the lines and struggling with sports (Barkley, 1997a; Wender, 1995). Any one of these symptoms alone does not constitute a diagnosis of Hyperactivity. A diagnosis of Hyperactivity requires a number of these symptoms to be present simultaneously. Hyperactivity symptoms such as these are not necessary for a diagnosis under the umbrella ADHD classification, i.e. a diagnosis of ADHD-I (also known as ADD) does not require any Hyperactive symptoms to be present (American psychiatric association, 2013; Wender, 1995).

The main dimension of impulsivity which is challenging in children with ADHD is inhibitory control (Avila, Cuenca, Felix, Parcet, & Miranda, 2004). Impulsivity in children may display itself in a number of ways including, impatience, irritability, recklessness and fearlessness (Figure 2.4). These children may interrupt others or interject at inappropriate times. Older children may display characteristics of antisocial behaviour and conduct disorder (CD). This may include symptoms such as lying and petty theft, setting fires and fighting (Barkley, 1997a; Wender, 1995). Disorganisation is very prominent in children with ADHD. This may manifest as tasks being completed in a disorganised and untidy manner, or not completed timeously or at all (Martin, 2014; Wender, 1995).

Children with ADHD fail at requests, due to forgetfulness or distraction (Kiive & Harro, 2013). This is unlike individuals with oppositional defiant disorder (ODD) and CD who fail to do so intentionally (Loeber, Burke, Lahey, Winters, & Zera, 2000). Interpersonal relationships may be significantly influenced by the presence of ADHD (Ferguson, 2000). Peers, parents and teachers find children with ADHD rude, bossy, stubborn and domineering often leading to peer rejection (Ferguson, 2000; Wender, 1995). Children with ADHD might seem attention-seeking and are often teased for their shortcomings. Also, these children may be lacking in social empathy (unaware of others' feelings), equivalent to a much younger child (Wender, 1995). Ferguson (2000) noted parental frustration, marital discord and divorce in families due to children affected with ADHD.

Children with ADHD often have variable moods and emotional liability (Figure 2.4). Situational context reinforces these mood outbursts. Hot temper is also characteristic of these children (Sobanski *et al.*, 2010; Wender, 1995). Some children have a decreased ability to experience pleasure, an early symptom of comorbid major depression which occurs in

approximately 9% of ADHD cases (Blackman, Ostrander, & Herman, 2005). Children with ADHD often feel helpless and assume a defeatist attitude, accompanied by low self-esteem (Wender, 1995). This can be brought about by negative reinforcement and conflict from peers and adults or by biological factors similar to those experienced by manic depressives (Schroeder & Kelley, 2009; Wender, 1995).

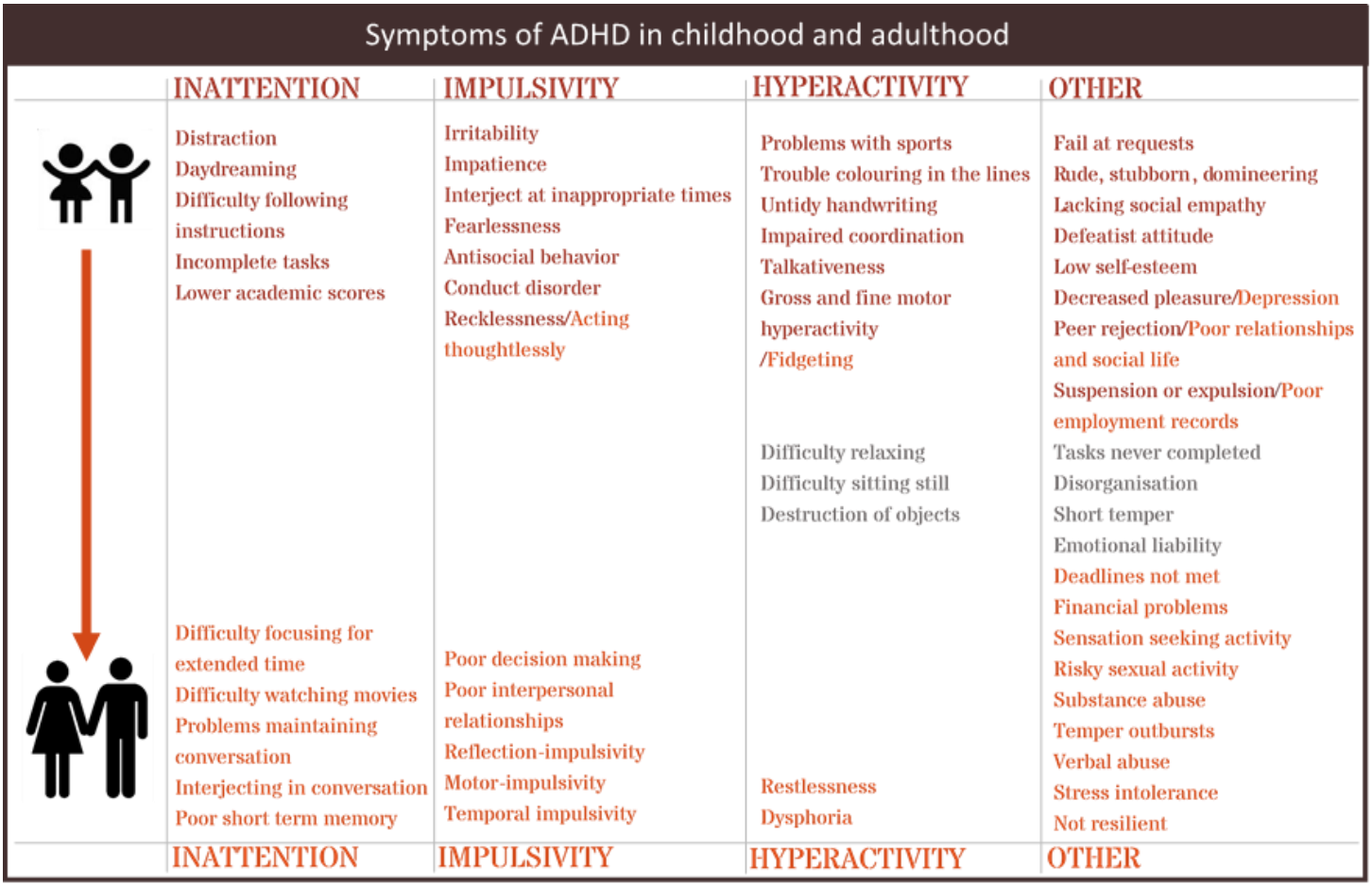


Figure 2.4: Comparison of ADHD symptoms from childhood through to adulthood (symptoms indicated in red occur in childhood, those in orange occur in adulthood; items in grey text occur throughout the lifespan; orange text alongside red text indicates a symptom which manifests slightly differently in adulthood, however, is still similar to the childhood manifestation).

### 2.2.2 Classification of ADHD in adults

Adulthood ADHD manifests similarly to childhood ADHD, but may present in more diverse and intricate ways due to developmental influences and changing life experiences.

Inattention in adulthood becomes less prominent, but remains stable through adolescence (Wender, 1995; Whalen, Jamner, Henker, Delfino, *et al.*, 2003). However, this trait does not disappear completely and may manifest itself if an individual is expected to continually focus for periods of time. Individuals who further their studies after school will most likely still experience attentional problems, as they experienced in childhood (Rabiner *et al.*, 2008; Wender, 1995). Attention problems may also manifest in adulthood in other areas of life, such as watching movies, maintaining conversation or interjecting with unrelated topics. These individuals may also have difficulties with short term memory and lose their keys or wallet, or forget meetings (Wender, 1995). Adults who know they have ADHD may realise their shortfalls and intentionally seek interesting or stimulating employment (Wender, 1995).

Wender (1995) has suggested that Hyperactivity in adults may manifest less than in childhood, decreasing to fidgeting and restlessness (Figure 2.4). However, Teicher *et al.* (2012) suggested that the manifestation of Hyperactivity in adult individuals with ADHD is significant. These individuals may find it difficult to relax and to sit still. Adults, regardless of whether or not they have ADHD, are better able to inhibit inappropriate behaviour (Velanova, Wheeler, & Luna, 2009). Dysphoria (negative affect due to anxiety) (Reber, Allen, & Reber, 2009) may manifest in the event of an individual being forced into immobility (Wender, 1995).

Unlike the decline of inattention and hyperactivity into adulthood, impulsivity increases to the point of self-injury. Impulsivity mainly occurs as poor decision making, negatively influencing work, and interpersonal relationships (Figure 2.4) (Wender, 1995). Caswell *et al.* (2015) have suggested that impulsivity should not be considered as a single construct, but rather a number of constructs, including reflection-impulsivity (tendency to make irrational decisions), motor-impulsivity (inability to inhibit behaviour) and temporal impulsivity (inability

to delay gratification). This is supported by the increased variation seen in the manifestation of adulthood impulsivity (Weiss, 2010).

Disorganisation becomes more prominent in adulthood. Childhood disorganisation may be overshadowed by structures implemented and enforced by parents and/or educators. The lack of this structure can cause the work space and even the individual's home to become extremely messy. A number of tasks (household or work or otherwise) may be taken on at any one time and never completed (Clarke *et al.*, 2005; Wender, 1995). This is probably why ADHD is often associated with poor employment records and financial problems (D. Das et al., 2012; Whalen, Jamner, Henker, Delfino, et al., 2003). Adults with ADHD often experience stress intolerance due to their characteristic irritability and inability to complete tasks which causes them to struggle to remain calm under pressure. High stress may cause more impulsivity and disorganisation and less competence which causes even greater stress (Wender, 1995; Whalen, Jamner, Henker, Delfino, *et al.*, 2003).

Although there is not much information on the effects ADHD has on interpersonal relationships in adults, it manifests in a similar way to that in childhood. Due to better impulse control and improved social understanding, the influence may be less severe (Wender, 1995). Regardless of this, relationship quality and social life may be negatively influenced by ADHD (Clarke et al., 2005; D. Das et al., 2012; Semeijn et al., 2015). This is in line with studies that have found that non-ADHD individual's appraisals of individuals with ADHD tended to be negative (Canu, Newman, Morrow, & Pope, 2007; McKee, 2014). Poor non-ADHD peer appraisal may result from a lack of emotional support and difficulty managing interpersonal conflict by individuals with ADHD (McKee, 2014).

Adults also experience short temper and emotional instability associated with ADHD, as in childhood (Figure 2.4) (Rabiner *et al.*, 2008; Skirrow & Asherson, 2013; Wender, 1995; Whalen, Jamner, Henker, Delfino, *et al.*, 2003). Adults with ADHD often have temper outbursts which are spontaneous, rather than as a result of brooding over anger. Verbal abuse and vandalism are often present (Wender, 1995). Apart from aggression, long periods of depression may also be experienced (D. Das et al., 2012; Semeijn et al., 2015; Wender, 1995). Even individuals displaying few ADHD symptoms may experience depression (D. Das et al., 2012). College students with ADHD tend to show elevated depression levels, particularly if their struggle with academic performance preventing them access to competitive universities (Rabiner *et al.*, 2008). It is important to note that depression occurs most often in individuals with inattentive symptoms (D. Das et al., 2012). An attempt is often made to escape the low peak of the mood cycle by acting impulsively and engaging in sensation seeking activity (Wender, 1995). This can present as risky sexual activity in young adults (Flory, Molina, Pelham, Gnagy, & Smith, 2006) and substance abuse (Clarke *et al.*, 2005; Lambert, 2005; Wender, 1995). Depression and ADHD appear to have a cause-and-effect relationship, where difficulties in dealing with ADHD characteristics leads to anxiety, which may cause depression.

### 2.2.3 Controversies about the aetiology of ADHD

A clinically valid diagnosis of ADHD is supported by showing positive response to treatment and the statistical distinction from similar disorders. Faraone (2005) supported the statistical plausibility of ADHD as a syndrome by noting that not all of the symptoms are accounted for by similar developmental and learning disorders. Tait (2009) concluded that ADHD is indeed a valid disorder due to the success of treatment with Ritalin (Methylphenidate), as well the fact that symptoms both explain and can be explained by ADHD. Despite many

validations, some authors still believe there is no scientific evidence for the existence or nonexistence of ADHD as a disorder (Wheeler, 2010). However, it is somewhat lacking in etiological validity concerning the causes and developmental mechanisms of ADHD at an individual level (Faraone, 2005; Nigg, 2006). Concerns have also arisen about the idea that ADHD is solely a childhood disorder (Clarke *et al.*, 2005). This has led to a revision of the diagnostic criteria for ADHD in the DSM-V (American psychiatric association, 2013). The hope is that this will allow adults with ADHD to receive the treatment they need from clinicians (American psychiatric association, 2013; Clarke *et al.*, 2005).

### 2.2.4 Difficulties with diagnosing ADHD

Besides the need for the validation of ADHD as a disorder, it is important to identify the underlying causes due to its highly variable nature. Weiss (2010) noted the difficulties clinicians face in diagnoses due to the variability and level of impairment of ADHD symptoms. Of concern is the increased use of psychostimulant medication (such as Ritalin and D-amphetamines) as treatment, particularly in terms of the potential effects on neural development in children (Lesch & Gutknecht, 2005; Nigg, 2006; Shanks *et al.*, 2015). Psychostimulant medication is predominantly used in the treatment of ADHD (Diller, 1996; Kimko, Cross, & Abernethy, 2012; Scheffler, Hinshaw, Modrek, & Levine, 2007) and medications such as Methylphenidate (also known as Ritalin) have been used to treat ADHD since the early 1960s (Ayd Jr., 1964; Conrad, 1975; Ehrlich, Fronkova, & Slegr, 1960; Knights & Hinton, 1969). Often if one of these stimulants is ineffective, the other is prescribed due to the different mechanisms which they act on (Shanks *et al.*, 2015; Volkow, 2006; Volkow *et al.*, 2001). This medication improves the core symptoms of ADHD by about 80% (Najib, 2009; Stein *et al.*, 2011), as well as improvements in comorbid conditions and academic performance (Biederman *et al.*, 2011;

Knights & Hinton, 1969; Konrad, Neufang, Fink, & Herpertz-Dahlmann, 2007; Mehta *et al.*, 2000; Schachter, King, Langford, & Moher, 2001; Scheffer, Kowatch, Carmody, & Rush, 2005). Clinical trials have shown that 40% of patients respond to both Methylphenidate and D-amphetamine treatment, whilst 26% respond only to Methylphenidate and 35% only to D-amphetamine treatment. Important to note is that dosage stimulant treatments must be adapted for each ADHD patient (Connor, 2005).

As with any medications, there are side effects of stimulant medication which include physiological effects (insomnia, appetite loss, headaches, stomach aches, dizziness and drowsiness), affective symptoms (irritable mood and aggression, dysphoria, depression and social withdrawal) and motor symptoms (tics) (Ahmann, Waltonen, Theye, Olson, & Van Erem, 1993; Hazell & Stuart, 2003; Vance & Luk, 2001; Vance, Luk, Costin, Tonge, & Pantelis, 1999). Short-term side effects of stimulant use in ADHD patients may include insomnia, decreased appetite, irritability, depressed mood and anxiousness. Young children (around pre-school age) have been found to experience more severe symptoms in relation to mood and social withdrawal than older children (Charach, Ickowicz, & Schachar, 2004; Connor, 2002). More severe side effects have also been found in individuals also displaying autism and mental retardation. Adults may experience elevated blood pressure and pulse rate (Rapport & Moffitt, 2002). Acute side effects are rarer and may include motor and vocal tics, especially in individuals with a pre-existing tic condition. Psychosis may also occur, especially if a pre-existing psychotic condition (such as Schizophrenia or mania) is present. Psychosis may also occur as a result of overdose (Bloom, Russell, Weisskopf, & Blackerby, 1988; Koehler-Troy, Strober, & Malenbaum, 1986). Long term effects of stimulant use may include appetite

suppression, weight loss and anorexia and thus weight should be carefully monitored throughout treatment (Connor, 2005).

About 70% to 80% of patients show improvements with treatment with psychostimulants, however, 20% to 30% of patients show no improvement (D. J. Fox, Tharp, & Fox, 2005). While these medications are effective whilst the patient continues treatment, if they stop taking the medication all of their symptoms return. Thus long term improvements are not seen with psychostimulant medication (D. J. Fox *et al.*, 2005).

Increase in medication use is of concern because this points to the medicalisation of behaviours (Wheeler, 2010). That is, treating behavioural patterns without having a valid reason for treatment (Oxford dictionary, 2015). These behavioural treatments are dictated by societal norms of unacceptable and preferred behaviours (Nigg, 2006; Wheeler, 2010). It is thus essential to uncover all of the etiological factors which contribute to ADHD, both in terms of psychology and biology (Nigg, 2006).

Debates around ADHD may stem from two major sources, first, environmental components causing ADHD-like symptoms, and secondly, significant symptom overlap in comorbid disorders (Cook *et al.*, 1995; Eubig *et al.*, 2010; Schettler, 2001; Wang *et al.*, 2008; Wender, 2000). Often the symptom overlap between ADHD and comorbid disorders is significant. Common comorbid disorders associated with ADHD fall across multiple types of disorders, such as anxiety disorders (Vance & Luk, 2001), mood disorders (Wozniak *et al.*, 2004), disruptive behaviour disorders (Gadow & Nolan, 2002; Sibley *et al.*, 2014), academic skills disorders (Ek, Westerlund, Holmberg, & Fernell, 2011; Mayes & Calhoun, 2007; Vance & Luk, 2001) and tic disorders (Castellanos *et al.*, 1996; S. E. Stewart *et al.*, 2006).

### *a. Anxiety disorders*

Anxiety disorders encompass any disorders where extreme anxiety is the primary characteristic (Reber *et al.*, 2009). Hammerness *et al.* (2010) found that comorbidity between anxiety and ADHD often lead to mental health treatment, either by medication or counselling. Comorbidity between ADHD and anxiety occurs at a prevalence of about 20-30%, this associated with both the inattentive and combined type ADHD (Humphreys, Aguirre, & Lee, 2012; Vance & Luk, 2001). Parents with anxiety disorders tend to have an increased susceptibility to have children with anxiety comorbid with ADHD (Vance & Luk, 2001). Interestingly, Humphreys *et al.* (2012) found that individuals with ADHD and comorbid anxiety were more likely to have CD or ODD compared to controls. While the two disorders have been shown to share risk factors, they have been shown to transmit independently of each other in families (Perrin & Last, 1996). Individuals with ADHD are often reported to have severe anxiety, as well as self-reported depressive symptoms (Kitchens, Rosen, & Braaten, 1999).

### *b. Mood disorders*

Mood disorders are characterised by excessive and inappropriate depression and/or elation (Reber *et al.*, 2009). Wozniak *et al.* (2004) noted that a large proportion of individuals with bipolar depression also had symptoms of ADHD. Bipolar disorder (BPD) is a mood disorder characterised by alternating periods of depression (symptoms include extreme and intense feelings of inadequacy and despondency, decreased activity and reactivity, pessimism, and sadness) and mania (symptoms include inappropriate elation, impulsivity and increased motor activity) (Reber *et al.*, 2009). Attention-Deficit Hyperactivity Disorder shares a number of symptoms with BPD, including impulsivity, aggression, hyperactivity, impaired social relationships, substance abuse, and educational underachievement (L. E. Arnold *et al.*, 2012).

Together, the two conditions display worsened affect, increased depression, shorter periods of non-depressive symptoms, and increased risk of comorbid conditions (Tamam *et al.*, 2008). About 20% of adults diagnosed with ADHD fit the diagnostic criteria for BPD, similarly about 30% of individuals diagnosed with BPD also fit the criteria for ADHD (A. Brown *et al.*, 2012; Kessler *et al.*, 2006). While children with ADHD do not show full depression, they have been reported to display anhedonia (an inability to feel pleasure), which later develops into depression (Blackman *et al.*, 2005). Bipolar disorder comorbid with attentional problems as well as cognitive deficits associated with ADHD have been found to show familial tendencies, suggesting a genetic link (Faraone, Biederman, Mennin, Wozniak, & Spencer, 1997; Faraone *et al.*, 2001; Greenwood *et al.*, 2012; Yang *et al.*, 2014).

### *c. Disruptive behaviour disorders*

Disruptive behaviour disorders include ADHD, ODD and CD, and are characterised by significant disruptive behaviours (Reber *et al.*, 2009). Oppositional defiant disorder and ADHD display a strong comorbid connection, with them appearing together in about 30-50% of cases (Gadow & Nolan, 2002; Vance & Luk, 2001; van Goozen *et al.*, 2004). However, studies have found sure differences in ODD and ADHD, thus constituting a distinction between the disorders (Gadow & Nolan, 2002; Luman *et al.*, 2009). Van Goozen *et al.* (2004) noted that while executive functioning deficits were present in individuals with both ADHD and ODD, they were not present in individuals with only ODD. These two conditions together manifest with lower IQ, especially displayed in conjunction with verbal and visual-spatial aspects such as difficulty with verbal fluency and academic performance (Vance & Luk, 2001). These individuals have also been reported to display worse symptoms of inattention and impulsivity than individuals with only ADHD (Gadow & Nolan, 2002). However, some neurocognitive problems associated

with ADHD are experienced to a lesser or different degree when ODD is also present (Luman *et al.*, 2009). They also tend to have worsened long-term outcomes and more often commit offences and abuse substances, display antisocial personality, and find it difficult to maintain employment (Vance & Luk, 2001).

All comorbidity between ADHD and CD began with comorbidity between ADHD and ODD. In about 2-3% of cases defining characteristics of ODD change to constitute a CD diagnosis (Vance & Luk, 2001). In general, conduct problems occur at a prevalence of about 6.9%, with individuals with ADHD having a lifetime prevalence of 67.9% of comorbidity with conduct problems (Ebejer *et al.*, 2012). Symptoms of ADHD comorbid with CD include increased aggression, anxiety, lower self-esteem and depressive symptoms, as well as increased substance abuse (Sibley *et al.*, 2014; Vance & Luk, 2001).

### *d. Academic skills disorders or learning disorders*

Academic skills disorders or Learning Disorders (LD) are childhood disorders characterised by impairments in academic functioning (Reber *et al.*, 2009). About 20-30% of Primary school aged children with ADHD have comorbid LD. This includes unusual difficulty with reading, writing, spelling and arithmetic (Ek *et al.*, 2011; Mayes & Calhoun, 2007; Vance & Luk, 2001). Learning, attention, graphomotor, and processing speeds appear to be affected in individuals with ADHD (Mayes & Calhoun, 2007). Mayes and Calhoun (2007) found that comorbidity between ADHD and LD had significant impairments in written expression. Individuals with LD also show some inattention problems, however, not enough to warrant an ADHD diagnosis. There appears to be a common genetic component between ADHD and LD (DuPaul & Volpe, 2009).

### *e. Tic disorders*

Tourette's syndrome is a tic disorder of the nervous system characterised by involuntary movements and sounds. It and ADHD have been found to show a neurobiological overlap (Comings, 2001; Pauls *et al.*, 1986; S. E. Stewart *et al.*, 2006). Castellanos *et al.* (1996) have suggested greater neurological immaturity in boys with comorbid ADHD and Tourette's. Spencer *et al.* (1998) also reported neurological deficits and a worsened condition than ADHD alone. However, they also suggested that these two conditions together increase risk for additional comorbid conditions. These include obsessive compulsive disorder (OCD), mood disorders, disruptive behavioural disorders, anxiety disorders and cognitive dysfunction. Tourette's syndrome and ADHD are typically displayed as severe disruptive behaviours and cognitive deficits (Castellanos *et al.*, 1996; Spencer *et al.*, 1998; S. E. Stewart *et al.*, 2006; Sukhodolsky *et al.*, 2003).

## 2.3 Environmental influences on ADHD: Manifestation and severity

Environmental factors account for only 10-15% of the variation found in the disorder (Larsson, Larsson, & Lichtenstein, 2004). Attention-Deficit Hyperactivity Disorder may also manifest because of phenocopies (environmentally induced phenotype) of the disorder caused by maternal prenatal smoking or alcohol use, environmental toxins or previous viral infection (Barkley, 1997a; Eubig *et al.*, 2010; Schettler, 2001; Wang *et al.*, 2008; Wender, 2000). Environmental components include chemical exposure, dietary aspects and lead poisoning (Eubig *et al.*, 2010; Schettler, 2001; Wang *et al.*, 2008; Wender, 2000). During foetal development the brain is highly susceptible to environmental interference. Environmental disturbances could have serious long-term side effects on the developing foetus (Kalia, 2008). The prenatal environment can be affected by hormones released by the mother's body in the

face of stressors which could epigenetically or physically alter the developmental processes of the foetus (Grizenko *et al.*, 2012; Motlagh *et al.*, 2010; Rodriguez & Bohlin, 2004b; Wender, 2000). Through the use of positron emition technology (PET), researchers have found that the lack of firing in the nerve cells of the brain in certain areas affect particular behavioural actions. For example, decreased activity in the prefrontal cortex results in underdevelopment and may cause inattention (Bush, Valera, & Seidman, 2005; Kranz *et al.*, 2009; Wender, 2000). Aside from the more commonly discussed stress and nicotine exposure, other, scarcer chemicals may predispose an individual to ADHD-like symptoms (Braun, Kahn, Froehlich, Auinger, & Lanphear, 2006; Han *et al.*, 2015). These chemicals may include mercury, manganese, polychlorinated biphenyls or pesticides (Schettler, 2001).

### *a. Nicotine*

Prenatal exposure to smoking has been implicated as an epigenetic effect on the aetiology of ADHD by some research studies (Braun *et al.*, 2006; Lindblad & Hjern, 2010; Motlagh *et al.*, 2010; Neuman *et al.*, 2007; Rodriguez & Bohlin, 2004b; Schmitz *et al.*, 2006), and conflicted by others (Altink *et al.*, 2009). Rodriguez and Bohlin (2004) found that prenatal smoking had a moderate effect on the presence of ADHD (Figure 2.5). During brain development, exposure to nicotine may cause changes in the replication of neural cells thus altering the structure and responsiveness of the synaptic neurochemistry (Ernst, Moolchan, & Robinson, 2001; Neuman *et al.*, 2007). Altink *et al.* (2008) noted that prenatal maternal smoking was not related to the severity of ADHD so much as the presence of the disorder. They also noticed that girls exposed to prenatal smoking experienced more severe ADHD symptoms than did boys also exposed. This same result was found by Braun *et al.* (2006), where they discovered a 4.6 fold increase in ADHD risk for girls, as opposed to a 2.1 fold increased risk in

boys. Altink *et al.* (2009) have found that even paternal smoking has a link to inattention in children with ADHD. This link was, however, not found for where postnatal exposure occurred (Braun *et al.*, 2006). Nicotine exposure may affect the nicotine receptors or the dopamine pathway thus changing the chemistry of the brain. It is also plausible that nicotine exposure could reduce blood flow and increases the level of carboxy-haemoglobin passed to the foetus causing malnutrition and hypoxia (Ernst *et al.*, 2001; Milberger, Biederman, Faraone, & Jones, 1998; Motlagh *et al.*, 2010). Todd and Neuman (2007) proposed that prenatal nicotine exposure creates nicotinic receptor complexes which increase the release of dopamine causing the post synaptic dopamine D4 receptors to change the pattern of neurite outgrowth resulting in lasting neural changes. Rodriguez and Bohlin (2004) also noted that exposure to smoking, as well as stress, in the first ten weeks of pregnancy displayed significant associations with ADHD.

### *b. Stress*

Prenatal stress as an epigenetic cause of ADHD has been supported by some (Grizenko *et al.*, 2012; Motlagh *et al.*, 2010; Rodriguez & Bohlin, 2004b), but not by others (Meijer, 1985; Thapar & Rutter, 2009). Foetuses exposed to prenatal stress display inattention and disturbed activity in childhood (Grizenko *et al.*, 2012; Motlagh *et al.*, 2010; Rodriguez & Bohlin, 2004b) (Figure 2.5). Bergman *et al.* (2007) noted decreased cognitive ability and increased fearfulness. O'connor *et al.* (2002, 2003) found that maternal anxiety late in pregnancy resulted in hyperactivity and inattention in children. This was found for children at four years (O'connor *et al.*, 2002) and at eight years of age (T. G. O'Connor, Heron, Golding, Glover, & The AL SPAC Study Team, 2003), in both girls and boys. Rodriguez and Bohlin (2004) found a significant correlation between ADHD and prenatal stress. Prenatal stress affects a foetus by the induction

of epigenetic effects on the expressions of genes, particularly those genes involved in stress response (Rodriguez & Bohlin, 2004b).

### *c. Mercury*

Mercury (Hg) is often obtained in the diet, especially in the event of consumption of contaminated fish (Mahaffey, Clickner, & Bodurow, 2004). Although all fish contains traces of mercury, some fish contains more than others. For example, shark, swordfish, king mackerel, or tilefish contain high levels of mercury (Davidson et al., 1998). Mercury is potent and damaging to foetal neurodevelopment (Figure 2.5) and may affect enzymatic activity, the functioning of cellular membranes, and neurotransmitter release and levels (Steuerwald *et al.*, 2000; Zahir, Rizwi, Haq, & Khan, 2005). The effects of mercury exposure include deficits in IQ, language development, memory, attentional control, visual-spatial perception, and some gross motor skills (Boucher *et al.*, 2012; Schettler, 2001; Zahir *et al.*, 2005). Exposure to mercury showed a fourfold increase in likelihood of developing attention problems (Boucher *et al.*, 2012; Zahir *et al.*, 2005). The estimated acceptable dose which does not cause damage is anything under 0.1ug Hg/kg/day, however, most contaminated fish contains above this level (Schettler, 2001). This is why most pregnant women are discouraged from eating fish.

### *d. Manganese*

Manganese (Mn) is often present in particular work environments, while trace elements are necessarily obtained from the diet (found in nuts, grains, seeds and legumes) for enzymatic control. Manganese predominantly effects infant development (Figure 2.5). Human breast milk contains 6ug Mn/L (Vuori, Makinen, Kara, & Kuitunen, 1980). Children absorb more and excrete less manganese than adults, however, unnecessary excess exposure in children can lead to Hyperactivity and have long lasting effects on the brain (Aschner & Aschner, 2005;

Schettler, 2001). Excess manganese accumulation, known as manganism, also manifests similarly to Parkinson's disease (Aschner & Aschner, 2005). However, whereas Parkinson's begins on one side of the body, manganism displays bilateral tendencies. Symptoms may include tremors, dysphoria, mental changes, and speech and balance difficulties (Cersosimo & Koller, 2006).

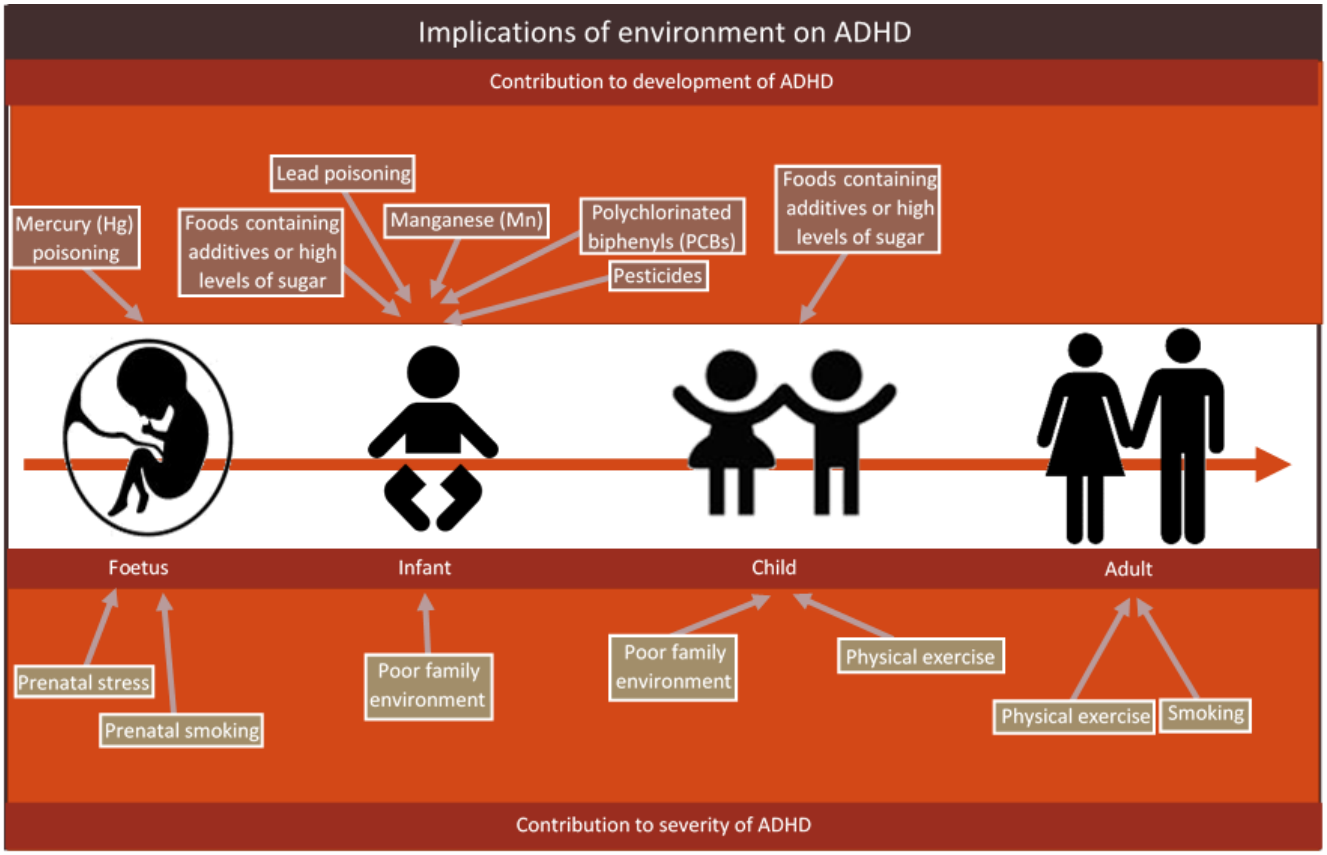


Figure 2.5: Environmental factors which contribute to the development and severity of ADHD (indicated above the timeline in dark brown boxes) and ADHD-like symptoms (indicated below the timeline in light brown boxes) at various life stages.

### *e. Polychlorinated biphenyls*

Polychlorinated biphenyls are man-made chemical compounds previously used in the insulation electrical transformers and capacitors (Jacobson & Jacobson, 1996). Exposure to polychlorinated biphenyls (PCBs) may cause hyporeflexia, delays in psychomotor activity and cognitive development, as well as lower IQ (Schantz, 1996). Infants are generally affected by PCBs. Polychlorinated biphenyls are predominantly obtained via diet, but may also be inhaled

from polluted air (Norström *et al.*, 2010) (Figure 2.5). These chemicals often effect the metabolism of thyroid hormone, decreasing the levels (Schettler, 2001). Thyroid hormone is also essential in brain development as it assists with neural growth, cell migration, cell differentiation, and cell signalling. Thus changes which occur could result in neurological complications (Schantz, 1996).

### *f. Pesticides*

While little data is available concerning pesticides, available studies have displayed adverse effects on motor skills, attention, learning, and memory (Eskenazi, Bradman, & Castorina, 1999; Schettler, 2001). Pesticide exposure has also been implicated in a number of other conditions including cancer, immunological, and reproductive dysfunction. Particularly, pesticides have been implicated in developmental delays (Eskenazi *et al.*, 1999).

### *g. Lead poisoning*

Lead (Pb) poisoning has also been implicated in the aetiology of ADHD (Boucher *et al.*, 2012; Braun *et al.*, 2006; Eubig *et al.*, 2010; Wang *et al.*, 2008; Wender, 2000). The absorption of large quantities of lead may cause psychological and neurological problems (Goodlad, Marcus, & Fulton, 2012). The precise mechanism in which lead alters psychological and neurological functioning is not yet known, however, three theories regarding the possible mechanism do exist. These suggest that problems may occur due to oxidative stress, deregulation of calcium signalling, or abnormal neural transmission caused by changes in gene expression (Senut *et al.*, 2012). Hyperactive-impulsive symptoms manifest in the event of increased lead exposure (Boucher *et al.*, 2012). Children who ingest lead in the form of lead paint from walls or parts of their cribs may develop ADHD-like symptoms. Breathing

automobile fumes from unleaded fuels increased the prevalence of lead poisoning, as well as Hyperactive symptomology in infants (Wender, 2000).

### *h. Diet*

Diet has long been accepted as a major cause of Hyperactivity symptoms in children. In particular, foods containing additives or high levels of sugar (such as Coca-Cola™) have been implicated (Stevenson *et al.*, 2010; Wolraich, Wilson, & White, 1995). Food additives such as aspartame and food colouring such as tartrazine have been associated with ADHD in a number of early studies (Carter *et al.*, 1993; Rippere, 1983; Spring & Sandoval, 1976; Taylor, 1979). Sugar containing foods may only indirectly influence ADHD by influencing cognitive functioning (M. A. Fox, Chen, & Holmes, 2003; Ryan, Vega, & Drash, 1985). A low sugar diet with good nutritional and protein intake may improve the symptoms of ADHD, however, it will not eliminate the disorder. It is important for individuals affected with ADHD to take in a well-balanced diet (Pelsser *et al.*, 2008).

While environmental factors may constitute this exposure to physical chemicals or hormone exposure during foetal development, it may also occur in more abstract forms, for example, stress and poor sleep. All of these factors may further worsen existing symptoms of ADHD.

## 2.4 Environmental influences on ADHD: The affected individual

The severity of ADHD may be affected by a number of environmental components. These components include psychological stress and family environment, sleep, developmental difficulties, stimulants, and exercise (Dewey, Kaplan, Crawford, & Wilson, 2002; Konofal, Lecendreux, & Cortese, 2010; Lambert, 2005; Laufer & Denhoff, 1957; Pontifex, Saliba, Raine,

Picchietti, & Hillman, 2013; Skosnik, Chatterton, Swisher, & Park, 2000; van der Niet *et al.*, 2014; Yochman, Ornoy, & Parush, 2006). Each of these elements may have varying effects on the presentation of ADHD.

### *a. Psychological stress and poor family environment*

Psychological stress and poor family environment have been implicated as a factor in the development of poor behavioural regulation and inattention (Skosnik *et al.*, 2000). Parents with ADHD may find it difficult to maintain consistent discipline and routine, or may be exceptionally harsh in their disciplining (E. H. Arnold *et al.*, 1997). Mokrova *et al.* (2010) assessed the role of "home chaos" in children with ADHD. "Home chaos" refers to a home environment which is excessively noisy and crowded, and has a lack of structure and routine. They found that parents with ADHD provide a home environment similar to the one described in the concept of “home chaos”. This could then be detrimental to the development of executive functioning in children, thus causing ADHD-like symptoms.

In contrast, a positive family environment enables a child with ADHD to better maintain attentional control and self-control, thus improving a child's academic functioning and social functioning (Eisenberg *et al.*, 2005; Joussemet *et al.*, 2005). Schroeder and Kelley (2009) found that families with children affected with ADHD reported higher levels of conflict and familial disorganisation. This resulted in poorer functioning when coming from a maladjusted home environment. However, it is important to note that these correlations were not significant and may thus exert only a small effect on the severity of ADHD.

### *b. Sleep*

Although sleep problems are not necessary for the diagnosis of ADHD. The association between sleep and attention, implies a significant role in ADHD (Konofal *et al.*, 2010; Laufer & Denhoff, 1957). Baum *et al.*, (2014) found that a restriction of sleep to 6.5 hours caused significant behavioural problems, such as irritability and emotional outbursts in the general population. Galland *et al.* (2009) found that individuals with ADHD have a longer sleep latency period, even when treated with Methylphenidate. Sleep disturbance may be caused by a number of factors including sleep-disorder breathing, periodic limb movements, and restless leg syndrome (Konofal *et al.*, 2010; Owens, 2006). Li *et al.* (2006) found a 40% prevalence of ADHD in individuals with sleep-disorder breathing. Karpinski *et al.* (2008) noted a deficiency in executive functioning in individuals with sleep-disorder breathing, specifically snoring. Sleep-disorder breathing is commonly caused by enlarged tonsils, attentional problems and behavioural problems. A tonsillectomy can improve the condition (Dillon *et al.*, 2007; H.-Y. Li *et al.*, 2006). Approximately 44% of ADHD individuals suffer from restless leg syndrome, causing significant sleep disturbance (Cortese *et al.*, 2005; Konofal *et al.*, 2010). Because sleep is so essential to proper human functioning (T. E. Brown & McMullen, 2001; Buckhalt, El-Sheikh, & Keller, 2007), it is likely that a lack thereof might cause further deterioration of symptoms, particularly in concentration.

### *c. Developmental difficulties*

Developmental difficulties in coordination have been linked to attention and concentration deficits and movement impairments (Dewey *et al.*, 2002; Piek, Pitcher, & Hay, 1999; Yochman *et al.*, 2006). Reiersen *et al.* (2008) and Kopp *et al.* (2010) found a link between ADHD and both coordination problems and symptoms of autism. Motor impairments have been noted in all ADHD types (Pitcher, Piek, & Hay, 2003). Even though gross motor problems

were more prominent in individuals with autism spectrum disorder, it still showed a significant association to individuals with ADHD (Kopp *et al.*, 2010). Brossard-Racine *et al.* (2012) found a significant improvement in motor functioning in children with ADHD after just three months of stimulant medication use (such as Methylphenidate).

### *d. Stimulants*

Lambert (2005) found that individuals with ADHD often seek out tobacco, cocaine, and/or amphetamines as a means of self-medication to alleviate symptoms of ADHD. Smokers with ADHD also tend to experience more severe withdrawal symptoms when attempting to quit (McClernon *et al.*, 2011). Individuals with more severe hyperactive/impulsive symptoms have been found to have greater difficulty in refraining from smoking (Covey, Manubay, Jiang, Nortick, & Palumbo, 2008). When treated with Methylphenidate, ADHD smokers tend to smoke more (Vansickel, Stoops, Glaser, Poole, & Rush, 2011). However, this was not found in a study by Whalen *et al.* (2003) in an adolescent population.

### *e. Exercise*

Studies have suggested that exercise can provide relief from ADHD symptoms (Pontifex *et al.*, 2013; van der Niet *et al.*, 2014; Verret, Guay, Berthiaume, Gardiner, & Béliveau, 2012). Improvements in executive functioning due to exercise have been noted in both ADHD and non-ADHD individuals (A.-G. Chen, Yan, Yin, Pan, & Chang, 2014; van der Niet *et al.*, 2014). Physical exercise is successful in reducing stress, negative affect, anxiety, or depressive symptoms, as well as improving cognitive functioning, poor impulse control, and inattention (Archer & Kostrzewa, 2012; Robison *et al.*, 1999). Pontifex *et al.* (2013) found that 20-minutes

of moderately intense aerobic exercise improved attention and cognitive speed in both ADHD individuals and healthy controls. They also found additional benefits for behaviour modulation in individuals with ADHD. Verret *et al.* (2012) found improvements in attention and behaviour, as well as reported improvements in social interaction, anxiety, and depression symptoms. However, physical exercise appears only to have a significant effect on improving executive functioning if performed long-term (Ziereis & Jansen, 2015). Long-term physical exercise may also improve motor impairments in ADHD individuals (Pan *et al.*, 2014; Verret *et al.*, 2012; Ziereis & Jansen, 2015).

## 2.5 Biological factors of ADHD

As with many neurological abnormalities the contributions are complex and varied (Retz & Rösler, 2009; Waldman & Gizer, 2006). Biological or genetic factors have been largely implicated in the aetiology of ADHD (Bralten *et al.*, 2013; Heiser *et al.*, 2004; Pazvantoğlu *et al.*, 2013). Genetic factors cause alterations in the development and functioning of the brain (Konrad & Eickhoff, 2010). Environmental influences may not directly cause ADHD. A gene-environment interaction may bring about the manifestation of ADHD, whereas a gene-environment correlation may influence the severity of the symptoms (Barkley, 1997a; Hurtig *et al.*, 2007; Wender, 2000).

The genetic link to ADHD means that siblings, parents, and other close relatives may also experience or have experienced similar symptoms (Agha, Zammit, Thapar, & Langley, 2013; S. E. Stewart *et al.*, 2006; Wender, 2000). Parental ADHD has been linked to an increase in the severity of ADHD in their offspring, particularly with regards to inattention, and conduct disorder. This may be due to genetics, environment, or gene-environment interplay (Agha *et al.*, 2013). Twin studies and adoption studies have confirmed this genetic link to ADHD

(Greven, Rijsdijk, Asherson, & Plomin, 2011; Greven, Rijsdijk, & Plomin, 2011; Holmes *et al.*, 2002; Morrison & Stewart, 1973; M. O'Connor, Foch, Sherry, & Plomin, 1980; Schachar, 2014; Sprich, Biederman, Crawford, Mundy, & Faraone, 2000; Van't Ent *et al.*, 2007; Wender, 2000; Willcutt *et al.*, 2007; Willerman, 1973).

### 2.5.1 Genetic mechanisms

Genetic influences of ADHD have not been indicated in chromosomal abnormalities such as extra chromosomes or loss of chromosomes (aneuploidy), fragility of chromosomes or transmutations, but rather polymorphisms that might include small sequence changes (like variable number of tandem repeats, VNTRs) or single nucleotide polymorphisms (SNPs) which alter the level of expression of certain genes (Barkley, 1997a). Genetics has received the strongest support as the greatest contributor to the aetiology of ADHD (Biederman *et al.*, 2008; Brookes *et al.*, 2006; Guan *et al.*, 2008; Heiser *et al.*, 2004; D. Li, Sham, Owen, & He, 2006; Mick, Wozniak, Wilens, Biederman, & Faraone, 2009; Oades *et al.*, 2008; Payton *et al.*, 2001; Plomp, Van Engeland, & Durston, 2009; Ribases *et al.*, 2007; Tsutsumi *et al.*, 2009). This also means that the condition is hereditary, being passed on from parents to their children (Barkley, 1997a). In terms of disorders where only one gene contributes to the condition, an individual is likely to develop the disorder. However, disorders such as ADHD are complex, meaning that many genes exert a small effect to contribute to the disorder as a whole, and environmental factors further influence the phenotypic expression of these genes. Family, twin and adoption studies can be used to estimate heritability, which can then imply either shared genetic or environmental influences (Nigg, 2006). Approximately 10% to 35% of first-degree relatives of individuals with ADHD also have the disorder (Agha *et al.*, 2013; Barkley, 1997a; W. Chen *et al.*, 2008; Faraone *et al.*, 2000; S. E. Stewart *et al.*, 2006). Greater similarity can be seen between

biological parents and adopted away children, than that child and the adoptive parents (Sprich *et al.*, 2000). Overall twin studies have shown much higher concordance for ADHD in monozygotic twins compared to dizygotic twins (W. Chen *et al.*, 2008; Gillis, Gilger, Pennington, & DeFries, 1992; Holmes *et al.*, 2002; M. O'Connor *et al.*, 1980). Monozygotic twin studies have revealed a heritability coefficient of 0.8-0.9 for clinically recognised ADHD (Gillis *et al.*, 1992; Willcutt *et al.*, 2007; Willerman, 1973). The more severe the symptomology of ADHD, the greater the contribution of additive genetic factors (Bralten *et al.*, 2013).

As previously discussed, additive environmental influences also contribute to the severity of ADHD. Shared environment implies similar environmental influences with a similar phenotypic outcome, whereas non-shared environment implies similar environmental influences with a different phenotypic outcome. Shared environment (including social class, family education, home environment and nutrition) in twins contributes only about 5 % of the variance of ADHD (Lehn *et al.*, 2007; Payton *et al.*, 2001). Non-shared environmental factors (including the social environment and any non-genetic biological factors which affect one twin and not the other) contribute about 15% to 20% of the variance to the aetiology of ADHD (Lehn *et al.*, 2007; Nikolas *et al.*, 2012).

With multiple possible genetic causes manifesting in the same manner, ADHD can be considered a heterogeneous condition (Barkley, 1997a; Bralten *et al.*, 2013; Oades *et al.*, 2008) resulting in difficulties with genetic diagnosis. Variable penetrance, where the same genetic constitution and psychological experiences manifest to a greater or lesser degree (Whalen, Jamner, Henker, Delfino, *et al.*, 2003) have also been observed. This variable penetrance may be caused by gene-gene interaction (epistasis), environmental factors (gene-environment interaction), or regulation of gene expression (epigenetics).

### 2.5.2 Neurological aspects

Regions of the brain associated with maintaining attention have been found to be the frontal and parietal regions, and in particular the medial and lateral sub-regions of these areas, as well as the temporal region, and parts of the posterior cingulate cortex and insula (Hopfinger, Buonocore, & Mangun, 2000; Woldorff *et al.*, 2004) (Figure 2.6). Hyperactivity can be described as a deficit in motor control and response inhibition (Schoemaker, Ketelaars, van Zonneveld, Minderaa, & Mulder, 2005; Spieser, Wildenberg, Hasbroucq, Ridderinkhof, & Burle, 2015; Woldorff *et al.*, 2004). Electrical stimulation of the supplementary motor complex has been shown to curb the behavioural expression of action impulses (Spieser *et al.*, 2015). Response inhibition or impulsivity has also been mapped to the frontal areas of the brain, in particular the prefrontal cortex, lateral orbitofrontal cortex, superior temporal gyrus, medial orbitofrontal cortex, cingulate gyrus, basal ganglia, and inferior parietal lobe (Horn, Dolan, Elliott, Deakin, & Woodruff, 2003; Kim & Lee, 2011; Spinella, 2004) (Figure 2.6).

Previously researchers noted that damages and lesions in the frontal lobe, particularly the prefrontal cortex, brought about similar symptomology to ADHD. These symptoms included inattention, lack of inhibition, emotion regulation, and poor organisation of behaviour (Barkley, 1997a; Friedman & Rapoport, 2015). Neurological anomalies have been implicated in the aetiology of ADHD for a number of reasons (Friedman & Rapoport, 2015). The most obvious is that ADHD symptoms may include learning and language difficulties or disabilities and abnormal motor control which have been linked to neurological dysfunction (Friedman & Rapoport, 2015; Kiive & Harro, 2013; Killeen, Russell, & Sergeant, 2013). Prematurity and low birth weight can cause neurodevelopmental issues and are also possible causative factors of

ADHD (Barkley, 1997a). Improvements in ADHD symptoms with stimulant treatments also points to a neurological cause (Barkley, 1997a; Tait, 2009; Vaidya & Stollstorff, 2008).

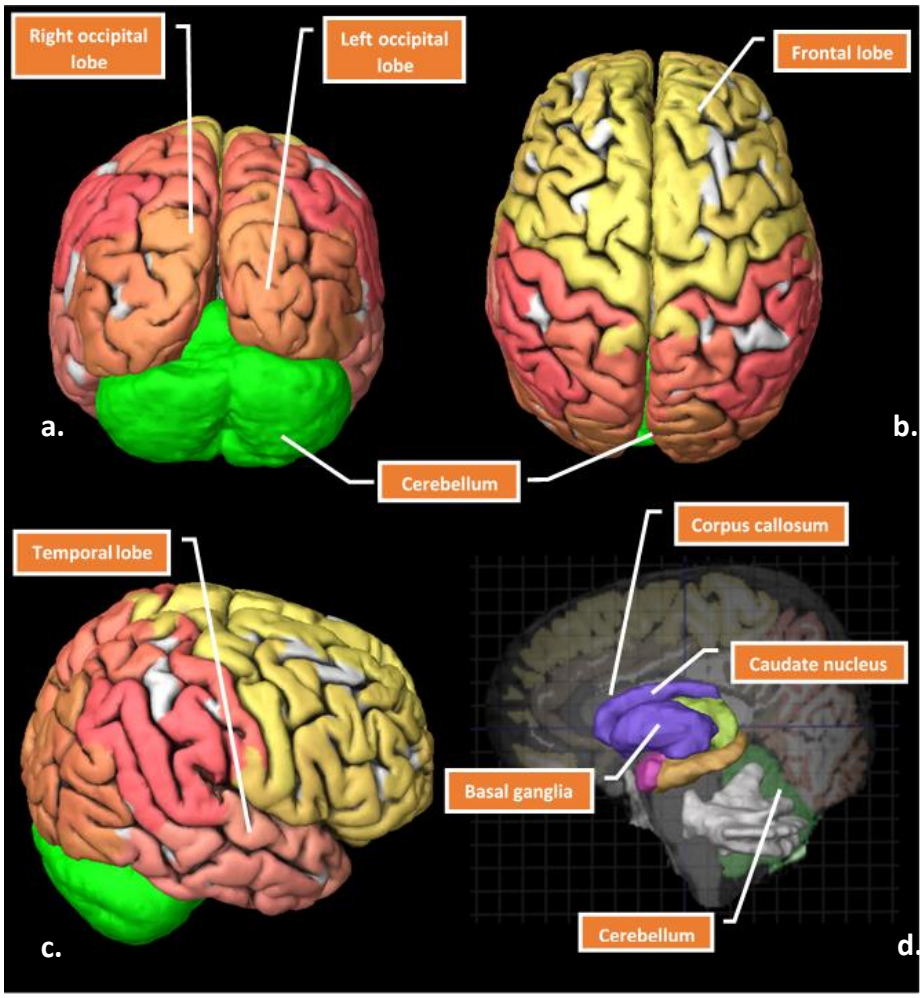


Figure 2.6: Major regions of the brain showing associations with ADHD, with particular reference to the (a) posterior view, (b) superior view, (c) right side view, and (d) medial view (smaller neural elements within these major regions have been implicated in ADHD).

Interestingly, magnetic resonance imaging (MRI) scans have revealed that individuals with ADHD have a smaller rostral body and splenium of the corpus callosum than children without ADHD symptoms (Friedman & Rapoport, 2015; Van't Ent *et al.*, 2007). This area of the brain controls the transfer of information between hemispheres (Barkley, 1997a; Van't Ent *et al.*, 2007). Still more recent studies have shown a smaller, orbitofrontal regions, basal ganglia, right globus pallidus regions, and caudate nucleus (part of the basal ganglier group), prefrontal

cortex, cerebellum, occipital and parietal-temporal regions (Castellanos *et al.*, 2002; Friedman & Rapoport, 2015; Nakao, Radua, Rubia, & Mataix-Cols, 2011; Shaw *et al.*, 2007, 2012; Valera, Faraone, Murray, & Seidman, 2007; Van't Ent *et al.*, 2007). Particularly Castellanos *et al.* (2002) found a reduction in cerebrum and cerebellum size with specific ties to ADHD-C. Shaw *et al.* (2007) also found a postponement in the growth rate of the prefrontal cortex in particular. Research suggests that developmental abnormalities which take place in the prefrontal region of the brain are a large causal factor in the development of ADHD (Friedman & Rapoport, 2015; Shaw *et al.*, 2007, 2012; Spencer, Biederman, & Mick, 2007; Valera *et al.*, 2007). The cerebellum, occipital-parietal, and temporal regions control a range of cognitive functionality related to attention and Hyperactivity, including spatial attention, motor control, vision and the transfer of visual information, and face-object recognition (Van't Ent *et al.*, 2007). It is important to note that regions identified did not incur damage, they were, however, reduced in size, thus eliminating the possibility of brain damage. These regions are subject to developmental problems, probably underpinned by genetics (Barkley, 1997a; Shaw *et al.*, 2012; Vaidya & Stollstorff, 2008). This is because a variation in gene expression may cause a change in developmental speed and size of the product. Reduced stimulation of brain regions may also stunt development. Baroni and Castellanos (2015) have suggested that the human connectome project has allowed for the identification of anatomical structure involved in ADHD.

Studies have also begun to move from a focus on brain regions involved in ADHD to the neural pathways involved (Castellanos *et al.*, 2008; Friedman & Rapoport, 2015). Early examinations of cerebral blood flow in the prefrontal cortex of the brain were common in individuals with ADHD. Studies using PET (positron emission transmission) have found that

metabolic activity is diminished in the anterior frontal region of the brain and that there is a reduction in *SERT* binding in cortical and subcortical sites in ADHD adolescents (Bush *et al.*, 2005; Kranz *et al.*, 2009). This shows that decreased activity in this part of the brain may be indicative of ADHD (Barkley, 1997a). Due to the high activity of the serotonergic pathway in the prefrontal cortex in particular, assumptions can be made that deficiencies in this pathway may be integral in the manifestation of ADHD (Kranz *et al.*, 2009; Mette *et al.*, 2011). To understand the genetics of serotonin and the serotonergic pathway in ADHD it is important to first understand the working of the serotonergic synapse.

### 2.5.3 Serotonin function in the synapse

Serotonin (5-HT) is a monoamine neurotransmitter which is related to the pleasure system. Serotonin is essential in learning and cognition. It has been implicated in a number of psychopathological disorders, including aggression, depression, anxiety, and addiction (Cao *et al.*, 2013; Cunningham & Anastasio, 2014; Fabbri, Marsano, & Serretti, 2013; Gao, Zhu, Wei, Li, & Lai, 2011; Goldman, Glei, Lin, & Weinstein, 2010; Gonda, Juhasz, Laszik, Rihmer, & Bagdy, 2005; Ho *et al.*, 2012b; Katsuragi *et al.*, 1999; McMahon *et al.*, 2006; Noskova *et al.*, 2009; Oades *et al.*, 2008). These characteristics are central to disorders where disinhibition is implicated, such as in bulimia, antisocial personality disorder, conduct disorder, and suicidal ideation and tendencies (Guimarães *et al.*, 2009; Pazvantoğlu *et al.*, 2013). Serotonin has also been linked to impulsive personality types and deficits in inhibition which makes this system a good candidate in the aetiology of ADHD (Guimarães *et al.*, 2009; Oades *et al.*, 2008). Oades *et al.* (2008) suggested that serotonin was significantly implicated in children with ADHD, particularly with aggression and cognitive impulsivity problems. When observing the serotonergic pathway it is important to consider four major processes (Oades *et al.*, 2008):

1. synthesis through tryptophan hydroxylase conversion;
2. signal transduction in the postsynaptic neuron by 5-HT2 receptors;
3. negative feedback by 5-HT1 receptor stimulation;
4. the efficiency of reuptake into the presynaptic neuron by the serotonin transporter (*SERT*).

Tryptophan obtained from the diet (L-tryptophan) first crosses the blood-brain barrier by diffusion and is then converted into 5-hydroxytryptophan (5-HTP) by tryptophan hydroxylase. This is then synthesised to 5-HT (5-Hydroxytryptamine, serotonin) by aromatic L-amino acid decarboxylase (AADC) (Barker & Barasi, 1999; Siegel, Albers, & Brady, 2006). Vesicular storage of serotonin occurs by $Fe^{+}$ (iron ion) binding to serotonin in the presence of serotonin-binding protein (SBP) which aids packaging by high affinity transference. Exocytosis by calcium influx releases both 5-HT and SBP, and serotonin. Serotonin can then stimulate receptors (5-HT2) on the post-synaptic membrane (Siegel *et al.*, 2006).

Termination of serotonin transmission occurs mainly by two mechanisms (Figure 2.7). Firstly, negative feedback is initiated by stimulation of the presynaptic autoreceptors (5-HT1). Secondly, by serotonin reuptake into the presynaptic neuron by serotonin transporters (*SERT* or *5-HTT*). Active transmission of 5-HT occurs through *SERT* by a $NA^{+}$ (sodium ion), $Cl^{-}$ (chlorine ion) action. Termination can also occur by reuptake via other transporters (such as the dopamine and norepinephrine transporters, DAT and NET, respectively) into the glial cells and even non-serotonergic neurons. The organic cation transporter (OCT), the plasma membrane monoamine transporter (PMAT), NET, and DAT are all capable of removing serotonin from the synaptic space (Purves, 2004; Siegel *et al.*, 2006).

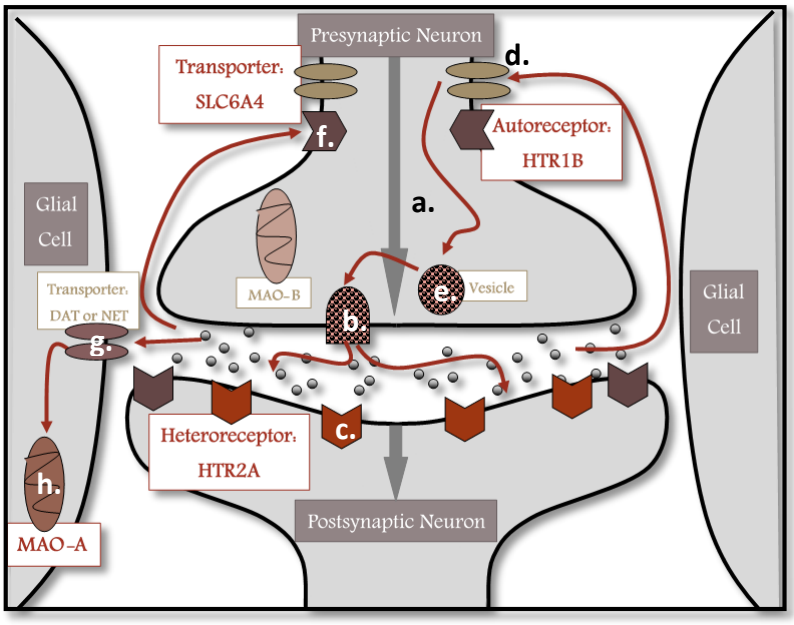


Figure 2.7: Simple representation of the structure of the serotonergic pathway showing the (a) incoming stimulus, (b) vesicular exocytosis, and (c) stimulation of heteroreceptors, the reuptake of excess serotonin by the (d) serotonin transporter for repackaging into (e) vesicles, the stimulation of the (f) presynaptic autoreceptor for negative feedback, and the removal of excess serotonin via other (g) transporter mechanisms for metabolism by (h) Monoamine Oxidase-A (MAO-A).

The serotonin system is also subjected to MAO (Monoamine oxidase) metabolism for removal of excess serotonin. Serotonin is converted to 5-hydroxy-indolacetaldehyde and oxidised to 5-hydroxy-indolacetic acid (5-HIAA) by a Nicotinamide adenine dinucleotide-dependant ($NAD^+$-dependant) aldehyde dehydrogenase. The preferred mechanism of metabolism of serotonin is MAO-A (Monoamine oxidase A), however, serotonin neurons contain predominantly MAO-B (Monoamine oxidase B). There is homology between the different neurochemical transporters (*SERT*, DAT, and NET). Each transporter can thus play a compensatory role by reuptaking any of the monoamine neurotransmitters (serotonin, dopamine, or norepinephrine). However, each transporter has a higher affinity for its corresponding neurotransmitter (e.g. *SERT* has a higher affinity for serotonin). Monoamine oxidase B (MAO-B) functions by metabolising dopamine and norepinephrine reuptaken through *SERT* into the serotonergic neuron. This causes synaptic specialisation by ensuring that

serotonin activity is the primary function of that particular neuron. A specialised synapse is one which has strong synaptic connections between the pre- and post-synaptic neurons, whereas a lack of specialisation shows dynamic and less specific interactions. Serotonin, however, displays synaptic specialisation in some areas in the brain, but not in others which may hold important differences in information processing. In synapses lacking specialisation, serotonin may be released, but have to diffuse over large distances to cause an action. Serotonin may thus be a neuromodulator determining activity in the brain of synapses at large distances from the serotonergic terminal (Barker & Barasi, 1999; British neuroscience association & European Dana alliance for the brain, 2003; Purves, 2004; Siegel *et al.*, 2006). Studies have suggested that serotonin availability is prominent in cognition and could thus be a causative factor in ADHD (Kiive & Harro, 2013). Reports of brain activation previously mentioned point to a mediating role of serotonin in ADHD (Castellanos *et al.*, 2008; Friedman & Rapoport, 2015; Kranz *et al.*, 2009; Mette *et al.*, 2011).

## 2.6 ADHD as a deficit in executive functioning: A unifying theory

Higher order functions, also known as executive functioning processes account for complex cognition (McCabe, Roediger, McDaniel, Balota, & Hambrick, 2010). Because cognition is a pliable concept, there is much debate about what should be included under the collective name of executive functions. Some researchers will include or exclude certain components based on intellectual decision making. There is, however, a general consensus that many of the cognitive processes deficient in individuals with ADHD fall within the spectrum of executive functioning and complex cognition (Doyle *et al.*, 2005; Gapin, 2009; Johnson, 2015; Mandell & Ward, 2011; McCabe *et al.*, 2010; Rinsky & Hinshaw, 2011; van Goozen *et al.*, 2004; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005; Ziereis & Jansen, 2015). Complex

cognitive processes include, but may not be limited to, cognitive flexibility (such as shifting mental sets and updating task demands), resistance to prepotent responding and sustaining attention and behaviour, goal-directed behaviour and goal maintenance, strategic planning, monitoring and regulation of performance, impulse control and self-regulation, as well as working memory (Mandell & Ward, 2011; Rinsky & Hinshaw, 2011).

Morphologically executive functioning has been linked to the prefrontal cortex of the brain using functional magnetic resonance imaging scans (fMRI) and treatment with antidepressant medication (Herrera-Guzmán *et al.*, 2010; Paloyelis, Mehta, Kuntsi, & Asherson, 2007; Rubia *et al.*, 1999). Decreased blood flow to the prefrontal regions has been found in individuals with ADHD, with this increasing when stimulant medication is used (Konrad *et al.*, 2007). Treatment of ADHD with antidepressants like selective serotonin reuptake inhibitors have pointed to improvements in executive functioning (Herrera-Guzmán *et al.*, 2010). The serotonergic system is highly active in the prefrontal cortex, and is specifically involved in inattention, impulsivity and inhibition (Guimarães *et al.*, 2009; Pazvantoğlu *et al.*, 2013; Siegel *et al.*, 2006). Thus it appears that deficiencies in the serotonergic system may negatively affect executive function processes. However, intricate neuronal networks are most likely in place to link various other regions of the brain in order to make executive functioning possible (Yang *et al.*, 2014). Individuals with ADHD have shown deficits in executive functioning, particularly in relation to working memory and response inhibition (McCabe *et al.*, 2010; Rinsky & Hinshaw, 2011; van Goozen *et al.*, 2004). This has led to the postulation that deficits in the prefrontal cortical regions in individuals with ADHD may cause depletions in neuropsychological functions such as executive functions.

Executive functioning deficits appear to provide a definitive link between ADHD symptoms, neurological and biological processes (Doyle *et al.*, 2005). Executive functioning explains the cognitive deficits and behavioural control problems in ADHD. Stress causes changes in executive functioning (Johnson, 2015), resulting in anxiety noted in ADHD (Johnson, 2015; Whalen, Jamner, Henker, Delfino, *et al.*, 2003). Ziereis and Jansen (2015) and Gapin *et al.* (2015) have found that physical exercise significantly improves both cognitive functioning and motor activity in ADHD individuals. Executive functioning mediates cognitive, behavioural and psychological aspects of ADHD.

## 2.7 Conclusions: The Attention-Deficit Hyperactivity Disorder definition

Because growth and development, and particularly brain development, is still very much in the process of occurring in children, certain medications may interact differently. For example, neurons in the developing brain have a different function to those in the adult brain, and, therefore, medications targeting these areas will have different effects. Methylphenidate may desensitise the neurons which may later result in substance abuse (Lakhan & Hagger-Johnson, 2007). In terms of short-term adverse effects, Schachter *et al.* (2001) noted that most trials underreported adverse finding, but that severely decreased appetite, insomnia, stomach aches, drowsiness and dizziness were among the most common. About 20% to 50% of patients display these adverse effects, as well as headaches, anxiety and irritability (D. J. Fox *et al.*, 2005).

The FDA (FDA, 2015) has suggested that Ritalin (Methylphenidate) be prescribed to patients six years and older, however, little data regarding the adverse effects of Methylphenidate on children is available. Trials have been limited for two main reasons, first, obtaining ethical approval for drug testing on children is difficult, as is, secondly, obtaining

informed consent from parents to use their children in clinical trials (Lakhan & Hagger-Johnson, 2007). Despite this lack of clinical data, Methylphenidate is still being prescribed to younger children, and even more often than it has been in the past (Fullerton *et al.*, 2012; Karanges, Stephenson, & McGregor, 2014; Öner *et al.*, 2014; Ponizovsky *et al.*, 2014; Safer *et al.*, 1996; Štuhec, Locatelli, & Švab, 2015; Sutcliffe & Wong, 2006; Zito *et al.*, 2000).

Despite its challenging history, the validity of ADHD as a significant psychological disorder is undoubted. Attention-Deficit Hyperactivity Disorder is clearly a complex neurodevelopmental condition, characterised predominantly by depleted higher order cognition (also known as executive functioning) and reduced behavioural inhibition. The disorder is represented by three main symptoms, namely inattention, hyperactivity and impulsivity which combine in different manners to form three subtypes of the collective disorder ADHD. Other symptoms - although variable from individual to individual, and predominantly influenced by environmental situations - include depression, moodiness, poor interpersonal relationships, disorganisation, and stress intolerance. These are not primary indicators, but contribute to the perceived severity of the disorder and should be considered during diagnosis. Suggestions that ADHD is primarily a childhood disorder are flawed. The validity of progression into adulthood has been established. This is evident in the significant impairments still experienced by individuals with ADHD in adulthood. Environment is a large component in the perceived severity of ADHD, however, it is important to note that this may also share a biological component. Symptoms of ADHD combined with a biological predisposition to depression, bipolar, or anxiety, compound. This makes ADHD present much worse. Other environmental components which increase or decrease the severity of ADHD may include prenatal stress and smoking, family environment and physical exercise.

Kandel (1998) suggested that experiences may alter brain structure by modifying gene expression thus changing mental functioning because the neuronal and synaptic connections are altered. Experiences which could alter brain function may encompass social and psychological events, as well as, trauma and psychopathology, hormonal changes, and developmental experiences (Garralda & Raynaud, 2012; McEwen, 2012). These neuronal changes may in turn cause changes in behaviour. A psychopathological brain is one that is disordered (Graham, 2013). This disorder is predominantly the result of genetics. A single gene encodes a specific protein, this protein may in turn affect the development, regulation and maintenance of neural pathways which in turn influences behaviour (Bellgrove & Mattingley, 2008). However, it is necessary to notice that an alteration in a single gene is, in most cases, not enough to cause large changes to a behavioural phenotype, therefore, many genetic variations must be required to cause these changes (Barkley, 1997a; Cicchetti & Cohen, 2006). Environmental factors can greatly reinforce an already genetically predetermined disordered brain, and thus environment should be tailoured in order curb the maladaptive pathway (Gray & Hannan, 2007). If this is not done, a cycle may occur where experiences may further disorganise an already disordered brain (Cicchetti & Cohen, 2006).

# Chapter 3

# Quantification of attention and hyperactivity related disorders

## Abstract

Studies in the social and behavioural sciences often make use of questionnaires as a method of data collection. These questionnaires are designed to collect data in a range of ways. Mixed methods approaches, which comprise of qualitative and quantitative data, are of particular use for increasing the understanding of theoretical concepts. Questionnaires measuring ADHD, while comprehensive in assessing the three characteristics (inattention, hyperactivity and impulsivity), are somewhat lacking in questions pertaining to additional environmental characteristics potentially associated with ADHD (including smoking, psychological problems, exposure to hypoxic conditions, and learning disabilities). This study assessed a number of environmental characteristics in relation to ADHD. Additionally, the efficacy of a self-report scale versus a semi-structured interview for the purposes ADHD research was assessed. Results revealed strong associations between ADHD and a number of assessed environmental characteristics and showed that ADHD presentation can be largely affected by these. The interview and self-report scales used were found to provide similar quantitative scores, however, did not produce the same resulting diagnosis. Additionally, the number of observed characteristics noted during the semi-structured interview corroborated the ADHD diagnosis provided by the scale.

**Keywords:** Adult Self Report Scale, Diagnostic Interview for Adults with ADHD, Environment, Mixed methods, Weiss Functional Impairment Rating Scale

## 3.1 Introduction: The quantification of ADHD in adults

Human behavioural studies oftentimes make use of questionnaires as a primary form of quantification because they are a seemingly simple form of collection and analysis of data (Munn *et al.*, 1990). However, as with any form of data capturing, questionnaires do have limitations. Firstly, the response rate is often low or the questionnaire is not fully completed (Cook *et al.*, 2000). Secondly, of vital consideration is that individuals completing questionnaires may understand the questions differently to the researcher thus making interpretation complicated. Thirdly, with sensitive subjects, the "Hawthorne effect" may occur in which participants may feel the need to adapt their answers so as not to reflect themselves poorly in the eyes of the researcher (Roethlisberger & Dickson, 1939). For all these reasons and many more it is essential in any form of research to select questionnaires with utmost care and critical thinking.

If we consider the neurodevelopmental disorder, ADHD, it immediately becomes apparent that the quantification of such a disorder using self-report questionnaires could prove to be more problematic than usual (McGough & Barkley, 2014). According to its classification, ADHD comprises three subtypes of varying severity, as discussed in detail in Chapter 2. Of these three, ADD (predominantly inattentive; ADHD-I) is the least severe, followed by the predominantly hyperactive and impulsive type (ADHD-HI) and finally a combined type (encompassing inattention, impulsivity and hyperactivity; ADHD-C) which is the most severe (Barkley *et al.*, 2008). These are the most commonly recognised characteristics, and the ones essential for diagnosis according to the DSM-V. However, there are a number of other characteristics which may arise due to the presence of ADHD (Ferrer et al., 2010; Hurtig et al., 2007; Tamam et al., 2008). One can thus already deduce that it may be difficult for an

individual with ADHD to complete a self-report questionnaire. It may be more viable to assess ADHD using an interview, rather than a self-report scale. Research into ADHD is, however, essential into learning more about its manifestation and development and thus a form of quantification is certainly necessary.

There are a vast number of standardised questionnaires available for the quantification of ADHD, both in children and in adults. These are currently primarily based on the DSM-IV (The Diagnostic and Statistical Manual of Mental Disorders: Fourth Edition). Considering the shifting history of the classification of ADHD throughout the years, it is not unreasonable to wonder whether it is wise to use a generalised classification method, such as the DSM-IV, on which to base quantitative research. Some of these questionnaires include (Rösler *et al.*, 2006) the Wender Utah Rating Scale (WURS) (Wender, 1995), the Childhood Symptom Scale – Self Report Form (ChSS-SRF) (Barkley & Murphy, 2006), the Conners Adult ADHD Rating Scales (CAARS) (Conners *et al.*, 1999), the Current Symptoms Scale (CSS-SR) (Barkley & Murphy, 2006), Adult Self-Report Scale (ASRS) and the ASRS Screener (Adler *et al.*, 2003a; Kessler *et al.*, 2005), the ADHD Rating Scale-IV (ADHD-RS-IV) (DuPaul *et al.*, 1998), and the Brown ADD Rating Scale (Brown ADD-RS) (Brown, 1996). There are also a number of interviews which have been constructed for the purpose of diagnosing ADHD. These include Wender-Reimherr Adult Attention Deficit Disorder Scale (WRAADDS) (Reimherr, 2004), Conners' Adult ADHD Diagnostic Interview for DSM-IV (CAADID) (Epstein *et al.*, 2001), Adult Interview (AI) by (Barkley, 1998), Brown ADD Diagnostic Form (ADD-DF) (Brown, 1996), and Adult ADHD Investigator Symptom Rating Scale (AAISRS) (Adler *et al.*, 2003b). Alternative to these interviews there are other interviews which have not yet been extensively tested and validated such as the Diagnostic Interview for Adults with ADHD (DIVA) (Kooij & Francken, 2010). The first step then in studying

ADHD is to select a questionnaire which will provide significant and informative results. Only questionnaires used in this study will be discussed in further detail.

### 3.1.1 Self-Report Questionnaire

A self-report questionnaire involves the individual completing a set of questions in their own time. It may be advantageous in that individuals may have more time to consider their answers (Gadow *et al.*, 2002; Robins *et al.*, 2009). However, this may also allow them to consider the negative images their answers may portray and thus cause them to answer differently for fear of being judged. In assessing a disorder such as ADHD a self-report scale may be disadvantageous in that individuals with ADHD display inattentive tendencies, thus resulting in the inability to focus adequately to complete the questionnaire (Robins *et al.*, 2009).

When selecting questionnaires for research purposes, it is essential to determine the type of information which is needed for the subsequent analysis. Quantitative data is predominantly used in the field of Science due to the factual and measurable nature. Social and Behavioural Science, however, often employs a mixed-methods approach, by including qualitative responses from open-ended questions. This combination of confirmatory (quantitative) and exploratory (qualitative) questions provides the opportunity to be verify and generate theories simultaneously (Teddlie & Tashakkori, 2009). Johnson *et al.* (2007) conclude that mixed methods research can provide an increased understanding and validation.

#### *a. Adult ADHD Self-Report Scale*

The ASRS consists of 18 questions, seven of which are aimed at assessing inattention, and 11 of which are aimed at assessing hyperactivity/impulsivity (Adler *et al.*, 2003a; Kessler *et*

*al.*, 2005). Because both the ADHD-HI and ADHD-C comprise a combination of hyperactivity and impulsivity, there is no need to make a distinction between these two characteristics. This scale can thus be used to distinguish between ADHD-I, ADHD-HI and ADHD-C (Kessler *et al.*, 2007). The first six questions of the ASRS may be used as a screener for ADHD (known as the ASRS v1.1 Screener) (Adler *et al.*, 2003a). The additional 12 questions expand on the assessment of ADHD, providing more information about the severity of the disorder. The questions contained in the ASRS are based on the criteria contained in the DSM-IV. Each question is marked on a Likert scale from 0 to 4 (0 being never, 1 being rarely, 2 being sometimes, 3 being often and 4 being very often), with participants being asked to rate the frequency of their symptoms. Scores range from 0 to 18 (Adler *et al.*, 2003a; Kessler *et al.*, 2005, 2007; Daigre *et al.*, 2009; van de Glind *et al.*, 2013).

### *b. Weiss Functional Impairment Rating Scale – Self Report*

There are two forms of the Weiss Functional Impairment Rating Scale, one which assesses impairment in the self (WFIRS-S), and one that assesses impairment by means of asking a parent (WFIRS-P) (Gibbins & Weiss, 2007). The Weiss Functional Impairment Rating Scale – Self Report (WFIRS-S) was designed by Margret D. Weiss to determine the ability of individuals to function in various environments (Weiss *et al.*, 2007). Advantageous with this self-report questionnaire is that it can be used by clinicians to obtain measurements of pre- as well as post-assessments of patients' problematic areas of functioning (Weiss, 2000; Weiss & Murray, 2003; Weiss *et al.*, 2007; CADDRA, 2011). This questionnaire is measured on a four-point Likert scale which ranges from zero to three, with zero being never or not at all, one being sometimes or somewhat, two being often or much and three being very often or very much. Additionally there is an option of 'Not applicable' which is not counted when scoring.

The overall impairment score for each section is calculated by summing the response scores (0 to 3) and then dividing by the number of questions answered on the scale (i.e. those questions answered not applicable are not included in the division process). Overall the mean score for all the domains of functional impairment is one in the general population, whilst the mean score for the risky activities domain is generally 0.5. Items scored a two or three are thus approximately two standard deviations outside the average functionality of ADHD individuals and are then considered significant impairments. Overall, each domain should have approximately two items with a score of two or a single item with a score of three to be considered a domain where an individual experiences impairment (Eddy, 2013).

### 3.1.2 Semi-Structured Interview

The main advantage of a semi-structured interview over a self-report scale is that the interviewer is able to observe the participants function and reacts to the questions posed. This also allows for the environment in which the questions are posed to be controlled, which is particularly important with regards to easily distracted individuals such as those with ADHD (Magnusson, 2006). This also allows the interviewer to have a standardised set of questions to ask, thus getting the same information from each participant. Altogether, this makes for easier observation and interpretation. A semi-structured interview comprises of both quantitative and qualitative responses, allowing for both confirmative and open ended questions to be asked.

#### *a. Diagnostic Interview for Adults with ADHD*

The Diagnostic Interview for Adults with ADHD or DIVA was originally used in the Netherlands hence the acronym refers to its original name *Diagnostisch Interview Voor ADHD*

*bij volwassenen* (Kooij & Francken, 2010). It is a semi-structured diagnostic interview which is used to assess ADHD characteristics in adults, as the name suggests. The interview assesses both childhood and adulthood characteristics and impairments allowing for a much more comprehensive data set. As with most of the questionnaires used to assess ADHD, DIVA also uses the DSM-IV criteria as a baseline for its questions. Each question is supplied with several examples which help both with clarity of the questions and the facilitation of discussion between the interviewer and the participant (Kooij & Francken, 2010; Semeijn *et al.*, 2013). Each participant is asked to provide examples for each question, which are then marked off by the interviewer if they are present. Based on the number of examples provided, the interviewer is required to determine whether the symptom is present in adulthood or was present in childhood. These symptoms are considered to be present if they are noted as impairments by the participant, or if they occur to a greater degree than is usually the case in individuals of the same peer group. Questions regarding the impairments ADHD has or has had on the participant's life are also included in the DIVA. Participants are asked to provide examples of impairments that may have occurred in work and education, relationships and family life, social contacts, free time and hobbies, and self-confidence and self-image. The ADHD diagnosis is made by calculating the number of symptoms present. Six symptoms should be present for either inattention or hyperactivity to warrant a diagnosis. These should be corroborated with impairments in at least two life areas and should not be explained away by other psychiatric conditions. The DIVA is available as a paid application for download onto iPad® (Apple®) (Stichting DIVA Foundation, 2015). This application allows the researcher to select from the examples as well as to include comments about participant's answers to each question and allows for quick and accurate translation of the interview into data sets. The responses are then emailed directly to the interviewer in CSV format. Semeijn *et al.* (2013)

considered individuals to have ADHD if they displayed at least four symptoms of inattention and/or hyperactivity/impulsivity during the six months prior to assessment and at least six symptoms of the same during childhood (childhood being 5 to 12 years of age). They also stipulated that individuals considered to have ADHD should meet the requirements for impairments in at least two areas of their lives in the six months prior to assessment, and in childhood (this is in line with the DSM-IV classification).

### 3.1.3 Demographic and environmental information

It is important to note, however, that these questionnaires do not consider or measure the additional characteristics that come with ADHD. These characteristics may include problems with sleep, development, learning, mental state and smoking. While not necessary for diagnosis, it is important to realise that these are common complaints in individuals with ADHD and may provide significant insights into this disorder of attention and hyperactivity as well as into its presentation, severity, progression, or underlying neural networks.

To further understand the manifestation of ADHD, questions regarding, medical, psychiatric, and developmental history need to be assessed in both ADHD individuals as well as in their first degree relatives. Individuals with ADHD have the potential to display the following medical conditions (Table 3.1): Enlarged tonsils, Stigmata of foetal alcohol syndrome (FAS) or foetal alcohol effects (FAE), History of anoxia or perinatal complications, Growth delay, Myotonic dystrophy, Anaemia, Traumatic brain injury, Hearing or visual problems, Neurofibromatosis, Injuries, Other genetic syndrome, Thyroid disorder, Diabetes, Developmental delays, Coordination problems, Sleep apnoea, Seizures, Medical complications of drug/alcohol use, *in utero* exposure to nicotine, alcohol or drugs, Cerebral palsy, Enuresis, Asthma, Lead poisoning. Similarly, individuals with ADHD may experience the following

psychological conditions (Table 3.2): Tourette's or tics, anxiety, autism spectrum disorder, learning disorder, conduct disorder, depression, sleep disorders, bipolar disorder, suicidal attempts, oppositional defiant disorder, violent gestures towards others. Developmental difficulties assessed included gross and fine motor control, language difficulties, odd behaviours and mood. First degree relatives of individuals with ADHD often present with the following health and psychological conditions, which could explain the presence of ADHD: pregnancy problems, legal convictions, epilepsy, alcohol/drug problems, congenital disorders, ADHD (confirmed), ADHD (probable), depression, suicide, mental retardation, Tourette's or tics, sleep disorders, anxiety, learning disorders, bipolar, psychosis, personality disorder, autism spectrum disorders.

Table 3.1: A summary of possibly related medical problems to ADHD, as indicated by previous studies reviewed in the literature in Chapter 2.

| Environmental component | Relation to ADHD |
|---|---|
| Enlarged tonsils | ▪ Sleep-disorder breathing is commonly caused be enlarged tonsils and often occurs in individuals with ADHD<br>▪ Attentional and behavioural problems often improve with removal of tonsils<br>(Li *et al.*, 2006; Dillon *et al.*, 2007) |
| Stigmata of FAS/FAE | ▪ Prenatal alcohol exposure has been implicated as a causative factor of ADHD<br>▪ Exposure to alcohol prenatally causes cognitive problems similar to those found in dyslexia<br>▪ ADHD is often diagnosed in children with FAS and children of alcoholic parents<br>(Brown *et al.*, 1991; Mick *et al.*, 2002; Coffin *et al.*, 2005; Han *et al.*, 2015) |
| History of anoxia or perinatal complications | ▪ Premature birth often results in hypoxic-ischaemic encephalopathy (periods where the brain is deprived of oxygen)<br>▪ Other complications may include birth asphyxia, respiratory distress syndrome and preeclampsia<br>▪ These have been found to show associations with ADHD<br>▪ Oxygen deprivation during critical periods of brain development affects sleep problems, locomotor problems and executive functioning deficits<br>(Lou, 1996; Decker & Rye, 2002; Bass *et al.*, 2004; Getahun *et al.*, 2012) |
| Growth delay | ▪ Growth delays (both in terms of height and weight) have especially been found in children with ADHD being treated with stimulant medications<br>(Lisska & Rivkees, 2003; Poulton & Cowell, 2003; MTA Cooperative Group, 2004) |
| Myotonic dystrophy | ▪ Some symptoms which occur in myotonic dystrophy also occur in individuals with ADHD |

| | |
|---|---|
| | ▪ These may include sleep disorders and restless leg syndrome<br>(Laberge *et al.*, 2004; Yu *et al.*, 2011; Lam *et al.*, 2013) |
| Anaemia | ▪ Iron is a key ion in synthesising dopamine, which is thought to play a role in ADHD<br>▪ Low serum iron (ferritin) is associated with ADHD<br>▪ Iron deficiency may cause cognitive deficits and developmental problems associated with ADHD<br>(Lahat *et al.*, 2011; Abbas *et al.*, 2012; Berner *et al.*, 2015) |
| Traumatic brain injury (TBI) | ▪ TBI has been found to cause ADHD-like symptoms<br>▪ Damage to the frontal areas of the brain may result in symptoms of ADHD<br>▪ Individuals with comorbid TBI and ADHD display worsened attention, memory and executive functioning<br>(Konrad *et al.*, 2000; Max *et al.*, 2004; Slomine *et al.*, 2005) |
| Hearing or visual problems | ▪ Individuals with suspected ADHD may have underlying hearing or visual problems, rather than deficits in cognitive and executive functions<br>▪ Dyslexia, for example, may present similarly to ADHD due to frustration, but is correctable with specialised spectacles<br>▪ Visual problems may encompass difficulties in maintaining visual attention<br>▪ The conditions may co-occur, thus further worsening ADHD symptomology<br>(Knivsberg *et al.*, 1999; Eden & Vaidya, 2008; Laasonen *et al.*, 2012) |
| Neurofibromatosis (NF) | ▪ Individuals with Neurofibromatosis are at increased risk of also having ADHD<br>▪ Children with NF may also often display significant learning and social problems, similar to children with ADHD<br>▪ NF symptoms are significantly worsened with the co-occurrence of ADHD<br>(Kayl *et al.*, 2000; Koth *et al.*, 2000; Mautner *et al.*, 2002) |
| Injuries | ▪ Individuals with ADHD have been found to sustain more injuries than usual<br>▪ Both severity and frequency of injuries are worse in individuals with ADHD<br>▪ Injuries may result from inattentiveness, distraction and impulsiveness<br>(DiScala *et al.*, 1998; Mangus *et al.*, 2004; Lyon *et al.*, 2009) |
| Thyroid disorder | ▪ Thyroid disorder often causes Hyperactive symptoms<br>▪ Individuals with thyroid disorders are at increased risk of developing ADHD<br>▪ Individuals with both ADHD and thyroid disorder may benefit from treatment of the thyroid condition rather than issuing stimulant medication<br>(Ciaranello, 1993; Hauser *et al.*, 1993; Weiss *et al.*, 1993) |
| Diabetes | ▪ Learning disorders have been reported in individuals with diabetes<br>▪ Children with diabetes fail to pay attention in class<br>▪ Neuropsychological deficits in adults may result from extreme hypoglycaemia in childhood which causes mild brain damage<br>▪ These underlying symptoms of diabetes may present similarly to ADHD<br>(Ryan *et al.*, 1985; Fox *et al.*, 2003; Sanchez *et al.*, 2006; Delamater, 2009; Parent *et al.*, 2009) |
| Developmental delays | ▪ Developmental difficulties in coordination have been linked to attention and concentration difficulties<br>▪ A large proportion of individuals with developmental difficulties are diagnosed with ADHD<br>▪ Motor impairments have been noted in all ADHD types<br>(Piek *et al.*, 1999; Dewey *et al.*, 2002; Pitcher *et al.*, 2003; Yochman *et al.*, 2006) |
| Coordination problems | ▪ Developmental difficulties in coordination have been linked to attention and concentration difficulties<br>▪ Problems with coordination may also manifest as a result of Hyperactivity |

| | |
|---|---|
| | (Wender, 1995; Barkley, 1997; Piek *et al.*, 1999; Dewey *et al.*, 2002; Yochman *et al.*, 2006). |
| Sleep apnoea | ▪ Sleep apnoea may cause disturbances in sleep associated with ADHD (See sleep disorders, Table 3.1) |
| Seizures | ▪ ADHD may predispose individuals to seizures or epileptic episodes<br>▪ Similarly, individuals with seizures often experience attentional problems<br>▪ ADHD-I and not ADHD-HI appears to show this association<br>(Semrud-Clikeman & Wical, 1999; Hesdorffer *et al.*, 2004) |
| Medical complications of drug/alcohol use | ▪ Tobacco, cocaine and amphetamines are often sought as a means of self-medication to improve symptoms of ADHD<br>▪ Nicotine, cocaine and amphetamines stimulate dopamine neurons to produce more extracellular dopamine, thus heightening the feeling of reward obtained from these drugs<br>▪ Smokers with ADHD experience more severe withdrawal symptoms when trying to quit<br>▪ Individuals with higher hyperactive/impulsive symptoms have greater difficulty in refraining from smoking<br>▪ Treatment with methylphenidate causes ADHD smokers to smoke more, possibly because of an additive interaction between the improvement of symptoms with methylphenidate and the calming effect of smoking<br>▪ Untreated ADHD individuals generally smoked more<br>(Siegel *et al.*, 2006; Covey *et al.*, 2008; McClernon *et al.*, 2011; Vansickel *et al.*, 2011) |
| *In utero* exposure to nicotine | ▪ Prenatal smoking had a moderate effect on the presence of ADHD<br>▪ Even paternal smoking has a link to inattention in children with ADHD<br>▪ During brain development, exposure to nicotine may cause changes in the replication of neural cells thus altering the structure and responsiveness of the synaptic neurochemistry<br>▪ Prenatal maternal smoking is related to the presence of ADHD<br>▪ Girls exposed to prenatal smoking experience more severe ADHD symptoms than did boys also exposed<br>▪ Nicotine exposure may affect the nicotine receptors or the dopamine pathway thus changing the chemistry of the brain<br>▪ Nicotine exposure could also reduce blood flow and increase the level of carboxy-haemoglobin passed to the foetus causing malnutrition and hypoxia<br>(Milberger *et al.*, 1998; Ernst *et al.*, 2001; Rodriguez & Bohlin, 2004; Neuman *et al.*, 2007; Altink *et al.*, 2008, 2009; Motlagh *et al.*, 2010) |
| Cerebral palsy (CP) | ▪ Individuals with cerebral palsy display similar symptoms to those of ADHD, including deficits in attention, visuospatial cognition and executive functions<br>▪ Individuals with CP often experience learning and social difficulties<br>▪ Symptoms similar to ADHD may result from bilateral brain legions in individuals with CP<br>(Bottcher, 2010; Pirila *et al.*, 2011) |
| Enuresis | ▪ ADHD and enuresis often co-occur<br>▪ Both nocturnal and diurnal enuresis is more common in individuals with ADHD than is normal<br>(Robson *et al.*, 1997; Baeyens *et al.*, 2005, 2006) |
| Asthma | ▪ Asthma is common in individuals with ADHD-HI and appears to be due to genetic factors<br>▪ ADHD and asthma show similar comorbidity with anxiety and mood disorders |

| | |
|---|---|
| | ▪ ADHD and asthma appear, however, to be independently transmitted in families<br>▪ Dopamine may be at the crux of the two disorders, as inhaled dopamine causes bronchial dilation during severe asthma attacks<br>▪ Asthma may also relate to ADHD in that it causes hypoxic conditions which may stunt brain development and thus cause ADHD<br>(Biederman *et al.*, 1994; Fasmer *et al.*, 2011a; b; Mogensen *et al.*, 2011; Kwon *et al.*, 2014) |
| Lead poisoning | ▪ Absorption of large quantities of lead may cause psychological and neurological problems<br>▪ Hyperactive/impulsive symptoms manifest in the event of increased lead exposure<br>▪ Children who ingest lead in the form of lead paint on walls or parts of their cribs may develop ADHD-like symptoms<br>▪ Children in cities breathing automobile fumes (particularly before the introduction of unleaded fuels) showed Hyperactive symptomology due to lead poisoning<br>(Wender, 2000; Boucher *et al.*, 2012; Goodlad *et al.*, 2012) |

As detailed in Chapter 2, smoking in ADHD individuals, as well as immediate family is common. Familial environment, exposure to oxygen deprived conditions and parental trauma also show some form of commonality with ADHD. Other environmental components which could influence the presentation of ADHD included aspects of nutrition, self-care and personal hygiene, leisure, sleep, and exercise.

Table 3.2: A summary of possibly related psychological problems to ADHD, as indicated by previous studies reviewed in the literature in Chapter 2.

| Environmental component | Relation to ADHD |
|---|---|
| Tourette's or tics | ▪ Neurobiological overlap with ADHD<br>▪ No genetic link between Tourette's and ADHD<br>▪ Co-occur to display a worsened condition than ADHD alone and increases the risk for additional comorbid conditions<br>▪ Co-occurrence displays as severe disruptive behaviours and cognitive deficits<br>(Pauls *et al.*, 1986; Castellanos *et al.*, 1996; Spencer *et al.*, 1998; Comings, 2001; Sukhodolsky *et al.*, 2003; Stewart *et al.*, 2006) |
| Anxiety | ▪ Two disorders share risk factors<br>▪ Transmits independently of ADHD<br>▪ Children with ADHD comorbid with anxiety often have family members with anxiety disorders and ADHD; Parents with anxiety disorders are at increased risk of having children with anxiety and ADHD<br>▪ Comorbid anxiety is more common in ADHD-C than in the other ADHD variants<br>(Perrin & Last, 1996; Vance & Luk, 2001; Humphreys *et al.*, 2012) |

| | |
|---|---|
| Autism spectrum disorder (ASD) | ▪ There is a link between ADHD, coordination problems and symptoms of autism<br>▪ Gross motor problems are more prominent in individuals with ASD, but still significant in individuals with ADHD<br>(Kopp et al., 2010) |
| Learning disorder (LD) | ▪ ADHD and LD have a common genetic component<br>▪ Displays as difficulty with reading, writing, spelling and arithmetic<br>▪ Comorbid with ADHD learning, attention, graphomotor, and processing speeds are affected<br>▪ Individuals with only LD show some inattention problems, but not enough to warrant an ADHD diagnosis.<br>(DuPaul & Volpe, 2009; Ek, Westerlund, Holmberg, & Fernell, 2011; Kopp *et al.*, 2010; Mayes & Calhoun, 2007; Vance & Luk, 2001) |
| Oppositional defiant disorder (ODD) | ▪ ODD and ADHD display a strong comorbid connection<br>▪ Comorbidity manifests in lower IQ, especially in verbal and Visuo-spatial aspects such as difficulty with verbal fluency and academic performance, as well as worse symptoms of inattention and impulsivity than individuals with only ADHD<br>▪ Comorbidity results in worsened long-term outcomes and individuals more often commit offences and abuse substances, display antisocial personality and find it difficult to maintain<br>(Gadow & Nolan, 2002; Vance & Luk, 2001; van Goozen et al., 2004) |
| Conduct disorder (CD) | ▪ CD is the adult manifestation of ODD<br>▪ Symptoms of ADHD comorbid with CD include increased aggression, anxiety, lower self-esteem and depressive symptoms and increased substance abuse<br>▪ ADHD is predominantly genetic, but CD seems to have a greater relation to shared environment<br>▪ Often first-degree relatives have symptoms of CD<br>(Sibley et al., 2014; Vance & Luk, 2001) |
| Depression and Bipolar disorder (BPD) | ▪ A familial pattern suggests a genetic link between depression and ADHD<br>▪ Children display depression as anhedonia<br>▪ BPD and ADHD are transmitted as a unit, independent of other forms of ADHD<br>▪ Individuals with ADHD frequently self-report depressive symptoms<br>(Faraone *et al.*, 1997, 2001; Kitchens *et al.*, 1999; Blackman *et al.*, 2005; Greenwood *et al.*, 2012; Yang *et al.*, 2014) |
| Sleep disorders | ▪ Restriction of sleep to 6.5 hours causes significant behavioural problems, such as irritability and emotional outbursts<br>▪ Individuals with ADHD have a longer sleep latency period, even when treated with methylphenidate<br>▪ Sleep disturbance may be caused by a number of factors including sleep-disorder breathing, periodic limb movements and restless leg syndrome<br>▪ Because sleep is so essential to proper human functioning, it is likely that a lack thereof might cause further deterioration of symptoms, particularly in concentration<br>(Brown & McMullen, 2001; Braun *et al.*, 2006; Owens, 2006; Buckhalt *et al.*, 2007; Galland *et al.*, 2009; Konofal *et al.*, 2010) |
| Suicidal Attempts | ▪ Suicidal attempts may arise as a result of depression which is often comorbid with ADHD<br>▪ Impulsivity as a symptom of ADHD may also explain the increased risk of suicidal attempts in these individuals<br>(Lindström *et al.*, 2004; Impey & Heun, 2012) |
| Violent gestures towards others | ▪ Violence may relate to ODD and CD often co-occurring with ADHD |

| | |
|---|---|
| | ▪ Aggression and ADHD also share similar genetic pathways which may be why individuals with ADHD display increased violence<br>▪ ADHD individuals are more aggressive across all types of aggression (including proactive and reactive types)<br>(Vance & Luk, 2001; Gadow & Nolan, 2002; van Goozen *et al.*, 2004; Retz & Rösler, 2009; Connor *et al.*, 2010; Sibley *et al.*, 2014) |

The aims of this study are to determine the extent of environmental effect on ADHD, and whether it is necessary to consider these effects during the assessment of the condition. Further, the efficacy of a self-report internet-based questionnaire, or a structured interview, for the quantification of ADHD for research purposes will be assessed.

## 3.2 Methods

The protocol for this study was submitted for ethical clearance to the Ethics Committee of the Faculty of Health Sciences, and was approved by the board (Ecufs 95/2013A) on 25/07/2013 (Appendix 1).

The research methodology for this study follows a retrospective comparative cohort design. This involves a comparison between two cohorts, each selected with specific criteria. These two cohorts were unmatched. The two cohorts will henceforth be referred to as the Affected and Unaffected Cohorts. The Affected Cohort was comprised of individuals with a previous diagnosis of ADHD (including all three types). Conversely, the individuals in the Unaffected Cohort were required to have none or few enough symptoms of ADHD not to warrant a diagnosis. Participants for both the Affected and Unaffected Cohorts were selected based on availability and willingness to participate. Both males and females over the age of 18 were asked to participate. Informed consent (Appendix 2.1) was obtained from each participant.

Both a self-report internet-based questionnaire and a structured interview were used as methods of quantification in this study. These quantitative methods served not to re-diagnose ADHD, but rather to determine a baseline upon which each participant may be measured. This is important because different doctors, psychologists and psychiatrists will use various methods to measure and classify psychological disorders such as ADHD.

The CADDRA (Canadian ADHD Resource Alliance) ADHD assessment form (CADDRA, 2011) was used as a guideline for collecting demographic and environmental information from participants (Appendix 2.2). Standard demographic information was collected, including gender, age, ethnicity, education, and occupation. This was collected for the participant as well as the participant's mother, father and partner. The Adult ADHD Self-Report Scale for Adults (ASRS) (Appendix 2.3) and the Weiss Functional Impairment Rating Scale – Self Report (WFIRS-S) (Appendix 2.4) were chosen to make up the online self-report questionnaire. The Diagnostic Interview for Adults with ADHD (DIVA) (Appendix 3) was used in addition to the self-report scale, for 8 individuals in this study. The DIVA was coupled with a list of potential physical characteristics indicative of hyperactive and inattentive symptoms, which the interviewer was required to note if they occurred during the interview process (Appendix 4). The Affected Cohort was requested to complete the self-report scale (including the demographic questionnaire, ASRS and WFIRS-S) in its entirety. These individuals were also asked to take part in the semi-structured interview. The Unaffected Cohort was required only to complete the demographic questionnaire and the pre-diagnostic scale of the ASRS.

### 3.2.1 Statistical procedures

Quantitative data were analysed using IBM® SPSS (IBM Corp, 2013) and Microsoft® Excel (2013). Scores for medical, psychological, and developmental problems were calculated

by summing the number of mentioned problems. Smoking severity was calculated by summing the amount of times individuals answered "yes" to a set of five questions (regarding habitual smoking, difficulty refraining from smoking, number of cigarettes dependant on external factors, smoking to relieve ADHD symptoms, and relapse), as well as adding a score for the number of times an individual has tried to stop smoking previously (1=1-2 times; 2=3-4 times; 3=4-5 times; 4=6 or more times). Hypoxia scores were also calculated by the number of times individuals answered "yes" to a set of five hypoxic instances (regarding altitude, sleep apnoea, respiratory failure, pollution, and premature birth). Scores for poor diet were calculate by adding the number of days per week individuals do not eat nutritional meals and the number of times they eat foods high in sugar and additives (1=1-2 times a week; 2=3-5 times a week; 3=Almost every day in each case). Severity of sleep was calculated by summing the number of times answered "yes" to a set of six questions (regarding not dreaming regularly, difficulty falling asleep, difficulty maintaining sleep, daytime sleepiness, and presence of snoring, and restless leg syndrome). Other environmental factors were considered as a presence only. The ASRS full diagnosis scores were calculated by summing the number of times each symptom scenario occurred for each of 18 scenarios. Similarly, inattentive scores were calculated for the nine scenarios pertaining to inattentiveness, and hyperactive scores for the nine scenarios pertaining to hyperactivity. Functional impairments were noted in the various areas according to the guidelines proposed by Weiss (2000). Initial analysis involved various correlations to determine whether potential associations were present. Significant correlations (where $p<0.05$) were assessed by linear regression analysis.

Scores from the ASRS and DIVA were converted into standardised Z-scores for comparison purposes. The Wilcoxon signed-rank test was then performed to determine

whether there were differences between the scores achieved from the ASRS test compared to the DIVA test. Correlations were also performed to determine whether there was an association between the two sets of scores. Characteristics of inattention and/or hyperactivity observed during the interview (DIVA) were correlated with the symptom scores and diagnosis result determined by DIVA to identify any associations.

## 3.3 Results[a]

### 3.3.1 Demographic information

A total of 29 individuals with ADHD and 45 individuals without agreed to take part in this study (Figure 3.1). Of these, 25 individuals in the Affected Cohort completed the online survey (four individuals provided DNA, but did not complete the survey), while 45 Unaffected Cohort individuals completed the survey.

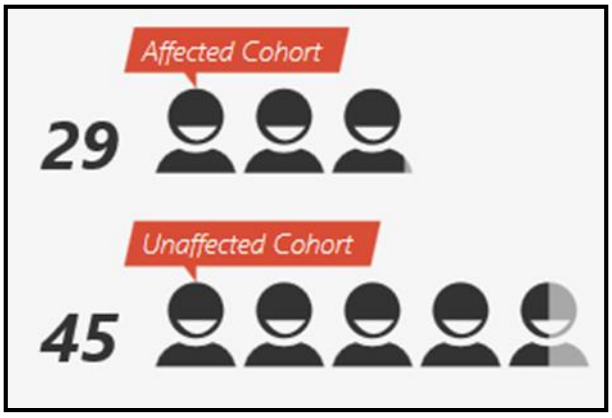


Figure 3.1 Proportion of individuals making up the Affected and Unaffected Cohorts used in this study.

Females were over-represented in the total sample population at 64%, however, within the Affected Cohort the gender divide was relatively equal (12 males and 13 females) while the

[a] Details of statistical analysis can be found in Appendix 7

proportion of females (*n*=21) in the Unaffected Cohort was much larger than the proportion of males (*n*=7) (Figure 3.2).

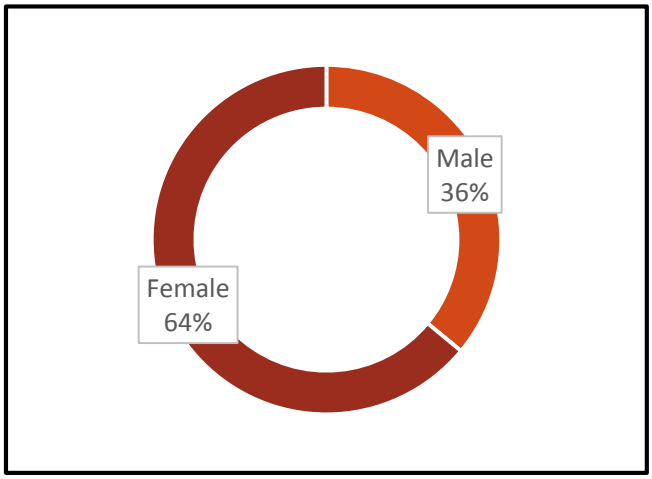


Figure 3.2 Pie chart denoting the proportion of males and females in sample population.

Educational level of the sample was fairly high, with everyone at least having completed matric (*n*=35; 66%). The majority of individuals in both the Affected (*n*=15) and Unaffected Cohorts (*n*=20) had completed matric. A number of individuals had completed postgraduate studies (*n*=12; 23%), this was true for both the Affected (*n*=7) and Unaffected Cohort (*n*=5). A few individuals had completed undergraduate studies (*n*=6; 11%), and this was equal in both Cohorts (*n*=3) (Figure 3.3).

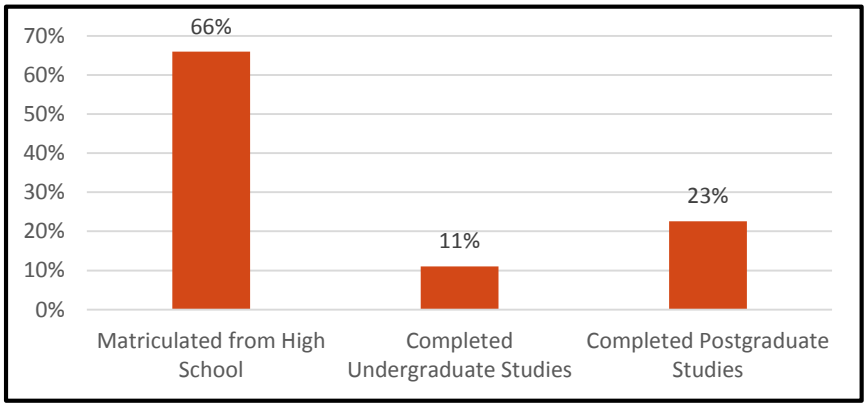


Figure 3.3 Educational level of sample population.

The majority of individuals in the Affected Cohort have been diagnosed with ADHD combined type (*n*=15; 54%), followed by the predominantly inattentive type (*n*=10; 36%) and only very few individuals have the hyperactive/impulsive type (*n*=3; 11%) (Figure 3.4).

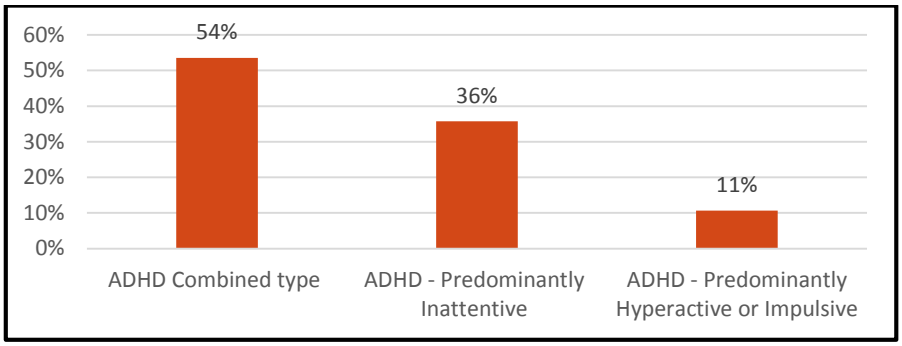


Figure 3.4 Division of ADHD types within the Affected Cohort of the sample population.

Proportionately, the use of medical specialists was fairly even amongst GP's, psychologists, psychiatrists, paediatricians, and other medical professionals at two to four individuals in each case, however, five individuals admitted to self-diagnosis.

### *a. Participant-related*

Predominant medical conditions experienced by both Affected and Unaffected Cohorts were asthma (*n*=4, 14% and *n*=4, 50%, respectively) and anaemia (*n*=4, 14% and *n*=3, 38%, respectively) (Table 3.3). Problems associated more often or solely with the Affected Cohort included enlarged tonsils, coordination problems, history of anoxia or perinatal complications, hearing or visual problems, diabetes, developmental delays, thyroid disorder, sleep apnoea, seizures, and *in utero* exposure to nicotine, alcohol or drugs.

Table 3.3 Comparative frequency of medical problems experienced by the Affected and Unaffected Cohorts, as assessed by the demographic questionnaire based on the CADDRA guidelines.

| Medical problem | Affected Cohort | Unaffected Cohort |
|---|---|---|
| Not applicable | 12 | 17 |
| Asthma | 4 | 4 |
| Anaemia | 4 | 3 |
| Enlarged tonsils | 5 | 1 |
| Coordination problems | 3 | - |
| History of anoxia or perinatal complications | 2 | - |
| Hearing or visual problems | 2 | - |
| Diabetes | 2 | - |
| Developmental delays | 2 | - |
| Thyroid disorder | 1 | - |
| Sleep apnea | 1 | - |
| Seizures | 1 | - |
| *In utero* exposure to nicotine, alcohol or drugs | 1 | - |

The predominant psychological complaints amongst the Affected Cohort included depression (*n*=8; 35%), anxiety disorders (*n*=6; 26%), learning disorders (*n*=4; 17%), and sleep disorders (*n*=3; 13%) (Table 3.4). While depression (*n*=5; 45%) was also frequent amongst the Unaffected Cohort, it was not as prevalent as in the Affected Cohort, as was the case with anxiety disorders (*n*=2; 18%).

Table 3.4 Comparative frequency of psychological problems experienced by the Affected and Unaffected Cohorts, as assessed by the demographic questionnaire based on the CADDRA guidelines.

| Psychological condition | Affected Cohort | Unaffected Cohort |
|---|---|---|
| Not applicable | 12 | 17 |
| Depression | 8 | 5 |
| Anxiety disorder | 6 | 2 |
| Learning disorder | 4 | 0 |
| Sleep disorders | 3 | 1 |
| Suicidal Attempts | 1 | 2 |
| Oppositional defiant disorder | 1 | 0 |
| Bipolar disorder | 0 | 1 |

Most developmental difficulties were experienced much more within the Affected Cohort, however, language difficulties appeared to be just as prevalent in both the Affected and Unaffected cohorts (Table 3.5). Bad temperament during childhood also appeared to be more prevalent in the Affected Cohort (*n*=24) as opposed to the Unaffected Cohort (*n*=27). Only one individual in the Unaffected Cohort mentioned having a learning disorder not included in the options provided, however, this individual did not indicate what this learning disorder was. For the Affected Cohort, all learning disorders were mentioned twice or more (Table 3.5), and other learning disorders mentioned included three mentions of concentration or focus issues, and one of an unspecified learning condition which was treated by visual therapy.

Table 3.5 Comparative frequency indicating common problems experienced by the Affected and Unaffected Cohorts during childhood.

| | Affected Cohort | Unaffected Cohort |
|---|---|---|
| **Developmental difficulties** | | |
| Difficulties in gross motor control (crawl, walk, gym, sports) | 6 | 1 |
| Difficulties in fine motor skills (tracing, shoe laces, writing) | 9 | 1 |
| Language difficulties (first language, first words, full sentences, stuttering) | 3 | 3 |
| Odd behaviours noted (rocking, flapping, no eye contact, odd play, head banging, etc.) | 6 | 1 |
| **Temperament** | | |
| Difficult/Hyperactive | 14 | 3 |
| Easy/Calm | 10 | 24 |
| **Learning disorder** | | |
| Dyslexia | 5 | 0 |
| Dysorthographia | 2 | 0 |
| Dyscalculia | 2 | 0 |
| Dysphasia | 2 | 0 |
| Other | 3 | 1 |

The majority of individuals in the Affected Cohort are, or have been, habitual smokers (Table 3.6). Of these individuals, the majority (*n*=10; 77%) feel that the amount they smoke is based on external factors. In both the Affected and Unaffected Cohorts the general consensus

is that smoking relieves feelings of restlessness and irritability. Relapse appears to be high across both groups. Generally the Affected Cohort used nicotine based products one to 15 times a day (*n*=10; 77%). The Affected Cohort commonly reported attempting to quit smoking one to two times (*n*=6; 46%), but also reported four to five times (*n*=3; 23%), and even six or more times (*n*=2; 15%). The Unaffected Cohort only reported attempts to quit smoking one to two times (Table 3.6).

Table 3.6 Comparative frequency of the smoking history in the Affected and Unaffected Cohorts.

| | | Affected Cohort | | Unaffected Cohort | |
|---|---|---|---|---|---|
| | | *n* | % | *n* | % |
| Are you or have you ever been a habitual smoker? | Yes | 13 | | 2 | |
| Do you find it difficult to refrain from smoking in places where smoking is not allowed? | Yes | 2 | 15% | 1 | 50% |
| | No | 9 | 69% | 2 | 100% |
| Is the number of cigarettes you smoke per day often influenced by other factors? | Yes | 10 | 77% | 1 | 50% |
| | No | 1 | 8% | 1 | 50% |
| After not smoking for a while, do you feel you need to smoke to relieve feelings of restlessness and irritability? | Yes | 10 | 77% | 2 | 100% |
| | No | 2 | 15% | 0 | 0% |
| Have you tried to stop smoking only to relapse? | Yes | 10 | 77% | 2 | 100% |
| | No | 3 | 23% | 0 | 0% |
| On average, how many times per day do you need nicotine based products? | 1-5 | 5 | 38% | 0 | 0% |
| | 10-15 | 5 | 38% | 0 | 0% |
| | 20-30 | 1 | 8% | 1 | 50% |
| | 60 | 1 | 8% | 0 | 0% |
| How many times have you attempted to stop smoking? | 1-2 times | 6 | 46% | 2 | 100% |
| | 3-4 times | 1 | 8% | 0 | 0% |
| | 4-5 times | 3 | 23% | 0 | 0% |
| | 6 times or more | 2 | 15% | 0 | 0% |
| Most likely cause of relapse | Low self-control | 6 | 46% | 1 | 50% |
| | Influence from other smokers | 6 | 46% | 1 | 50% |
| | Limited cessation methods | 1 | 8% | 0 | 0% |
| | Little family or social support | 1 | 8% | 0 | 0% |
| | Other | 2 | 15% | 0 | 0% |

No difference was found between the dietary behaviour of the Affected and Unaffected cohorts (Table 3.7). On average, most individuals, both Affected and Unaffected Cohorts, eat foods high in sugar one to two times a week. Similarly, the majority of both groups eat foods high in additives one to two times a week.

Table 3.7 Comparative frequency showing nutritional and dietary habits of the Affected and Unaffected Cohorts.

| | | Affected Cohort | | Unaffected Cohort | |
|---|---|---|---|---|---|
| | | *n* | % | *n* | % |
| Nutritional meal (i.e. not fast food)? | 0-3 days a week | 8 | 32% | 11 | 39% |
| | 4-7 days a week | 17 | 68% | 17 | 61% |
| Eat foods high in sugar (e.g. sweets or sugary fruit)? | Never | 1 | 4% | 1 | 4% |
| | 1-2 times a week | 11 | 44% | 11 | 39% |
| | 3-5 times a week | 8 | 32% | 9 | 32% |
| | Almost every day | 5 | 20% | 6 | 21% |
| Eat foods high in additives (like MSG in crisps, artificial sweeteners in "diet" foods, refined sugars in candy or sodas and artificial flavourants) and artificial colourants? | Never | 3 | 12% | 4 | 14% |
| | 1-2 times a week | 10 | 40% | 15 | 54% |
| | 3-5 times a week | 6 | 24% | 5 | 18% |
| | Almost every day | 6 | 24% | 3 | 11% |

More than 50% of the Affected Cohort sleep six hours or less per 24-hour cycle (*n*=14; 56%), compared to only 36% (*n*=10) of individuals in the Unaffected Cohort. A slightly higher proportion of the Affected Cohort do not dream regularly (*n*=9; 36% as opposed to *n*=8; 29% in the Unaffected Cohort). The vast majority of ADHD individuals (*n*=19; 76%) have difficulty falling asleep, compared with only 43% (*n*=12) of the Unaffected Cohort. Similarly individuals in the Affected Cohort fail to maintain regular sleep patterns (*n*=17; 68%) compared to the Unaffected Cohort (*n*=12; 43%). More individuals in the Affected Cohort reported snoring (*n*=12; 48%) compared to the Unaffected Cohort (*n*=3; 11%). Similarly, more individuals in the Affected Cohort reported having restless leg syndrome (*n*=11; 44%) than in the Unaffected Cohort (*n*=4; 14%).

Table 3.8 Comparative frequency showing information surrounding sleep cycle in the Affected and Unaffected Cohorts.

| | | Affected Cohort | | Unaffected Cohort | |
|---|---|---|---|---|---|
| | | *n* | % | *n* | % |
| Hours of sleep per night (without any sleep aid)? | Less than 4 hours | 2 | 8% | 0 | 0% |
| | 4-6 hours | 12 | 48% | 10 | 36% |
| | 6-8 hours | 6 | 24% | 13 | 46% |
| | 8-10 hours | 5 | 20% | 5 | 18% |
| Do you dream regularly? | Yes | 16 | 64% | 20 | 71% |
| | No | 9 | 36% | 8 | 29% |
| Difficulty falling asleep | Yes | 19 | 76% | 12 | 43% |
| | No | 5 | 20% | 16 | 57% |
| Difficulty keeping regular sleep pattern | Yes | 17 | 68% | 12 | 43% |
| | No | 7 | 28% | 16 | 57% |
| Excessive daytime sleepiness | Yes | 11 | 44% | 16 | 57% |
| | No | 12 | 48% | 12 | 43% |
| Snoring | Yes | 12 | 48% | 3 | 11% |
| | No | 12 | 48% | 25 | 89% |
| Restless leg syndrome | Yes | 11 | 44% | 4 | 14% |
| | No | 12 | 48% | 24 | 86% |

Approximately 80% (*n*=20) of Affected Cohort exercise at least once a week compared with only 65% (*n*=18) of the Unaffected Cohort. All individuals in the Affected Cohort reported exercising one to two hours a day, as did the majority of Unaffected Cohort participants (*n*=16; 57%). Most individuals in the Unaffected Cohort reported gym as their exercise of choice (*n*=9; 32%), while the Affected Cohort reported other exercises more often (*n*=12; 48%), such as Jogging/running/walking, martial arts, horse riding, archery, cycling/spinning, squash/tennis, Zumba, and even trampoline. Exertion for both groups appears to be mildly to very physical, with more of the Affected Cohort rating the level of exercise they do very physical (*n*=7; 28%) compared to the Unaffected Cohort (*n*=5; 18%).

Table 3.9 Comparative frequency showing information concerning exercise habits of the Affected and Unaffected Cohorts.

| | | Affected Cohort | | Unaffected Cohort | |
|---|---|---|---|---|---|
| | | *n* | % | *n* | % |
| On average, how many days per week do you exercise? | 0 | 5 | 20% | 10 | 36% |
| | 1 | 5 | 20% | 0 | 0% |
| | 2 | 6 | 24% | 3 | 11% |
| | 3 | 5 | 20% | 6 | 21% |
| | 4 | 2 | 8% | 3 | 11% |
| | 5 | 2 | 8% | 1 | 4% |
| | 6 | 0 | 0% | 5 | 18% |
| On average, how many hours per day do you exercise? | None | 5 | 20% | 10 | 36% |
| | 1-2 | 20 | 80% | 16 | 57% |
| | 3-4 | 0 | 0% | 2 | 7% |
| What type of exercise do you do? | Gym | 3 | 12% | 9 | 32% |
| | Rugby/Cricket/ Soccer | 2 | 8% | 1 | 4% |
| | Dancing | 1 | 4% | 1 | 4% |
| | Yoga or Pilates | 2 | 8% | 2 | 7% |
| | Other | 12 | 48% | 5 | 18% |
| Level of exercise: Indicate how physically taxing the exercise that you do is | Become out of breath | 5 | 20% | 2 | 7% |
| | Work up a light sweat | 7 | 28% | 10 | 36% |
| | Sweat profusely | 7 | 28% | 5 | 18% |
| Do you feel as though exercise provides relief from your ADHD symptoms? | Yes | 11 | 44% | | |
| | No | 6 | 24% | | |

### *b. Familial*

Similar numbers of the Affected and Unaffected Cohorts reported familial health problems (*n*=15 and *n*=14, respectively). Predominant in both groups were pregnancy problems (*n*=7, 47% and *n*=6, 43%, respectively), and alcohol or drug problems (*n*=7, 47% and *n*=6, 43%, respectively). Three ADHD individuals in the Affected Cohort also reported epilepsy (Table 3.10).

Table 3.10 Comparative frequency of familial health conditions experienced by the relatives of Affected and Unaffected Cohorts.

| Health condition | Affected Cohort | Unaffected Cohort |
|---|---|---|
| Family health problems | 15 | 14 |
| Pregnancy Problems | 7 | 6 |
| Legal Convictions | 0 | 1 |
| Epilepsy | 3 | 1 |
| Alcohol/Drug Problems | 7 | 6 |
| Congenital Disorders | 1 | 2 |

More Affected than Unaffected individuals reported familial psychological problems (17 in the Affected Cohort as opposed to 13 in the Unaffected Cohort). Individuals in the Affected Cohort commonly reported either confirmed or probable ADHD in other family members (*n*=12; 71%). Depression was common in the families of both Affected (*n*=9; 53%) and Unaffected Cohort individuals (*n*=8; 62%). Sleep disorders, anxiety, and learning disorders were more commonly reported in the Affected Cohort's families, whereas bipolar, and suicide were commonly reported in the Unaffected Cohort's families (Table 3.11).

Table 3.11 Comparative frequency of familial psychological conditions experienced by the relatives of Affected and Unaffected Cohorts.

| Psychological condition | Affected Cohort | Unaffected Cohort |
|---|---|---|
| Family psychological problems | 17 | 13 |
| ADHD (confirmed) | 5 | 1 |
| ADHD (probable) | 7 | 1 |
| Tourette's or Tics | 0 | 0 |
| Depression | 9 | 8 |
| Sleep Disorders | 4 | 3 |
| Bipolar | 2 | 5 |
| Suicide | 2 | 6 |
| Anxiety | 4 | 3 |
| Psychosis | 0 | 0 |
| Mental Retardation | 0 | 1 |
| Learning Disorders | 5 | 3 |
| Personality Disorder | 1 | 0 |
| Autism Spectrum Disorders | 0 | 1 |

Compared to the Unaffected Cohort (*n*=5; 18%), the Affected Cohort reported maternal smoking more often (*n*=11; 44%) (Table 3.12). Of these, a large proportion (*n*=6; 55%) smoked during the ADHD individual's first five years of life. Paternal smoking showed similar patterns with 80% (*n*=20) of ADHD individual's fathers smoking, compared to 32% (*n*=9) of the Unaffected Cohort. Of these ADHD individuals, fathers smoked during the individual's first five years of life in 55% (*n*=11) of cases. Less than 50% of individuals in both samples reported other family members smoking. In both cases most individuals report that their family was particular about exposure to second hand smoke. This is reported less in individuals with ADHD (*n*=14; 56%) than Unaffected individuals (*n*=18; 64%).

Table 3.12 Comparative frequency of the smoking history of family members of the Affected and Unaffected Cohorts.

| | | Affected Cohort | | Unaffected Cohort | |
|---|---|---|---|---|---|
| | | *n* | % | *n* | % |
| Does your mother smoke or has she ever smoked? | Yes | 11 | 44% | 5 | 18% |
| | No | 14 | 56% | 22 | 79% |
| Mother smoke during first 5 years of life | Yes | 6 | 55% | 1 | 20% |
| Does your father smoke or has he ever smoked? | Yes | 20 | 80% | 9 | 32% |
| | No | 4 | 16% | 18 | 64% |
| Father smoke during first 5 years of life | Yes | 11 | 55% | 2 | 22% |
| Do any of your other family members smoke? | Yes | 12 | 48% | 13 | 46% |
| | No | 13 | 52% | 15 | 54% |
| Was your family particular about not exposing you to second hand smoke, especially while your mother was pregnant with you and during the first few years of life? | Yes | 14 | 56% | 18 | 64% |
| | No | 11 | 44% | 10 | 36% |

### 3.3.2 Basic descriptive statistics

Average ASRS pre-diagnosis scores are notably higher for the Affected Cohort ( $\overline{x}$ =4.56) compared to the Unaffected Cohort ( $\overline{x}$ =1.64) (Table 3.13). Similarly, pre-diagnosis scores for inattention and hyperactivity were higher for the Affected Cohort ( $\overline{x}$ =3.24 and

$\overline{x}$ =1.32, respectively) compared to the Unaffected Cohort ($\overline{x}$ =1.29 and $\overline{x}$ =0.36, respectively). This is also reflected in median and mode scores. Deviations from the mean are similar for both groups.

Table 3.13 Comparative basic descriptive statistics for the ASRS Pre-diagnosis data obtained from the Affected and Unaffected Cohorts.

| | Affected Cohort | | | Unaffected Cohort | | |
|---|---|---|---|---|---|---|
| | ASRS Pre-Diagnosis | ASRS Pre-Diagnosis: Inattention | ASRS Pre-Diagnosis: Hyperactivity | ASRS Pre-Diagnosis | ASRS Pre-Diagnosis: Inattention | ASRS Pre-Diagnosis: Hyperactivity |
| *n* | | 25 | | | 28 | |
| Mean $\overline{x}$ | 4.5600 | 3.2400 | 1.3200 | 1.6429 | 1.2857 | 0.3571 |
| Median $\widetilde{x}$ | 5.0000 | 3.0000 | 1.0000 | 1.0000 | 1.0000 | 0.0000 |
| Mode | 5.00 | 3.00[b] | 1.00[b] | 0.00 [b] | 0.00 [b] | 0.00 |
| Std. Deviation σ | 1.22746 | 0.92556 | 0.69041 | 1.61507 | 1.38396 | 0.55872 |

The average full diagnosis score for ADHD individuals was 7.84 with a median score of 8 and a standard deviation of 5.67 points from the mean (Figure 3.5). Inattentive symptoms show a mean score of 4.64, with a median score of 4 and 3.02 standard deviation points from the mean. Hyperactive symptoms show a mean score of 3.20, with a median score of 2 and 2.95 standard deviation points from the mean.

[b] There are multiple modes for these items, the lowest mode is displayed here.

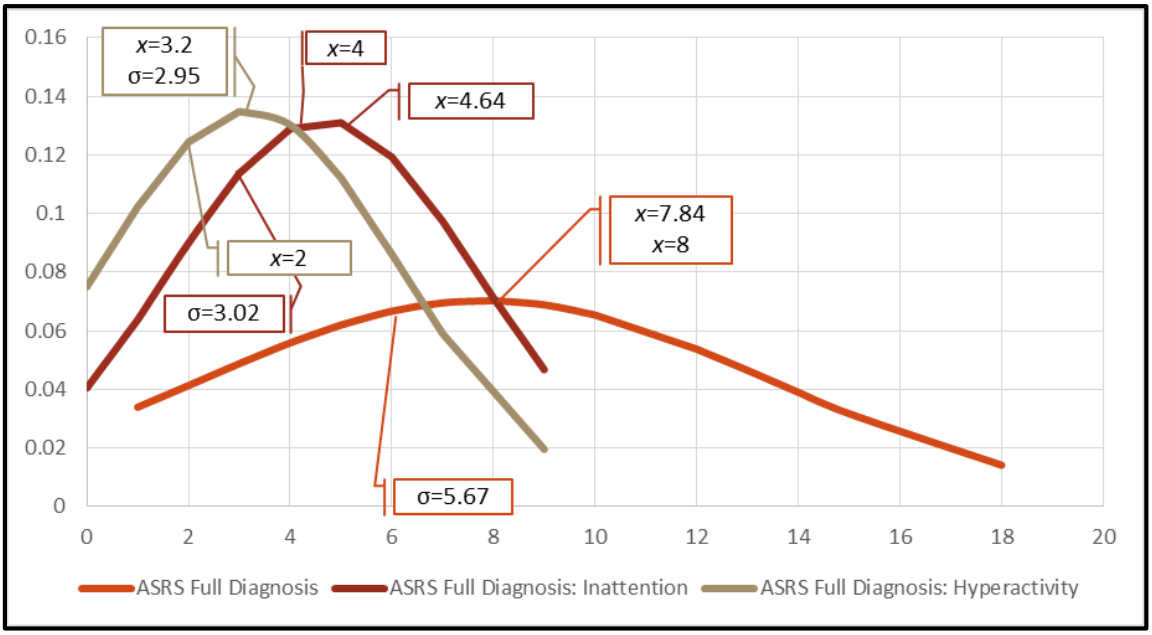


Figure 3.5: Normal distribution for the ASRS Full diagnosis scores, as well as for the inattention and hyperactivity scores (*n*=45).

Individuals in the Affected Cohort showed impairments in all areas assessed by the WFIRS (Table 3.14). Most commonly assessed impairments included poor self-concept (*n*=23; 92%), poor life-skills (*n*=21; 84%) and work impairment (*n*=20; 80%). Less commonly assessed included family impairment (*n*=18; 72%), increased risky activities (*n*=17; 68%) and social activities impairment (*n*=15; 60%) were noted. Self-reported familial impairments most commonly indicated were conflict with siblings (*n*=20; 80%), causing family members to take time away from work or activities (*n*=15; 60%), and made parenting difficult as a child (*n*=17; 68%). Impairments at school and work included difficulty keeping up with work required for the job (*n*=20; 80%), needing additional help (*n*=18; 72%), needing tutoring or extensive explanations (*n*=15; 60%), poor performance at school or work (*n*=22; 88%), and missing or being late for school or work (*n*=16; 64%). Self-reported impairments in general life skills which were commonly indicated encompassed excessive use of television, computer or video games (*n*=18; 72%), problems getting ready for school or work (*n*=19; 76%), problems getting ready for bed (*n*=16; 64%), problems sleeping (*n*=22; 88%), getting injured often (*n*=18; 72%),

avoiding exercise (*n*=16; 23%), and having trouble taking medication, or going to medical practitioners (*n*=15; 60%). Impairments in self-concept included negative feelings about self (*n*=22; 88%), not having enough fun (*n*=23; 92%), and being unhappy with life (*n*=20; 80%). Social impairments included issues participating in after-school or after-work activities (*n*=15; 60%), problems getting along with others (*n*=14; 56%), problems making (*n*=12; 48%), and keeping friends (*n*=11; 44%), difficulties with parties (*n*=12; 48%), and often buckling under peer pressure (*n*=13; 52%). Finally, excessive risky activities include saying mean or inappropriate things (*n*=17; 68%), smoking cigarettes (*n*=14; 56%), doing dangerous things (*n*=11; 44%), and taking part in illegal activities (*n*=11; 44%).

Table 3.14 Frequency table showing the proportion of impairment in each of the domains of the WFIRS in the Affected Cohort.

| WFIRS impairment | | *n* | % |
|---|---|---|---|
| Family Impairment | No | 7 | 28% |
| | Yes | 18 | 72% |
| Work Impairment | No | 5 | 20% |
| | Yes | 20 | 80% |
| Life Skills Impairment | No | 4 | 16% |
| | Yes | 21 | 84% |
| Self-concept Impairment | No | 2 | 8% |
| | Yes | 23 | 92% |
| Social Activities Impairment | No | 10 | 40% |
| | Yes | 15 | 60% |
| Risky Activities Impairment | No | 8 | 32% |
| | Yes | 17 | 68% |

### 3.3.3 Pearson's Product Moment correlations, Chi-Square tests, ANOVA tests and T-tests

Analysis of the presence of ADHD showed significant correlations to various environmental factors (Table 3.15). The ADHD pre-diagnostic scores obtained from the ASRS-S showed correlations to environmental components. Higher ADHD pre-diagnosis scores were significantly associated with an increase in prevalence of medical problems ($r$=0.500; $p$<0.01),

increase in prevalence of developmental problems ($r$=0.594; $p$<0.01), increase in prevalence of severe smoking ($r$=0.419; $p$<0.01), exposure to hypoxic conditions more often ($r$=0.410; $p$<0.01), and poorer sleep ($r$=0.474; p<0.01), as well as impairments on all WFIRS-S domains except family (Table 3.15). Higher pre-diagnosis inattention scores are associated with an increase in prevalence of medical problems ($r$=0.452; $p$<0.01), increase in prevalence of developmental problems ($r$=0.518; $p$<0.01), increase in prevalence of severe smoking ($r$=0.317; $p$<0.05), exposure to hypoxic conditions more often ($r$=0.354; $p$<0.05), and poor sleep ($r$=0.441; $p$<0.01), as well as more impairments at school/work ($r$=0.504; $p$<0.05), in life skills ($r$=0.458; $p$<0.05), and self-concept ($r$=0.418; $p$<0.05). Similarly, higher pre-diagnosis Hyperactivity scores are associated with an increase in prevalence of medical problems ($r$=0.432; $p$<0.01), increase in prevalence of developmental problems ($r$=0.550; $p$<0.01), increase in prevalence of severe smoking ($r$=0.481; $p$<0.01), exposure to hypoxic conditions more often ($r$=0.385; $p$<0.05), and poorer sleep ($r$=0.385; $p$<0.05), as well as impairments in more life skills ($r$=0.532; $p$<0.01), and Risky Activity ($r$=0.529; $p$<0.01).

Analysis of full ASRS scores also showed significant correlations to environmental factors. Higher ADHD full diagnosis scores were associated with an increase in prevalence of medical problems ($r$=0.590; $p$<0.01), increase in prevalence of psychological problems ($r$=0.490; $p$<0.01), increase in prevalence of developmental problems ($r$=0.564; $p$<0.05), increase in prevalence of learning disorders ($r$=0.362; $p$<0.05), increase in prevalence of severe smoking ($r$=0.495; $p$<0.01), exposure to hypoxic conditions more often ($r$=0.406; $p$<0.05), and poorer sleep ($r$=0.539; $p$<0.01), as well as more impairments in school/work ($r$=0.447; $p$<0.05), family ($r$=0.622; $p$<0.01), and risky activity ($r$=0.524; $p$<0.01). Higher ADHD full diagnosis inattentive scores were associated with an increase in prevalence of medical problems

($r$=0.477; $p$<0.01), increase in prevalence of developmental problems ($r$=0.562; p<0.01), increase in prevalence of severe smoking ($r$=0.399; $p$<0.05), and poorer sleep ($r$=0.543; $p$<0.01), as well as more impairments in school/work ($r$=0.535; $p$<0.01), family ($r$=0.458; $p$<0.05), life skills ($r$=0.513; $p$<0.01), social activities ($r$=0.444; $p$<0.05), and risky activity ($r$=0.528; $p$<0.01). Higher ADHD full diagnosis hyperactivity scores were associated with an increase in prevalence of medical problems ($r$=0.641; $p$<0.01), increase in prevalence of psychological problems ($r$=0.479; $p$<0.01), increase in prevalence of developmental problems ($r$=0.503; $p$<0.01), increase in prevalence of learning disorders ($r$=0.411; $p$<0.01), increase in prevalence of severe smoking ($r$=0.538; $p$<0.05), exposure to more hypoxic environments ($r$=0.454; $p$<0.01), and poorer sleep ($r$=0.474; $p$<0.01).

Attention-Deficit Hyperactivity Disorder, predominantly hyperactive-impulsive type is associated with an increase in prevalence of medical problems ($r$=0.386; $p$<0.01), increase in prevalence of developmental problems ($r$=0.383; $p$<0.01), increase in prevalence of learning disorders (r=0.294; $p$<0.05), and poorer sleep ($r$=0.290; $p$<0.05). By reshuffling the ADHD type variable, it is possible to identify possible associations with ADHD-I. Attention-Deficit Hyperactivity Disorder, predominantly inattentive type shows correlations to an increase in prevalence of medical problems ($r$=0.386; $p$<0.01), presence of psychological problems ($r$=0.356; $p$<0.01), increase in prevalence of developmental problems ($r$=0.463; $p$<0.01), increase in prevalence of severe smoking ($r$=0.375; $p$<0.01), and poorer sleep ($r$=0.395; $p$<0.01), as well as more impairments in life skills ($r$=0.423; $p$<0.05).

There was a statistically significant differences between groups as determined by one-way ANOVA (Table 3.16) of ADHD type for frequency of medical problems ($F$(3,49)=10.931, p<0.01), frequency of psychological problems ($F$(3,49)=3.249, p<0.05),

frequency of developmental problems ($F(3,49)=4.896$, $p<0.01$), severity of smoking ($F(3,49)=8.735$, $p<0.01$), exposure to hypoxic conditions ($F(3,49)=4.167$, $p<0.01$), and severity of sleep problems ($F(3,49)=4.040$, $p<0.05$).

Tukey post-hoc tests revealed statistically significant differences between the unaffected and combined type ADHD individuals ($p<0.01$), and between the inattentive and combined type ADHD individuals ($p<0.05$) in terms of medical problems. Psychological problems were also statistically significantly different in the unaffected and combined type ADHD individuals ($p<0.05$). Similarly, unaffected individuals differed significantly from combined type ADHD and inattentive individuals in terms of developmental problems ($p<0.05$ in both cases). Statistically significant differences were found between the unaffected and combined type ADHD individuals ($p<0.01$), between the inattentive and combined type ADHD individuals ($p<0.05$), and between the hyperactive and combined type ADHD individuals ($p<0.05$) in terms of smoking severity. This test revealed statistically significant differences between the unaffected and combined type ADHD individuals ($p<0.01$), and between the inattentive and combined type ADHD individuals ($p<0.05$) in terms of exposure to hypoxic conditions. Finally, Tukey post-hoc analysis revealed statistically significant differences between the unaffected and combined type ADHD individuals ($p<0.05$) in terms of severity of sleep problems.

Table 3.15: Correlations between ADHD and various environmental factors.

| | | Number Medical problems | Number Psychological problems | Number Developmental problems | Number Learning Disorders | Severity of smoking | Amount of hypoxic exposure | Severity of poor sleep | WFIRS Family | WFIRS School Work | WFIRS Life Skills | WFIRS Self-Concept | WFIRS Social Activities | WFIRS Risky Activities |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ASRS Pre-Diagnosis | *r* | .500** | .282 | .594** | .259 | .419** | .410** | .474** | .391 | .557** | .468* | .443* | .423* | .539** |
| | *p* | .001 | .067 | .000 | .094 | .005 | .006 | .001 | .053 | .004 | .018 | .026 | .035 | .005 |
| | *n* | 43 | 43 | 43 | 43 | 43 | 43 | 43 | 25 | 25 | 25 | 25 | 25 | 25 |
| ASRS Pre-Diagnosis: Inattention | *r* | .452** | .238 | .518** | .209 | .317* | .354* | .441** | .348 | .504* | .458* | .418* | .270 | .320 |
| | *p* | .002 | .125 | .000 | .179 | .039 | .020 | .003 | .088 | .010 | .021 | .038 | .192 | .119 |
| | *n* | 43 | 43 | 43 | 43 | 43 | 43 | 43 | 25 | 25 | 25 | 25 | 25 | 25 |
| ASRS Pre-Diagnosis: Hyperactivity | *r* | .432** | .276 | .550** | .272 | .481** | .385* | .385* | .229 | .314 | .217 | .228 | .389 | .529** |
| | *p* | .004 | .074 | .000 | .078 | .001 | .011 | .011 | .271 | .126 | .297 | .273 | .054 | .006 |
| | *n* | 43 | 43 | 43 | 43 | 43 | 43 | 43 | 25 | 25 | 25 | 25 | 25 | 25 |
| ASRS Full Diagnosis | *r* | .590** | .410* | .564** | .362* | .495** | .406* | .539** | .447* | .477* | .382 | .236 | .327 | .524** |
| | *p* | .000 | .011 | .000 | .025 | .002 | .011 | .000 | .025 | .016 | .059 | .255 | .111 | .007 |
| | *n* | 38 | 38 | 38 | 38 | 38 | 38 | 38 | 25 | 25 | 25 | 25 | 25 | 25 |
| ASRS Full Diagnosis: Inattention | *r* | .477** | .298 | .562** | .276 | .399* | .316 | .543** | .458* | .535** | .513** | .266 | .444* | .528** |
| | *p* | .002 | .069 | .000 | .094 | .013 | .054 | .000 | .021 | .006 | .009 | .198 | .026 | .007 |
| | *n* | 38 | 38 | 38 | 38 | 38 | 38 | 38 | 25 | 25 | 25 | 25 | 25 | 25 |
| ASRS Full Diagnosis: Hyperactivity | *r* | .641** | .479** | .503** | .411* | .538** | .454** | .474** | .309 | .291 | .164 | .143 | .135 | .369 |
| | *p* | .000 | .002 | .001 | .010 | .000 | .004 | .003 | .133 | .158 | .434 | .495 | .519 | .070 |
| | *n* | 38 | 38 | 38 | 38 | 38 | 38 | 38 | 25 | 25 | 25 | 25 | 25 | 25 |

Table 3.16 ANOVA for ADHD and various environmental factors.

| | | Number Medical problems | Number Psychological problems | Number Developmental problems | Number Learning Disorders | Severity of smoking | Amount of hypoxic exposure | Severity of poor sleep | WFIRS Family | WFIRS School Work | WFIRS Life Skills | WFIRS Self-Concept | WFIRS Social Activities | WFIRS Risky Activities |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ADHD type (1=ADHD-C; 2=ADHD-I; 3=ADHD-HI) | *F* | 10.931 | 3.249 | 4.896 | 2.467 | 8.735 | 4.167 | 4.040 | .939 | 1.291 | 2.178 | .266 | .479 | 1.400 |
| | *p* | .000 | .030 | .005 | .073 | .000 | .010 | .012 | .440 | .303 | .121 | .849 | .701 | .271 |

Pearson's Chi-Square analysis (Table 3.17) revealed statistically significant differences between the Affected and Unaffected cohorts in terms of the presence of psychological problems ($\chi^2(1)=7.666$, $p<0.01$), as well as between the different types of ADHD in terms of the presence of psychological problems ($\chi^2(1)=18.646$, $p<0.01$).

Table 3.17 Chi-Square test for ADHD and the presence of psychological problems.

| | | Presence Psychological problems |
|---|---|---|
| Affected (1) or Unaffected Cohort (2) | $X^2$ | 7.666 |
| | *p* | 0.006 |
| | *n* | 63 |
| ADHD type (1=ADHD-C; 2=ADHD-I; 3=ADHD-HI) | $X^2$ | 18.646 |
| | *p* | .000 |
| | *n* | 63 |

Analysis using the Independent samples T-test (Table 3.18) found that affected individuals had statistically significantly more medical problems ($t(29.636)=3.861$, $p<0.01$), developmental problems ($t(35.799)=3.138$, $p<0.01$), learning disorders ($t(24)=2.400$, $p<0.05$) and more exposure to hypoxic conditions ($t(38.737)=2.066$, $p<0.05$) compared to the Unaffected group. As well as more severe smoking habits ($t(32.627)=3.549$, $p<0.01$), and poorer sleep ($t(51)=3.336$, $p<0.01$).

Analysis using the Independent samples T-test (Table 3.18) also found that individuals who scored high on ADHD scales were statistically significantly more likely to have psychological problems. This was true for ASRS pre-diagnosis scores ($t(51)=-2916$, $p<0.01$), ASRS pre-diagnosis inattention scores ($t(51)=-2.151$, $p<0.05$), ASRS pre-diagnosis hyperactivity scores ($t(51)=-3.338$, $p<0.01$), ASRS full diagnosis scores ($t(43)=-3.688$, $p<0.01$), ASRS full diagnosis inattention scores ($t(43)=-3.132$, $p<0.01$), and ASRS full diagnosis hyperactivity scores ($t(43)=-3.794$, $p<0.01$).

Table 3.18 T-test for ADHD and various environmental factors.

| | | Number Medical problems | Number Psychological problems | Number Developmental problems | Number Learning Disorders | Severity of smoking | Amount of hypoxic exposure | Severity of poor sleep | Presence Psychological problems |
|---|---|---|---|---|---|---|---|---|---|
| Affected (1) or Unaffected Cohort (2) | *t* | 3.861 | 1.520 | 3.138 | 2.400 | 3.549 | 2.066 | 3.336 | |
| | *p* | .001 | .135 | .003 | .024 | .001 | .046 | .002 | |
| ASRS Pre-Diagnosis | *t* | | | | | | | | -2.916 |
| | *p* | | | | | | | | .005 |
| ASRS Pre-Diagnosis: Inattention | *t* | | | | | | | | -2.151 |
| | *p* | | | | | | | | .036 |
| ASRS Pre-Diagnosis: Hyperactivity | *t* | | | | | | | | -3.338 |
| | *p* | | | | | | | | .002 |
| ASRS Full Diagnosis | *t* | | | | | | | | -3.688 |
| | *p* | | | | | | | | .001 |
| ASRS Full Diagnosis: Inattention | *t* | | | | | | | | -3.132 |
| | *p* | | | | | | | | .003 |
| ASRS Full Diagnosis: Hyperactivity | *t* | | | | | | | | -3.794 |
| | *p* | | | | | | | | .000 |

### 3.3.4 Inferential statistics

Simple decision tree analysis showed a significant association between the presence of ADHD, paternal smoking and developmental problems (Figure 3.6, a). When considering the presence of ADHD, paternal smoking was predictable in 69% of cases. Individuals with ADHD whose fathers smoke also generally have developmental problems, predictable in 93.3% of cases. More complex decision tree analysis assessing ADHD types also showed this result (Figure 3.6, b). Paternal smoking was predictable in 41.4% of ADHD-I cases. Individuals with the inattentive subtype who also have a father that smokes generally have developmental problems, predictable in 60% of cases.

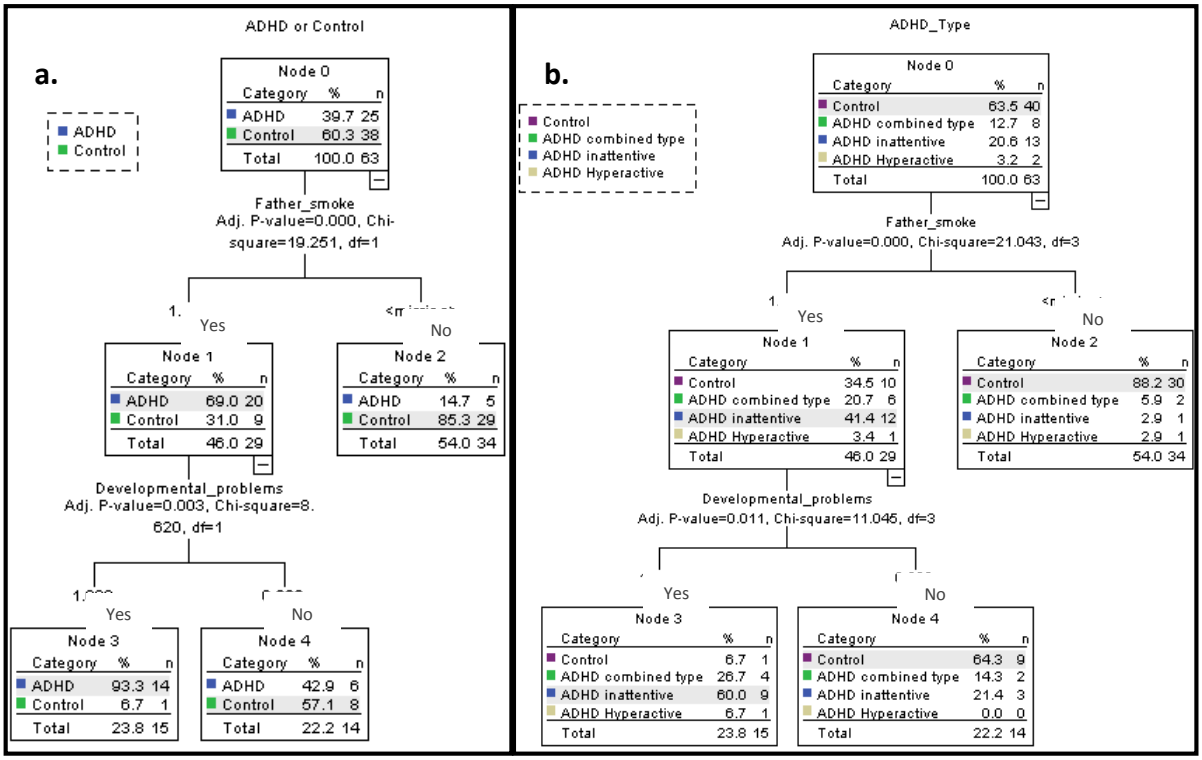


Figure 3.6: Decision tree analysis based on (a) ADHD presence, and (b) ADHD type.

Simple decision tree analysis showed a significant association between the presence of ADHD, exercise and medical problems. When considering the presence of ADHD, not exercising was predictable in 80% of cases. Individuals with ADHD who do not exercise also generally have medical problems, predictable in 66.7% of cases (Figure 3.7).

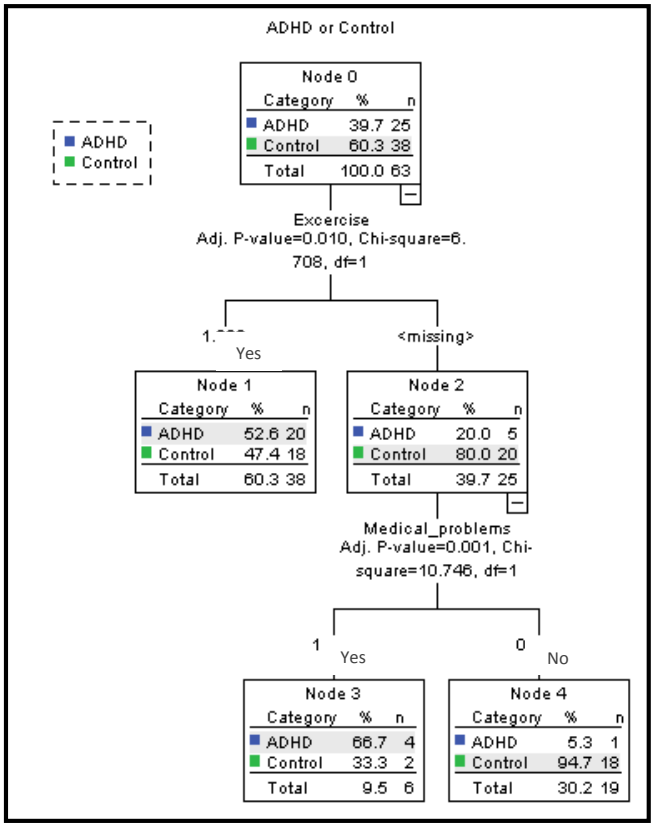


Figure 3.7: Decision tree analysis results based on ADHD presence, exercise and medical problems.

In order to perform multiple regression analysis, the two groups were distinguished as Affected and Unaffected and coded into a binary variable, henceforth referred to as ADHD presence and ADHD absence, respectively. A multiple regression was performed utilising the ADHD presence as the criterion and number of medical problems, presence of psychological problems, number of developmental problems, number of learning disorders, severity of smoking, exposure to hypoxic conditions, and quality of sleep as predictors in order to determine if ADHD could be predicted as a function of these. The analysis was found to be statistically significant [$F(7, 45)=3.318$, $p<0.01$], indicating that these environmental components are good predictors of ADHD presence (Figure 3.8). This multiple regression accounted for 24% of the variability, as indexed by the adjusted $R^2$ statistic. The variable of

number of medical problems, as indexed by its β value of 0.199, was shown to have the strongest relationship to ADHD presence.

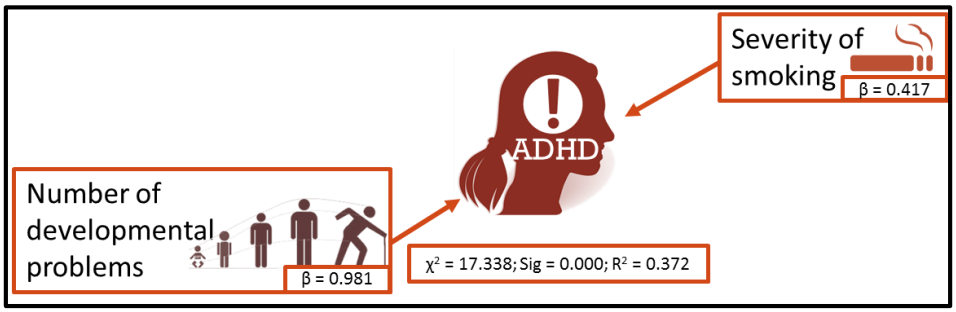


Figure 3.8: A visual representation of a binomial logistic regression testing the validity of the hypothesis where the presence of ADHD, as the criterion, is influenced by several predictors.

A logistic regression was performed to ascertain the effects of developmental problems and smoking severity on the likelihood that participants have ADHD. The logistic regression model was statistically significant [$\chi^2(2)=17.338$, $p<0.01$]. The model explained 37% (Nagelkerke $R^2$) of the variance in ADHD and correctly classified 72% of cases. Individuals with more developmental problems were 3 times more likely to have ADHD than those with fewer developmental problems. Both developmental problems, and severe smoking addiction were associated with an increased likelihood of exhibiting ADHD.

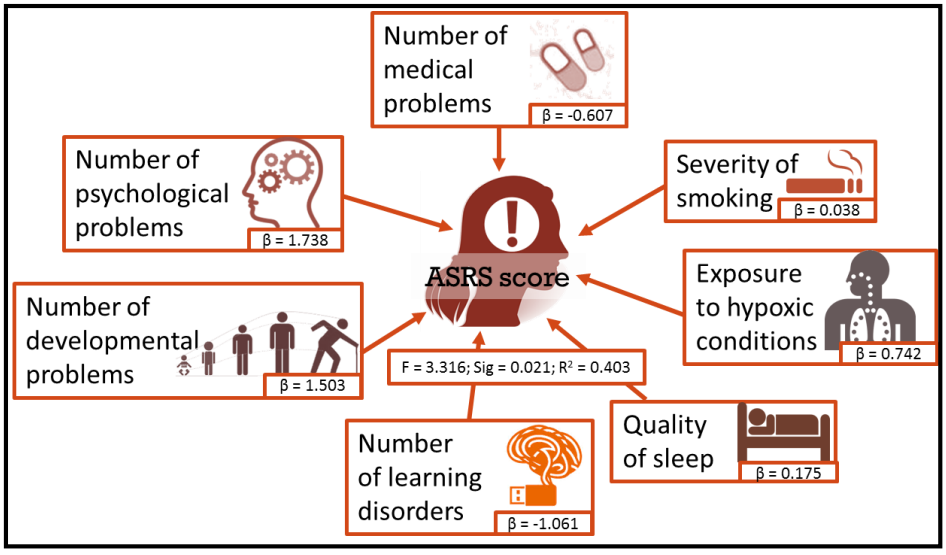

Figure 3.9: A visual representation of a multiple regression testing the validity of the hypothesis where the severity of ADHD (as measured by the full ASRS score), as the criterion, is influenced by several predictors.

If smoking severity was removed from this multiple regression and level of impairment at school or work, level of familial impairment, and level of risky activity added, a significant result was also found [$F(9, 15)=3.055$, $p<0.05$]. And the variability accounted for was 43.5% with the most significant predictor being school or work impairment (β = 1.902).

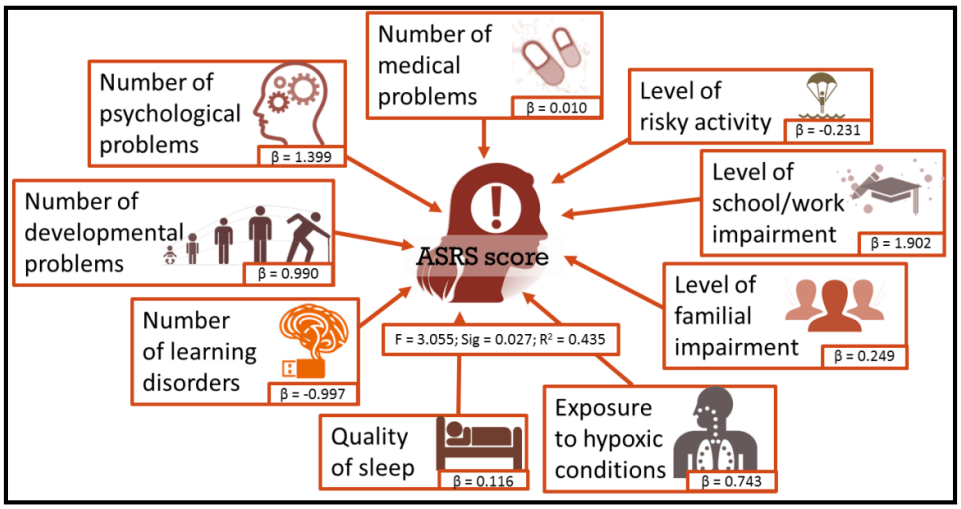


Figure 3.10 A visual representation of a multiple regression testing the validity of the hypothesis where the severity of ADHD (as measured by the full ASRS score), as the criterion, is influenced by several predictors (including environmental components and life impairments).

When considering ASRS inattention scores, number of medical problems, presence of psychological problems, number of developmental problems, severity of smoking, quality of sleep, level of life skills impairment, and level of school or work impairment were found to be significant predictors [$F(7, 17)=2.877$, $p<0.05$]. Variability was 35% and the strongest predictor was school or work impairment (β = 0.808).

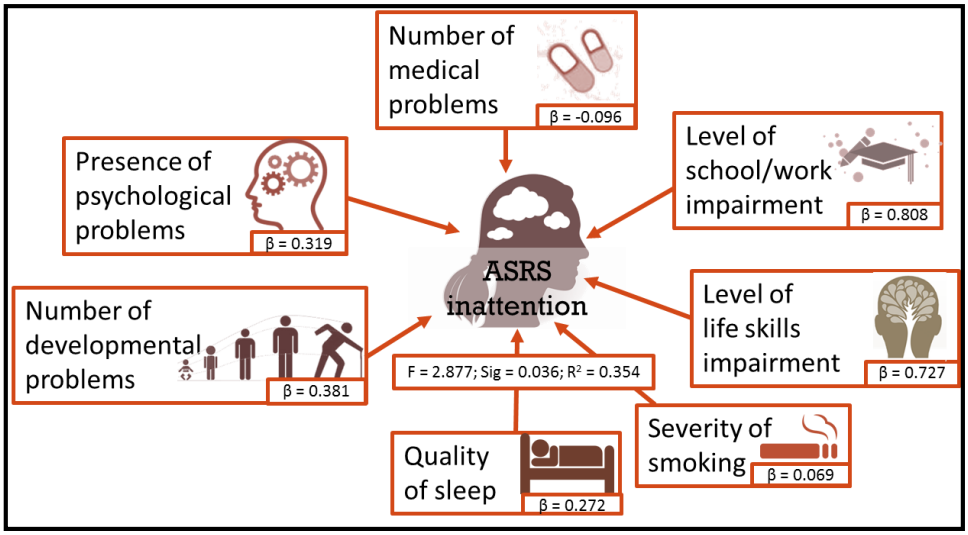


Figure 3.11 A visual representation of a multiple regression testing the validity of the hypothesis where the severity of inattention (as measured by the full ASRS inattention score), as the criterion, is influenced by several predictors (including environmental components and life impairments).

Similarly, hyperactivity scores were significantly predicted by number of medical problems, number of psychological problems, number of developmental problems, number of learning disorders, severity of smoking, exposure to hypoxic conditions, poor quality of sleep, and work impairment [$F(8,16)=2.852$, $p<0.05$]. The variability accounted for was 38% with the strongest predictor also being work impairment (β = 2.376).

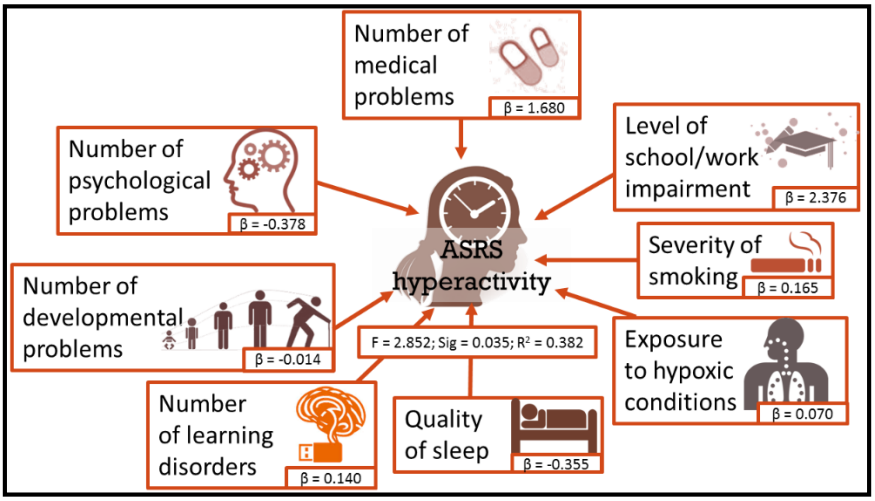


Figure 3.12 A visual representation of a multiple regression testing the validity of the hypothesis where the severity of Hyperactivity (as measured by the full Hyperactivity ASRS score), as the criterion, is influenced by several predictors (including environmental components and life impairments).

The same effects as tested in the binomial logistic regression were tested in a multinomial logistic regression. The logistic regression model was statistically significant, $\chi^2(6)=25.456$, $p<0.01$. The model explained 43% (Nagelkerke $R^2$) of the variance in ADHD and correctly classified 64% of cases. Individuals with more developmental problems were more likely to have ADHD inattentive type, whereas those that were heavy smokers were more likely to have ADHD combined type.

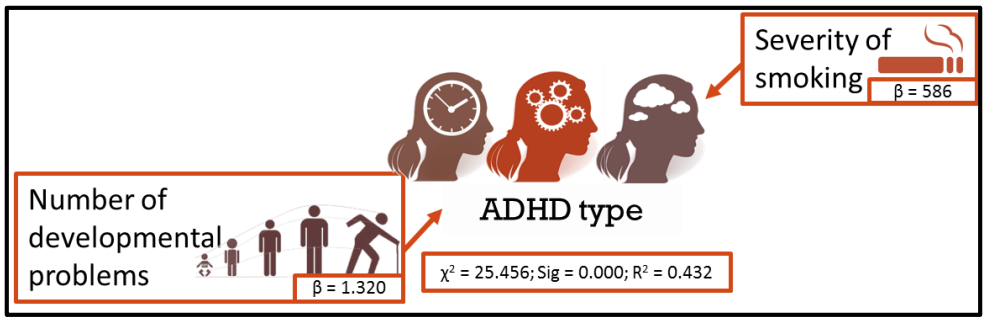


Figure 3.13 A visual representation of a multinomial logistic regression testing the validity of the hypothesis where ADHD type, as the criterion, is influenced by several predictors.

### 3.3.5 Statistical analysis of the semi-structured interview

Results of statistical testing using the Wilcoxon signed-rank test revealed no significant difference between the standardised scores on the ASRS and DIVA checklists ($p=0.882$). This was true even when the scores for each symptom of ADHD, i.e. inattention ($p=0.417$) and hyperactivity ($p=0.882$), were considered. Correlations also revealed significant associations between the two sets of scores for the full diagnosis scores ($r=0.895$, $p<0.01$), the inattention scores ($r=0.818$, $p<0.05$), and the hyperactivity scores ($r=0.740$, $p<0.05$) (Table 3.17).

The scores of the two questionnaires were similar, as determined by similar *Z-scores*. The final diagnosis of ADHD type (ADHD-I or ADHD-C), however, differed significantly (Table

3.16). A bivariate correlation between the two sets of diagnoses revealed a non-significant result ($r$=0.527, $p$>0.05).

Table 3.16: Resulting diagnostic criteria from both assessment scales (DIVA and ASRS), including the presence or absence of inattention and hyperactivity, as well as the final diagnostic decision (DIVA includes both adulthood and childhood information).

| | DIVA | | | | | | ASRS | | |
|---|---|---|---|---|---|---|---|---|---|
| ID | Inattention Adult | Hyperactive Adult | Diagnosis Adult | Inattention Child | Hyperactive Child | Diagnosis Child | Inattention | Hyperactive | Diagnosis |
| JMA13 | No | No | ADHD-I | Yes | No | None | No | No | None |
| JMA11 | No | No | None | No | No | None | Yes | No | ADHD-I |
| JMA19 | Yes | No | ADHD-I | Yes | No | ADHD-I | No | No | None |
| JMA02 | Yes | No | ADHD-I | Yes | No | ADHD-I | Yes | No | ADHD-I |
| JMA12 | Yes | No | ADHD-I | Yes | Yes | ADHD-C | Yes | No | ADHD-I |
| JMA14 | Yes | Yes | ADHD-C | Yes | Yes | ADHD-C | Yes | No | ADHD-I |
| JMA08 | Yes | Yes | ADHD-C | Yes | Yes | ADHD-C | Yes | No | ADHD-I |
| JMC70 | No | No | None | No | No | None | No | No | None |

Interviews using DIVA provided the opportunity to observe participants. The number of observable inattentive and/or hyperactive characteristics showed a positive correlation with the Hyperactive score as measured by the DIVA ($r$=0.860, $p$<0.01). However, no association was found when comparing the number of observed characteristics to the type of diagnosis, as determined by the DIVA (Table 3.18).

Table 3.17: Scores from both assessment scales (DIVA and ASRS), including their respective raw and *Z-scores*, calculated for the assessment of inattention and hyperactivity, as well as for a full score (DIVA includes both adulthood and childhood information).

| | DIVA | | | | | | | | | | | | ASRS | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ID | Inattention score Adult | | Inattention score Child | | Hyperactivity score Adult | | Hyperactivity score Child | | Full ADHD score Adult | | Full ADHD score Child | | Inattention score | | Hyperactivity score | | Full ADHD score | |
| | Raw | *Z* | Raw | *Z* | Raw | *Z* | Raw | *Z* | Raw | *Z* | Raw | *Z* | Raw | *Z* | Raw | *Z* | Raw | *Z* |
| JMA13 | 2 | -1.27 | 9 | 0.54 | 2 | -0.71 | 1 | -0.72 | 4 | -1.11 | 10 | -0.10 | 3 | -0.87 | 2 | -0.63 | 5 | -0.83 |
| JMA11 | 4 | -0.71 | 2 | -1.62 | 1 | -1.03 | 0 | -0.72 | 5 | -0.95 | 2 | -1.33 | 6 | 0.08 | 1 | -1.05 | 7 | -0.44 |
| JMA19 | 9 | 0.71 | 9 | 0.54 | 3 | -0.40 | 1 | -0.72 | 12 | 0.21 | 10 | -0.10 | 4 | -0.56 | 4 | 0.21 | 8 | -0.24 |
| JMA02 | 9 | 0.71 | 9 | 0.54 | 5 | 0.24 | 2 | -0.72 | 14 | 0.54 | 11 | 0.06 | 9 | 1.03 | 3 | -0.21 | 12 | 0.53 |
| JMA12 | 9 | 0.71 | 9 | 0.54 | 3 | -0.40 | 6 | 1.21 | 12 | 0.21 | 15 | 0.67 | 8 | 0.71 | 6 | 1.05 | 14 | 0.92 |
| JMA14 | 9 | 0.71 | 9 | 0.54 | 9 | 1.51 | 9 | 1.21 | 18 | 1.20 | 18 | 1.13 | 8 | 0.71 | 6 | 1.05 | 14 | 0.92 |
| JMA08 | 9 | 0.71 | 9 | 0.54 | 9 | 1.51 | 9 | 1.21 | 18 | 1.20 | 18 | 1.13 | 8 | 0.71 | 6 | 1.05 | 14 | 0.92 |
| JMC70 | 1 | -1.55 | 1 | -1.62 | 2 | -0.71 | 0 | -0.72 | 3 | -1.28 | 1 | -1.48 | 0 | -1.82 | 0 | -1.46 | 0 | -1.80 |

Table 3.18: Inattentive/hyperactive symptoms observed during the semi-structured interview (DIVA), along with the inattentive and hyperactive scores obtained from the scale and the final diagnosis measured by the scale.

| ID | Questions repeated | Fidgeting | Wavering focus | Wandering thoughts | Shifting in chair | Speaking faster | Restless legs | Number of symptoms | Inattention score Adult | Hyperactive score Adult | Diagnosis ADHD Adulthood DIVA |
|---|---|---|---|---|---|---|---|---|---|---|---|
| JMA13 | - | - | - | - | Yes | - | - | 1 | 2 | 2 | ADHD-I |
| JMA11 | - | - | - | - | - | - | - | 0 | 4 | 1 | None |
| JMA02 | Yes | Yes | Yes | Yes | - | - | Yes | 5 | 9 | 5 | ADHD-I |
| JMA12 | - | Yes | - | - | - | - | - | 1 | 9 | 3 | ADHD-I |
| JMA14 | Yes | Yes | Yes | - | - | - | Yes | 4 | 9 | 9 | ADHD-C |
| JMA19 | - | - | - | - | - | - | - | 0 | 9 | 3 | ADHD-I |
| JMA08 | - | Yes | Yes | - | Yes | Yes | Yes | 5 | 9 | 9 | ADHD-C |
| JMC70 | - | - | - | - | - | - | - | 0 | 1 | 2 | None |

## 3.4 Discussion

### 3.4.1 Analysis of environmental influences

Simple frequency analysis clearly shows an increase in prevalence of medical, psychological, developmental, and learning problems in the Affected Cohort. Notably, enlarged tonsils were frequent in the Affected Cohort, possibly because this leads to restriction in the airways, often causing poor sleep and ultimately worsening behavioural problems (Owens, 2009; Baum *et al.*, 2014). Chervin and Archbold (2001) noted increased Hyperactivity in children with sleep-disorder breathing, and Dillon *et al.* (2007) noted inattention and behavioural problems. Enlarged tonsils are the most common cause of sleep-disorder breathing (Li *et al.*, 2006). Dillon *et al.* (2007) also found that removal of the tonsils improved attention and behavioural problems, and that 50% of participants no longer showed symptoms of ADHD one year later. Coordination problems are linked to developmental difficulties also common in individuals with ADHD (Reiersen *et al.*, 2008; Kopp *et al.*, 2010). This study confirmed these findings, especially for difficulties in gross and fine motor control and skills. Depression and anxiety, as expected, were frequently mentioned by ADHD participants. This is supported by a number of studies (Kitchens *et al.*, 1999; Wozniak *et al.*, 2004; Hammerness *et al.*, 2010). Learning disorders, particularly dyslexia, were common in the Affected Cohort, as has often been described (Pope *et al.*, 2007; Laasonen *et al.*, 2010). This points to a link with the unifying theory of ADHD as a deficit in executive functioning (as described in Chapter 2).

Similar to other studies (Whalen *et al.*, 2003; Lambert, 2005; Flory *et al.*, 2011; Vansickel *et al.*, 2011), results showed that a large proportion of the Affected Cohort were smokers. Further results pointed to a severe addiction to smoking in a large proportion of ADHD smokers, evident in number of times they have tried to quit, but failed (1-2 times of

4-6+ times), and the number of nicotine based products they use per day (1-20). Generally participants from both groups attributed their relapse to poor self-control and influence from other smokers. Similar results have been found in other studies (Covey *et al.*, 2008; McClernon *et al.*, 2011). Nicotine is a MAO inhibitor (reducing the metabolism of serotonin), and thus causes the over stimulation of the serotonin receptor cells on the post-synaptic neuron, increasing the feeling of pleasure (Siegel *et al.*, 2006). This link between smoking and ADHD, suggests a further link to the serotonin system.

In comparison with the Unaffected Cohort, diet appears not to be poorer in the Affected Cohort and showed no significant correlations to ADHD.

The Affected Cohort also showed poorer sleep patterns than the Unaffected Cohort, particularly with regards to the amount of sleep obtained, difficulties in falling asleep and maintaining regular sleep patterns, as well as increased reports of snoring, and restless leg syndrome. This may be due to an inability to disengage due to the Hyperactivity symptoms often experienced in ADHD. Similar outcomes have been found with regards to sleep latency, i.e. the time between full wakefulness and sleep (Galland *et al.*, 2009) which may link to difficulties in falling asleep. Sleep maintenance may be affected by sleep disturbance from sleep-disorder breathing (often found in patients who snore) and restless leg syndrome (Owens, 2006; Konofal *et al.*, 2010).

Exercise appears to be an important factor in providing relief from ADHD symptoms, but is performed in moderation (1-2 hours for 1-5 days per week). This supports a number of other studies (Verret *et al.*, 2012; Pontifex *et al.*, 2013; van der Niet *et al.*, 2014). Pontifex *et al.* (2013) suggested that aerobic exercise could be used as an alternative to pharmaceutical treatment of ADHD.

Both maternal and paternal smoking was common amongst ADHD participants, particularly during the first five years of life. This is concerning due to developmental delays which may result from exposure to second hand smoke at such a young age (Ernst et al., 2001; Neuman et al., 2007). Maternal smoking has been linked to ADHD in many studies, particularly prenatal smoking (Rodriguez & Bohlin, 2004; Braun *et al.*, 2006; Schmitz *et al.*, 2006; Neuman *et al.*, 2007; Lindblad & Hjern, 2010; Motlagh *et al.*, 2010). Paternal smoking, although much less commonly studied, has also been linked to ADHD (Altink *et al.*, 2009; Zhu *et al.*, 2014) in some cases, but not others (Nomura *et al.*, 2010; Langley *et al.*, 2012).

### 3.4.2 Analysis of environmental influence on the presence of ADHD

Taken together, ANOVA, Chi-square analysis, T-tests and regression analysis reveals that multiple environmental factors are significantly related to, and can predict the presence, severity of symptoms, and type of ADHD present. The presence of ADHD is associated with an increased number of developmental problems and severe smoking addiction. While simple comparative tests (Chi-square and t-tests) showed a direct positive relationship between ADHD, presence of psychological disorders, increased medical problems, learning disorders, exposure to hypoxic conditions, and poor sleep, regression analysis of all these factors together did not produce a significant result for any single factor.

### 3.4.3 Analysis of environmental influence on the type of ADHD

When considering ADHD score as measured by the ASRS, similar results are noted, however, now the number of psychological problems and increased exposure to hypoxic conditions show significant associations to higher ASRS-determined scores, whereas increased number of medical problems and learning disorders are associated with lower scores.

Removing smoking severity from the model reveals associations with an increase in prevalence of medical problems, and severe familial and school or work impairment to higher ADHD scores, while risky activity scores are associated with lower ADHD scores. This may be because smoking shows a greater predictability of ADHD than medical problems and impairments. However, it is important to note that medical problems may be caused by smoking activity, and that one of the questions assessing risky activity regarded smoking.

### *a. Inattention*

Higher inattention scores show links to the presence of psychological problems, increase in prevalence of developmental problems, poorer quality of sleep, increase in prevalence of severe smoking addiction, and an increase in life skills and school or work impairment. Inattentive scores showed a negative association with medical problems in regression analysis.

Individuals with ADHD, particularly the inattentive type, generally had developmental problems, and a father that smoked. This may point to a negative developmental effect of second-hand smoke during childhood (Ernst *et al.*, 2001; Neuman *et al.*, 2007). Also, individuals with ADHD who did not exercise most often had medical problems, indicative of a possibly beneficial influence of exercise on physical health in individuals with ADHD (Fentem, 1994).

### *b. Hyperactivity*

Unlike inattentive associations, higher hyperactivity scores were linked to an increase in prevalence of medical problems, increase in prevalence of learning disorders and frequent exposure to hypoxic conditions. However, similar to inattention, high hyperactivity showed associations with severe smoking and school or work impairment. Further, ADHD-HI type is

predictable by increased medical and developmental problems, an increase in prevalence of learning disorders and poor quality sleep. Although ADHD-I is similarly associated with increased medical problems and poor sleep, it is also associated with the presence of psychological problems and increased severity of smoking.

### 3.4.4 Comparison of ADHD assessment methods

The ASRS-S provides a much better scale for quantification than the DIVA. The DIVA only counts the presence or absence of a symptom, rather than quantifying the average score for a set of questions surrounding a particular symptom. The DIVA, however, includes more questions to quantify each symptom, thus providing a more comprehensive result. This scale also has the added advantage of providing the participants with the opportunity to give their own explanations of the symptoms they experience, as well as giving the interviewer the opportunity to engage with, and observe the participants. The DIVA has the added advantage of uncovering ADHD present in childhood, as well as in adulthood, and encourages participants to consider both of these life stages in turn.

In terms of scores, the ASRS and DIVA produce very similar results, which are not statistically different from one another. However, when considering the final diagnosis produced by each scale, the results are not statistically similar. This may be due to the DIVA scale asking substantially more questions than the ASRS, and thus producing a more robust result. Observable characteristics noted in the interviews were found to be associated with Hyperactivity score.

## 3.5 Conclusions

The results of this study clearly show a significant environmental component associated to ADHD. This environmental component is related to ADHD in two ways: first, certain environmental factors, such as exposure to second-hand cigarette smoke, potentially worsen ADHD symptoms; and, second, environmental components, such as difficulty sleeping, may arise as a result of ADHD symptoms.

Both the DIVA and ASRS-S have pros and cons, however, the results obtained from each does not differ so significantly as to discount either one. For quantitative purposes, the most important aspect, which is the scores obtained from each, are extremely similar. This leads to the conclusion that either of these scales may be successfully used in the quantification of ADHD. It is, however, important to select the scale based on the type of information which is being studied, for example, mixed methods approaches might consider using the DIVA, as it allows for open-ended responses as well as data on the observable characteristics of each participant.

From this analysis we can begin to see a profile emerging that we can use to better diagnose and classify ADHD, its characteristics, and types. It is clear that exposure to hypoxic conditions and second-hand cigarette smoke may worsen the pre-existing ADHD condition. Additionally, ADHD appears to cause a number of symptoms which are not assessed by the diagnostic criteria in the DSM-V, but which appear to arise commonly due to the presence of the condition. These additional symptoms include, increased psychological, medical, and learning problems, and severe smoking activity, as well as impairments in a number of life functioning areas, such as the familial, social, and school or work environments, notably poor self-concept, and an increased affinity to perform risky activities. Furthermore, it appears that exercise could significantly benefit individuals with ADHD, not only in terms of relief from the

main symptoms of ADHD, but also to reduce medical problems commonly associated with the condition. Finally, this analysis points to evidence of a genetic link to ADHD, in that family members of individuals with ADHD often show similar symptoms, with ADHD either suspected or diagnosed, or other, less commonly mentioned symptoms of ADHD such as depression or learning disorders.

# Chapter 4

# Molecular analysis of serotonergic genes possibly modulating ADHD

## Abstract

Attention-Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder occurring in 4.8% of children and progressing to adulthood in approximately half of these. Due to significant neuroplasticity in child brain development, there is greater plausibility in performing a retrospective study on ADHD symptoms in adults. This can potentially be applied as a prospective study in children. Serotonin (5-HT) is highly active in the brain's prefrontal cortex. This area is responsible for learning and cognition, and associated with impulsivity and inhibition. Defective synaptic transmission causing inundation or deprivation of serotonin leads to the hyperkinetic syndrome and disruptive behaviours associated with ADHD. Polymorphisms in the *HTR1B* (rs6297), *HTR2A* (rs6311), and *SLC6A4* (rs25531 and *5-HTTLPR*) genes were assessed in a comparative cohort study between individuals with ADHD and those without. In total 52 individuals were genotyped (18 Affected Cohort, compared to 34 Unaffected Cohort individuals) to quantify significant correlations between the serotonin polymorphisms and ADHD symptoms. Results revealed a strong positive correlation between the presence of ADHD and polymorphisms in the serotonin system. Impulsive and hyperactive character traits were also strongly linked to polymorphisms in the serotonin system.

**Keywords:** Adults, Decision tree analysis, Receptor, Regression analysis, Transporter.

## 4.1 Introduction: Genetic modulation of ADHD

The serotonin (5-HT) neurotransmitter is essential in learning and cognition. It has been implicated in a number of disorders of disinhibition, including psychopathological disorders, aggression, depression, anxiety, and addiction (Guimarães *et al.*, 2009). It has been mapped to the prefrontal cortex of the brain, where it is particularly important in higher order cognitive functioning (Bush et al., 2005; Kranz et al., 2009). This executive functioning has been found to be deficient in individuals with ADHD, thus suggesting a link between ADHD and the serotonin system (Guimarães et al., 2009; Pazvantoğlu et al., 2013; Siegel et al., 2006). The serotonergic pathway functions by (1) the synthesis of serotonin through tryptophan hydroxylase conversion, (2) signal transduction in the postsynaptic neuron by 5-HT2 receptors, (3) negative feedback by 5-HT1 receptor stimulation, and (4) reuptake of serotonin into the presynaptic neuron by the serotonin transporter (*SERT*) (as discussed in Chapter 2) (Oades *et al.*, 2008).

Genetic influences of ADHD are thought to be in small sequence changes which alter the level of expression in certain genes. Attention-Deficit Hyperactivity Disorder appears to be a complex condition with many genes exerting small effects to contribute to the disorder as a whole. This disorder is also a genetically heterogenous condition. Studies of attention have implicated a number of genes in the aetiology of ADHD. Most of these genes somehow influence the expression of the gene in question thus influencing the molecular pathways that these genes work in (Bellgrove & Mattingley, 2008).

Polymorphisms were selected based on previous associations, particularly those that have shown strong associations in some studies (Baca-García *et al.*, 2005; Banerjee, Banerjee, Chatterjee, Sinha, & Nandagopal, 2012; Bellgrove & Mattingley, 2008; Bidwell *et al.*, 2011; Biederman *et al.*, 2008; Brookes *et al.*, 2006; Cao, LaRocque, & Li, 2013; Caylak, 2012;

Guimarães *et al.*, 2009; Guimaraes *et al.*, 2006; Laucht, Hohm, Esser, Schmidt, & Becker, 2007; Ribases *et al.*, 2007; Smoller *et al.*, 2006), but little or no association in others (Bellgrove & Mattingley, 2008; Brookes *et al.*, 2006; Caylak, 2012; Ho *et al.*, 2012; Ribases *et al.*, 2007).

### 4.1.1 *HTR1B*

The serotonin receptor 1B (*HTR1B*) is found on chromosome 6q14.3 to q16.3, is intronless and encodes a polypeptide consisting of 390 amino acids which creates a G-coupled protein receptor (Jin *et al.*, 1992). It acts as a presynaptic autoreceptor and a postsynaptic heteroreceptor. The *HTR1B* gene encoding for this receptor causes an excitatory action (Oades *et al.*, 2008). The 861G/C Single Nucleotide Polymorphism (SNP) (rs6296) in this gene has been implicated in the aetiology of ADHD, in particular, the G allele has been associated with the manifestation of ADHD (Guimarães *et al.*, 2009; Smoller *et al.*, 2006). This SNP is a synonymous mutation located in the coding part of the gene (exon 1) and thus does not result in an amino acid change. It is created by a G to C base pair change, where G is the ancestral allele and C is the variant allele (Figure 4.1) (Sherry *et al.*, 2001).

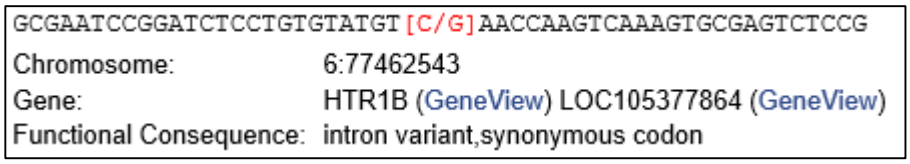


Figure 4.1: Indication of the location and ancestral allele of the 861G/C SNP (rs6296) on an assembly of the *HTR1B* gene reference sequence, as obtained from the National Centre for Biotechnology Information (NCBI).

### 4.1.2 *HTR2A*

The serotonin receptor 2A (*5-HT2A*) plays a role in regulating hyperactivity. It also modulates dopamine activity through interaction with ADHD medication (Guimarães *et al.*,

2006). The gene encoding for this receptor (*HTR2A*) has been linked to psychotic disorders, such as schizophrenia, suicide, ADHD, mood disorders, anxiety, and Alzheimer's disease (Piva, Giulietti, Nardi, Bellantuono, & Principato, 2010). Like *HTR1B*, *HTR2A* is also excitatory in nature (Oades *et al.*, 2008). The encoding gene (*HTR2A*) is located on chromosome 13q14 to 13q21 and creates a G-coupled protein receptor (Y. Nakamura *et al.*, 2010). It acts as a postsynaptic heteroreceptor. A SNP, commonly named -1438A/G (rs6311), is a cytosine to thymine base pair change on the forward DNA strand, with C being the ancestral allele. This nomenclature is a result of the reverse strand of DNA being sequenced. The SNP occurs within the promotor region of the *HTR2A* gene (De Luca, Likhodi, Kennedy, & Wong, 2007). It is a functional, synonymous substitution, which regulates the amount of receptors in the synapses (Chen, Shen, & Chen, 2009). Association studies have shown mixed results with the association of ADHD (Guimarães *et al.*, 2006; Pazvantoğlu *et al.*, 2013; Ribases *et al.*, 2007). Ribases *et al.* (2007) found that the -1438A/G SNP was implicated only in combined type ADHD in adults and children. Pazvantoğlu *et al.* (2013) found an association between the A allele and ADHD.

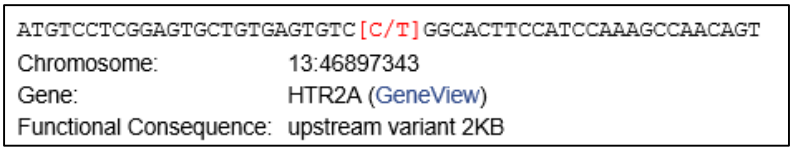


Figure 4.2: Indication of the location and ancestral allele of the -1438A/G SNP (rs6311) on an assembly of the *HTR2A* gene reference sequence, as obtained from the National Centre for Biotechnology Information (NCBI).

### 4.1.3 *SERT*

The serotonin transporter (*SERT* or *5-HTT*) actively transports serotonin from a by a $Na^+$ ion which binds to the serotonin, transporting it out of the synaptic cleft and back into the presynaptic neuron (Guimarães *et al.*, 2006; Reiner & Spangler, 2010). The gene encoding for

*SERT* (*SLC6A4*) is situated on chromosome 17q11.2 (Lesch *et al.*, 1994). A variable number of tandem repeats (VNTR) in this gene has been implicated in a number of psychopathological disorders, including ADHD (Guimarães *et al.*, 2006; Kiive & Harro, 2013). Controversial evidence, however, exists for the association of this polymorphism with ADHD (Bidwell *et al.*, 2011). The polymorphism, called *5-HTTLPR*, is located in the promoter region of the *SLC6A4* gene (Heils, Teufel, Petri, Stöber, *et al.*, 1996). It is a 22 bp VNTR with two allelic variations, namely, the L allele (long allele) containing 16 repeats or the S allele (short allele) containing 14 repeats (Figure 4.3). A 44bp insertion[3] causes this allelic variation (Figure 4.4) (Gokturk *et al.*, 2008; Sayin *et al.*, 2010). This polymorphism occurs within the promotor region of the gene, thus regulating expression and in turn the amount of functional transporters in the synapses. The S allele decreases gene transcription. Caspi *et al.* (2005) found that individuals carrying at least one S allele were more likely to display depressive symptoms than individuals with two L alleles. However, Kent *et al.* (2002) have found an over transmission of the L allele in ADHD individuals, as have Kiive and Harro (2013) and Retz *et al.* (2008). This implies an interaction between the two alleles, with the S allele being dominant over the L allele.

[3] While most articles do not specify whether this variation is an insertion or deletion, it may be postulated that it is an insertion due a second polymorphism (rs25531) rendering the inserted segment null and void, thus reverting the expression of the gene back to its original state (Heils, Teufel, Petri, Stober, *et al.*, 1996; Kiive & Harro, 2013; M. Nakamura, Ueno, & Tanabe, 2000; Wendland, Martin, Kruse, Lesch, & Murphy, 2006).

| | | | | |
|---|---|---|---|---|
| 1 | CCCTAC | TGCA | GCCCTCCC | AGCATC |
| 2 | CCC_CC | TGCA | A_CCTCCC | AGCA_ _ |
| 3 | ACTCCC | TGTA | CCCCTCCT | AGGAT_ |
| 4 | CGCTCC | TGCA | TCCCCC_ _ | ATTATC |
| 5 | CCCCCC | TTCA | CCCCTCGC | GGCAT_ |
| 6 | CCCCCC | TGCA | CCCCCC | AGCAT |
| 7 | CCCCCC | TGCA | GCCCCCCC | AGCAT_ |
| 8 | CTCCCC | TGCA | CCCC_C_ | AGCAT_ |
| 9 | CCCCCC | TGCA | GCCCTTCC | AGCAT_ |
| 10 | CCCCC_ | TGCA | CCTCTCCC | AGGAT_ |
| 11 | CTCCCC | TGCA | ACCC_CC | ATTAT_ |
| 12 | CCCCCC | TGCA | CCCCTCGC | AGTAT_ |
| 13 | CCCCCC | TGCA | CCCC_CC | AGCAT_ |
| 14 | CCCCCCA | TGCA | _CCC_CC | GGCAT_ |
| 15 | CCCCCC | TGCA | CCCCTCC | AGCAT_ |
| 16 | TCTCCT | TGCA | CCCTACC | AGTAT_ |

Figure 4.3: The 16 repeat sequences of the *5-HTTLPR* VNTR indicating the various base pair changes (in red) in each successive repeat, as well as the insertion (in orange boxes) which is responsible for the long allele (adapted from Heils *et al.* (1996)).

It has been suggested that a SNP within this region (rs25531) further regulates the expression of the gene by annulling the effects of the L allele in the presence of a G allele, creating a triallelic locus, thus functionally appearing to have the same effect as the S allele (Figure 4.5) (Kiive & Harro, 2013; Wendland, Martin, Kruse, Lesch, & Murphy, 2006). The alternate allele, the T allele, has been implicated in ADHD (Kent *et al.*, 2002). Gadow *et al.* (2013) found that the S allele of the VNTR or the G allele of the SNP in the presence of the L variant were more susceptible to severe ADHD.

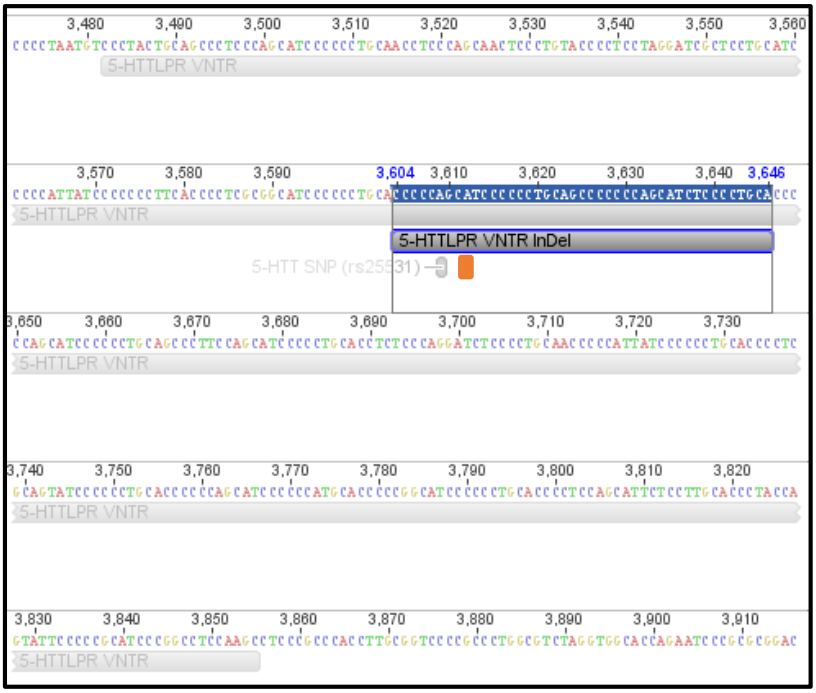


Figure 4.4: Indication of the location of the *5-HTTLPR* VNTR insertion (highlighted in blue), and the location and ancestral allele of the A/G (rs25531) SNP (denoted in orange) on an assembly of the *SLC6A4* gene reference sequence, as obtained from the National Centre for Biotechnology Information (NCBI).

All of these genes code for proteins which are essential in the correct functioning of the serotonergic pathway (Figure 4.5). The polymorphisms alter proteins which in turn affects the correct function of the pathway, either by regulating the number of functional receptors or transporters present (as in *HTR2A* and *SLC6A4*) in the synapse or by altering the functionality of the receptors (as in *HTR1B*).

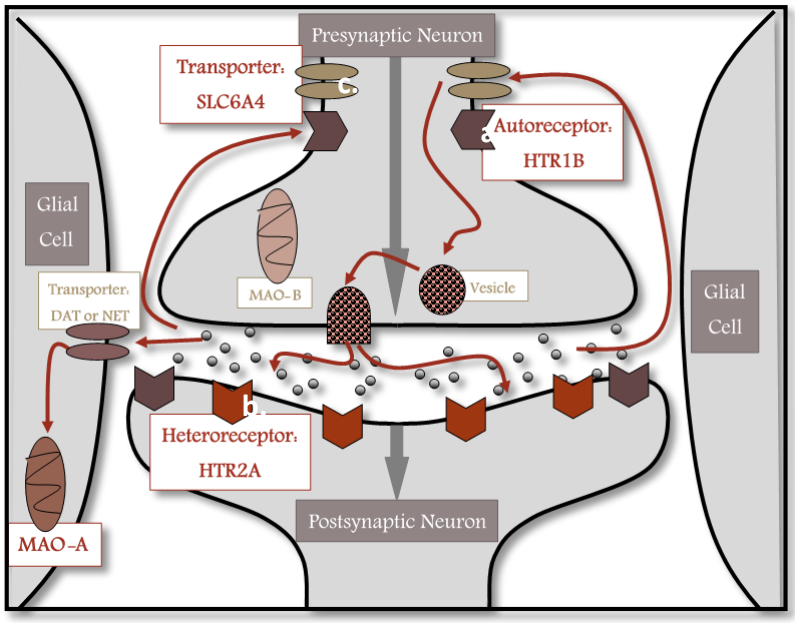


Figure 4.5: Simple representation of the structure of the serotonergic pathway indicating the (a) *HTR1B* autoreceptor, (b) *HTR2A* heteroreceptor, as well as the (c) *SERT* transporter, which will be assessed in this study.

This study aims to determine whether polymorphisms within specific gene regions of genes encoding specific components of the serotonin system are integral in the modulation of ADHD. These polymorphisms are located in the *HTR1B*, *HTR2A,* and *SLC6A4* genes.

## 4.2 Methods and materials

### 4.2.1 Quantification of ADHD

Attention-Deficit Hyperactivity Disorder was quantified using the Adult ADHD self-report scale (ASRS) and the Weiss functional impairment rating scale, self-report (WFIRS-S) (as explained in Chapter 3). Participants in the Affected Cohort were previously diagnosed with ADHD. The purpose of the questionnaire was thus not to provide individuals with a diagnosis, but rather to standardise diagnoses. Individuals in the Unaffected Cohort were a random convenience sample of individuals not displaying any of the characteristics associated with any of the ADHD subtypes.

### 4.2.2 *In silico* analyses

Previously designed primers were selected to amplify the specific region containing each of the polymorphisms (Table 4.1) (Heils, Teufel, Petri, Stober, *et al.*, 1996; Lappalainen *et al.*, 1998; T. Nakamura *et al.*, 1999; Wendland *et al.*, 2006). These primer sets were selected based on successful repetition by other studies (Jian Cao, LaRocque, & Li, 2013; Gadow *et al.*, 2013; Gonda, Juhasz, Laszik, Rihmer, & Bagdy, 2005; Hasegawa, Higuchi, Matsushita, & Miyaoka, 2002; Malan, 2013; Noskova *et al.*, 2009; Peyrot *et al.*, 2012; Radua *et al.*, 2013; Raznahan *et al.*, 2009). Previously designed primer sets were assessed for GC content as well as estimated melting temperature (Tm) (Table 4.1).

Table 4.1: Primer sets used to amplify *HTR1B* promoter region (Lappalainen *et al.*, 1998), *HTR2A* promoter region (T. Nakamura *et al.*, 1999), *HTTLPR* within the promoter region of *SLC6A4* (Heils, Teufel, Petri, Stober, *et al.*, 1996) and the *5-HTT* rs25531 SNP within the promoter region of *SLC6A4* (Wendland *et al.*, 2006).

| Gene | Polymorphism | Forward Primer | Reverse Primer | % GC F Primer | % GC R Primer | Tm F Primer | Tm R Primer |
|---|---|---|---|---|---|---|---|
| *HTR1B* | Rs6296 | GAAACAGACGCCCAACAGGAC | CCAGAAACCGCGAAAGAAGAT | 57.1% | 47.6% | 62.69 ˚C | 61.38 ˚C |
| *HTR2A* | Rs6311 | AAGCTGCAAGGTAGCAACAGC | AACCAACTTATTTCCTACCAC | 52.4% | 38.1% | 60.53 ˚C | 51.20 ˚C |
| *SLC6A4* | Rs25531 | TCCTCCGCTTTGGCGCCTCTTCC | TGGGGGTTGCAGGGGAGATCCTG | 65.2% | 65.2% | 73.63 ˚C | 72.74 ˚C |
| | VNTR | GGCGTTGCCGCTCTGAATGC | GAGGGACTGAGCTGGACAACCAC | 65.0% | 60.9% | 69.09˚C | 65.23 ˚C |

Desired primer sets and SNP locations were further mapped to reference sequences (Figures 4.6) obtained from NCBI GenBank® (Benson *et al.*, 2013), using Geneious 5© (Biomatters Ltd) (Kearse *et al.*, 2012) to determine fragment lengths and identify potential restriction enzymes to be used for genotyping (Figures 4.7p).

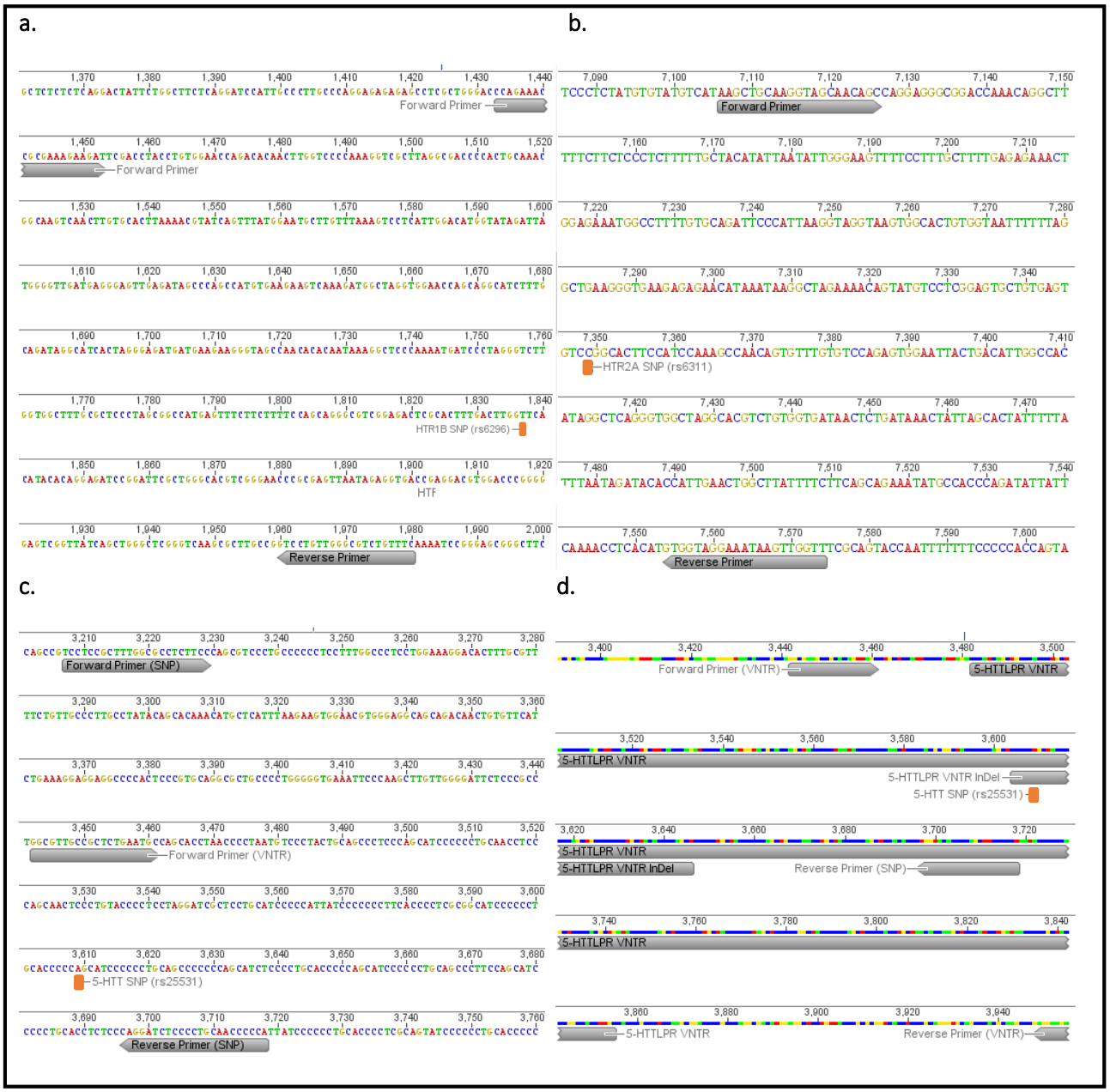


Figure 4.6: Annealing location of the primer sequences used, as well as the fragment to be amplified within each gene region, in relation to the corresponding polymorphisms for (a) the *HTR1B* rs6296 SNP (Lappalainen *et al.*, 1998), (b) the *HTR2A* rs6311 SNP (T. Nakamura *et al.*, 1999), (c) the *5-HTT* rs25531 SNP (Wendland *et al.*, 2006), and (d) the *5-HTTLPR* VNTR (Heils, Teufel, Petri, Stober, *et al.*, 1996). The relativity of the *5-HTT* SNP and *5-HTTLPR* can also be seen (d).

Restriction enzymes for digestion of PCR products (Table 4.2) were selected based on their ability to locate proximal SNP sequences and digest only in the presence of one of the SNP alleles (Figure 4.7). Further, desired restriction enzymes were those that digested only once within the parameters of the primer set in order to visualise specific DNA fragments

during gel electrophoresis, except for the *HTR1B* region that contained two potential digestion sites (Figure 4.7, a).

Table 4.2: Restriction enzyme sequence identification in relation to SNP location.

| Gene | Polymorphism | Restriction Enzyme | Restriction enzyme diagrams |
|---|---|---|---|
| *HTR1B* | Rs6296 | HincII | SNP location<br>5'- G T Y ↓ R A C -3'<br>3'- C A R ↓ Y T G -5'<br>Digestion site SNP location |
| *HTR2A* | Rs6311 | MspI | Digestion site SNP location<br>5'- C ↓C G G -3'<br>3'- G G C ↓ C -5'<br>SNP location Digestion site |
| *SLC6A4* | Rs25531 | MspI | |

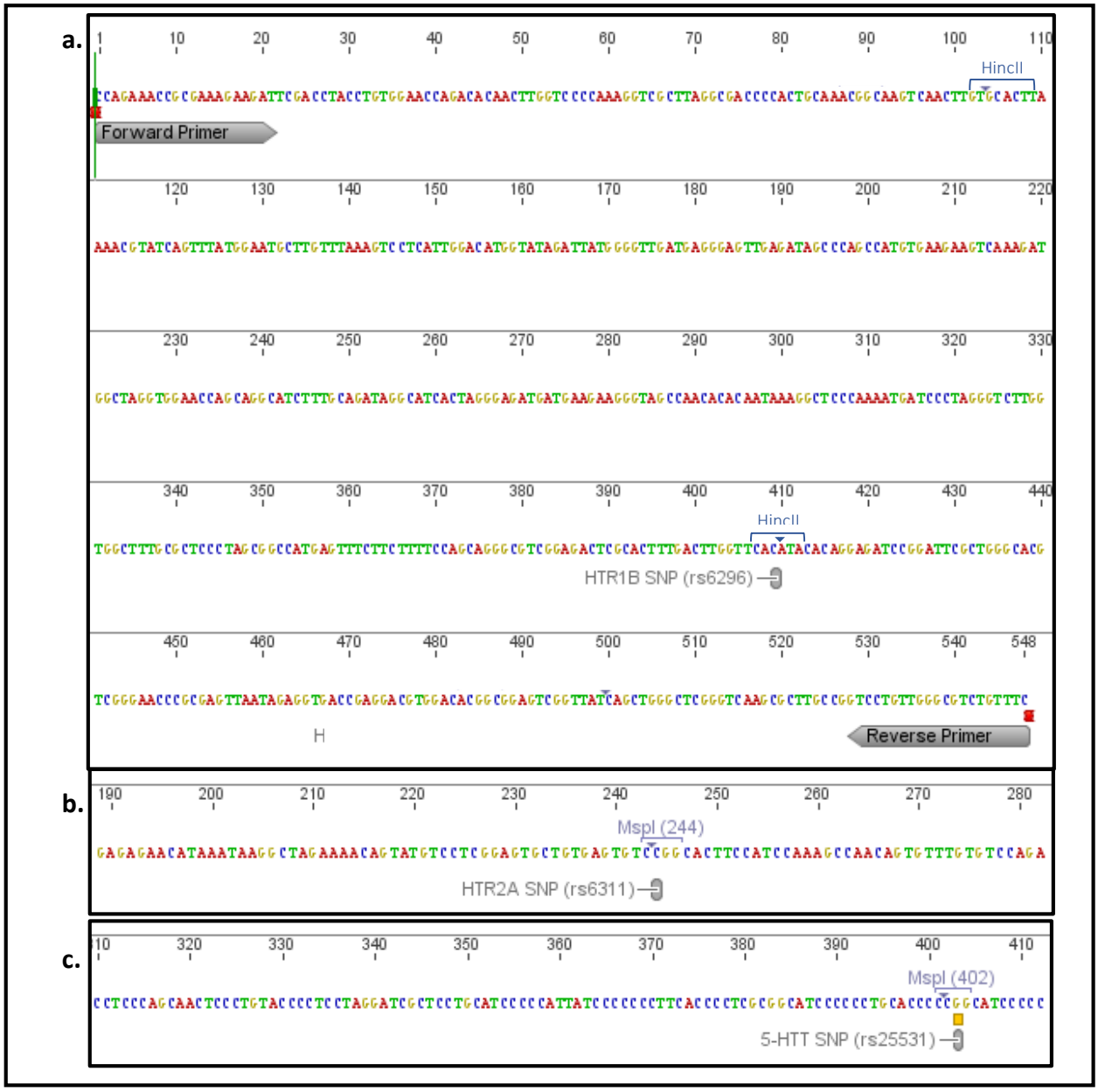


Figure 4.7: Digestion sites of restriction enzymes for *HTR1B* (a), *HTR2A* (b) and *5-HTT* SNP (c) (Kearse *et al.*, 2012).

Previous literature was used to determine which alleles were potentially associated with ADHD. The SNP database (NCBI) (Sherry *et al.*, 2001) was used to identify approximate allele frequencies (Table 4.3).

Table 4.3: Details of potential SNP alleles (Sherry *et al.*, 2001).

| Gene | Polymorphism | Restriction Enzyme | Associated allele | Ancestral allele | Variant allele | Sample group |
|---|---|---|---|---|---|---|
| *HTR1B* | Rs6296 | BceAI | G | G<br>0.677<br>0.812 | C<br>0.323<br>0.188 | Caucasian<br>African |
| *HTR2A* | Rs6311 | MspI | A | G<br>0.535<br>0.606 | A<br>0.465<br>0.394 | Caucasian<br>African |
| *SLC6A4* | Rs25531 | MspI | G | A<br>0.900 | G<br>0.100 | Not specified |
| | VNTR | - | L | | | |

### 4.2.3 DNA isolation

Participants were a random convenience sample. Genetic material was collected in the form of a saliva sample. Each participant deposited 1 ml of saliva into a collection tube containing 1 ml Lysis buffer. Extraction of DNA was performed using a salting out method based on that of (Quinque, Kittler, Kayser, Stoneking, & Nasidze, 2006). Quality and quantity of DNA were assessed using the NanoDrop™ Lite Spectrophotometer (Thermo Scientific) and agarose gel electrophoresis. All DNA was then diluted to 50 ng/µl for use in PCR reactions.

### 4.2.4 PCR amplification

Conventional PCR was performed with the primer sequences detailed in Table 4.1. Amplification reaction conditions were unique for each polymorphism (Table 4.4). Reaction conditions were optimised for the *5-HTT* SNP, and replicated from other studies for the *HTR2A*, *HTR1B* and *5-HTTLPR* polymorphisms (Malan, 2013; Odendaal, 2012).

The *HTR1B* and *HTR2A* gene regions were amplified using a 20 µl reaction mix containing: 100 ng/µl of DNA, 10 µl of DreamTaq™ Master Mix produced by Thermo Scientific (containing 2x DreamTaq buffer, 4 mM magnesium chloride ($MgCl_2$) and 0.4 mM of each dNTP (dATP, dCTP, dTTP and dGTP)) and 0.75 mM of each primer.

Amplification of the *SLC6A4*, *5-HTTLPR* gene region occurred using a 20 µl reaction mix containing: 100 ng/µl of DNA, 10 µl of KAPATaq™ HotStart DNA Polymerase produced by KAPABiosystems (containing 5 U/µl Wild-type Taq with HotStart antibody, 5x KAPA Taq HotStart Buffer ($Mg^{2+}$ free) and $MgCl_2$ (25 mM)), 0.25 mM of each primer and 4% Dimethyl sulfoxide (DMSO).

Table 4.4: Polymerase Chain Reaction temperature regimes for each amplified region.

| Gene region | PCR step | Temperature | Duration | Cycles |
|---|---|---|---|---|
| *HTR1B* | Initial denaturation | 94˚C | 5 min | 1 |
| | Denaturation | 94˚C | 20 sec | 31 |
| | Annealing | 61˚C | 45 sec | |
| | Extension | 72˚C | 30 sec | |
| | Final extension | 72˚C | 10 min | 1 |
| *HTR2A* | Initial denaturation | 94˚C | 5 min | 1 |
| | Denaturation | 94˚C | 20 sec | 30 |
| | Annealing | 60˚C | 1 min | |
| | Extension | 72˚C | 30 sec | |
| | Final extension | 72˚C | 10 min | 1 |
| *SLC6A4* | Initial denaturation | 95˚C | 7 min | 1 |
| | Denaturation | 98˚C | 30 sec | 3 |
| | Annealing | 63˚C | 30 sec | |
| | Extension | 72˚C | 1 min | |
| *5-HTTLPR* | Denaturation | 98˚C | 30 sec | 25 |
| | Annealing | 61˚C | 30 sec | |
| | Extension | 72˚C | 1 min | |
| | Final extension | 72˚C | 10 min | 1 |
| *SLC6A4* *rs25531* | Initial denaturation | 95˚C | 2 min | 1 |
| | Denaturation | 98˚C | 20 sec | 35 |
| | Annealing | 65˚C | 15 sec | |
| | Extension | 72˚C | 15 sec | |
| | Final extension | 72˚C | 5 min | 1 |

The *SLC6A4* rs25531 SNP was amplified using a 20 µl reaction mix containing: 100 ng/µl of DNA, 6 µl of KAPATaq™ HotStart DNA Polymerase produced by KAPABiosystems (containing 5 U/µl Wild-type Taq with HotStart antibody, 5 x KAPA Taq HotStart Buffer ($Mg^{2+}$ free) and $MgCl_2$ (25 mM)) and 0.75 mM of each primer.

Subsequent amplicons were visualised by gel electrophoresis on a 1% or 3% (m/v) agarose gel. For genotyping purposes this was sufficient for the *SLC6A4 5-HTTLPR* region. Further restriction enzyme digestion was necessary to visualise and genotype the *HTR1B* and *HTR2A* SNPs.

### 4.2.5 Restriction enzyme digestion

Post-PCR products for *HTR1B* was digested with the HincII restriction enzyme and *HTR2A* was digested with the MspI restriction enzyme (Thermo Scientific). As per the recommended protocol, each 32 µl reaction contained 18 µl nuclease free water, 2.8 µl of 10 x Buffer Tango™ (made up of 33 mM Tris-acestate {pH 7.9 at 37°}), 10 mM magnesium acetate, 66 mM potassium acetate, 0.1 mg/ml BSA {Bovine Serum Albumin}), 0.2 µl (10 U) of the particular restriction enzyme (HincII or MspI) and 10 µl of undiluted PCR product. Each reaction was incubated for a total of 16 hours at 37˚C for digestion to take place.

Genotyping was then performed by visualisation on a 2% agarose gel. While the *SLC6A4* SNP *rs25531* is also digestible by MspI, visualisation post-digestion is problematic due to the small proportion of individuals who carry the G allele. Thus, a number of samples were sequenced for the rs25531 SNP (29 in total). Three individuals were sequenced for each of the *HTR1B* and *HTR2A* SNPs, to ensure correct amplification of the region in question and to aid in genotyping using agarose gel electrophoresis.

### 4.2.6 Capillary electrophoresis

Preparation for amino acid sequences determination was done using the BigDye® Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems®). Sequencing PCR reactions were set up in individual PCR micro-tubes, as 10 µl reactions. Sequencing reactions were comprised

of 3.9 µl nuclease free water, 0.5 µl BigDye® premix, 1 µl of 5x Sequencing Buffer, 3.2 mM primer, 4% DMSO and 1 µl undiluted PCR product. Pre-Sequencing PCR occurred at the following temperature steps for 25 cycles: denaturation for 10 seconds at 96°C, annealing for 5 seconds at 50°C and extension for 4 minutes at 60°C.

Sequencing clean-up was performed as per protocol with EtOH/EDTA precipitation (Applied Biosystems, 2010). The resultant sequencing PCR product was cleaned by adding 2.5 µl of 125 mM EDTA and 25 µl of absolute ethanol (100% EtOH) to each sample. This was incubated for 15 minutes at room temperature followed by centrifugation at 4°C and 1650 g for 45 minutes. The supernatant was discarded and the product washed again with 30 µl of 70% EtOH followed by centrifugation at 4°C and 1650 g for 15 minutes. Again the supernatant was discarded and the samples left to dry at room temperature to ensure complete evaporation of the Ethanol. Sequencing product was then resuspended in injection buffer and analysed using the ABI3130 Genetic Analyser (Applied Biosystems). Sequences were assembled and edited using Geneious© 5 Software (Kearse *et al.*, 2012).

### 4.2.7 Statistical analysis

Statistical analysis was performed using IBM® SPSS statistics v22 (IBM Corp, 2013) package. This software was used to determine genotype and allele frequencies, and both bivariate and partial correlations. The SPSS software was also used to perform standard linear regression analysis, multiple regression analysis, logistical regression analysis, as well as decision tree analysis. The Hardy-Weinberg Equilibrium (HWE) was also calculated to determine whether the genotypic frequencies of each polymorphism were at equilibrium for the sample population. To calculate the $\chi^2$ statistic, a downloadable MS Excel sheet was used (Sehrawat, 2005). The observed data is added into this sheet which then provides the $\chi^2$

statistic and instructions on determining whether the population is in equilibrium or not. A population in equilibrium is one where the $\chi^2$ statistic is less than 3.841 (df).

Each polymorphism was examined, by regression analysis, for the effect of the alleles on ADHD. For additive effects to be tested, each genotype was coded as its own number (i.e. AA=1, AB=2, and BB=3). For interactive effects to be tested, each allele was coded separately (i.e. A=1, B=2). Two separate variables were created to test for interactive effects, where each of the alleles is hypothesised to be dominant (i.e. if A is hypothesised to be dominant, all individuals with AA or AB genotypes are coded as 1, and all individuals with BB genotypes are coded as 2).

## 4.3 Results and discussion[4]

A total of 21 Affected Cohort individuals and 40 Unaffected Cohort individuals provided DNA samples. These were successfully extracted and amplified in 18, and 34 cases, respectively.

During the process of extraction 3 aliquots were made of each sample. Samples which did not amplify during the PCR process were switched out with one of the other aliquots to control for possible DNA degradation. Subjects were not resampled due to limited resources. Polymerase chain reaction was performed multiple times, on samples which were difficult to amplify, with increased concentrations of DNA, different Taq polymerase, and alternative temperatures. This yielded limited improvement on the initial PCR.

[4] Details of statistical analysis can be found in Appendix 8.

Enzymatic digestion of the *5-HTT* SNP seemed not to work on test samples, however, this is due to the very low frequency of the G allele in the population. A larger sample group, and a 3% agarose gel clearly showed the distinction between the homozygous A and heterozygous (AG) individuals. The homozygous G variant occurs in only 10% in the population (Table 4.3), and was thus not present in this sample group. A total of 29 samples were sequenced for this polymorphism.

### 4.3.1 *In silico* analyses

Desired GC content of the primers was approximately 60% to ensure relative specificity in primer annealing, however, primer sets previously tested and showing positive results were not changed to fit this rule. Melting temperatures (Tm) were also assessed and preferred when both primers showed similar estimated Tm's to ensure the successful annealing of both primers during the PCR annealing cycle.

In preparation for analysis, Geneious© 5 (Kearse *et al.*, 2012) was used to create an approximate representation of the effects of restriction enzyme digestion (Figure 4.8). This virtual gel provides an approximation of fragment lengths and allows for premature identification of potential difficulties which may be experienced during genotyping.

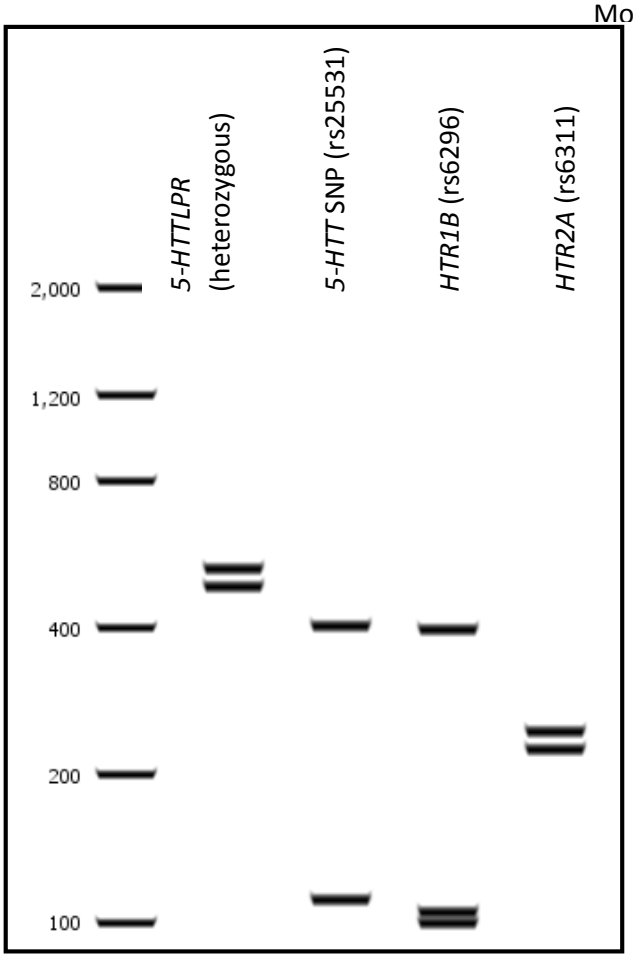


Figure 4.8: *In-silico* representation of the expected fragment sizes of heterozygous genotypes for each polymorphism (Kearse *et al.*, 2012). Lane 2 indicates a heterozygous individual for the *5-HTTLPR* VNTR, lane 3 indicates a single digested strand for the *5-HTT SNP*, lane 4 represents a single digested strand for the *HTR1B* SNP and lane 5 a single digested strand for the *HTR2A* SNP.

Alleles with low frequencies show potential to be unobserved in a small sample group, and thus a larger sample of the population is needed to increase the chances of observing all alleles. This is necessary to identify approximate required population size.

### 4.3.2 Additive and interactive effects

Both the *HTR1B* SNP and the *HTR2A* SNP showed additive effects, where the regression analysis was not significant when coded for interactive effects (Appendix 8). This is corroborated by associations between the *HTR2A* AG genotype and hyperactivity (Figure 4.13), and the association of the GG genotype of *HTR1B* (Figure 4.21). While the *5-HTT* SNP appears

to show additive effects (Figure 4.20), it is not possible to determine this due to the lack of individuals with the GG genotype in the sample.

The only interactive effect was observed in the *5-HTTLPR* polymorphism, where the S allele appears to be dominant [$F(1, 27)=13.966$, $p<0.05$; Criterion is ADHD presence; Predictor is *5-HTTLPR* S Dominant] (Appendix 8). Further calculations were based on these results.

### 4.3.3 *HTR1B*

The region of the *HTR1B* gene containing the SNP rs6296 was successfully amplified and digested with the appropriate restriction enzyme (HincII) in 47 individuals. Prior to digestion, the amplicon length of this region is 548 bp. Amplicon with a G allele at the SNP site is digested into two fragments of 452 bp and 96 bp each (Figure 4.9). Amplicon with a C allele present is digested into three fragments of 310 bp, 142 bp, and 96 bp each. In the event of heterozygotes four fragments are seen of 452 bp, 310 bp, 142 bp, and 96 bp each (Hasegawa *et al.*, 2002).

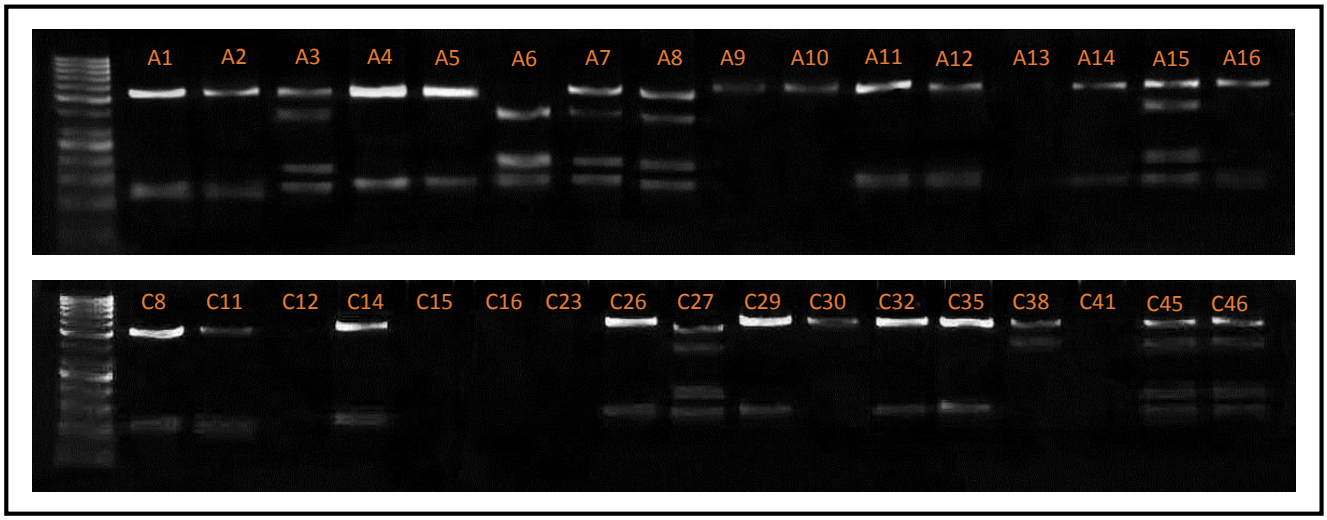


Figure 4.9: Image of a 3% agarose gel showing the digested *HTR1B* rs6296 promotor region for samples of the Affected Cohort in the top image and the Unaffected Cohort in the bottom

image (as indicated by the numbers in each lane, with the 50 bp O'GeneRuler DNA ladder (Thermo Scientific) in the first lane of the top and bottom images). [5]

Genotype frequencies were relatively similar across both the Affected and Unaffected Cohorts, however, the Affected Cohort showed a slightly higher frequency of the GG genotype and a lower frequency of the CC genotype. The Unaffected Cohort showed a similar distribution of genotypes to the European population (GG=51%; GC=43%; CC=6%) (Table 4.5), while the Affected Cohort showed a higher transmission of the GG genotype than any population assessed in the 1000 genomes project (Cunningham *et al.*, 2015). Favour of the G allele in the Affected Cohort is evident in the allele frequencies with a frequency of 81% (as opposed to 66% in the Unaffected Cohort). The *HTR1B* SNP was in Hardy Weinberg equilibrium in the sample group according to the $\chi^2$ statistic ($\chi^2$=2.658641) (Table 4.5).

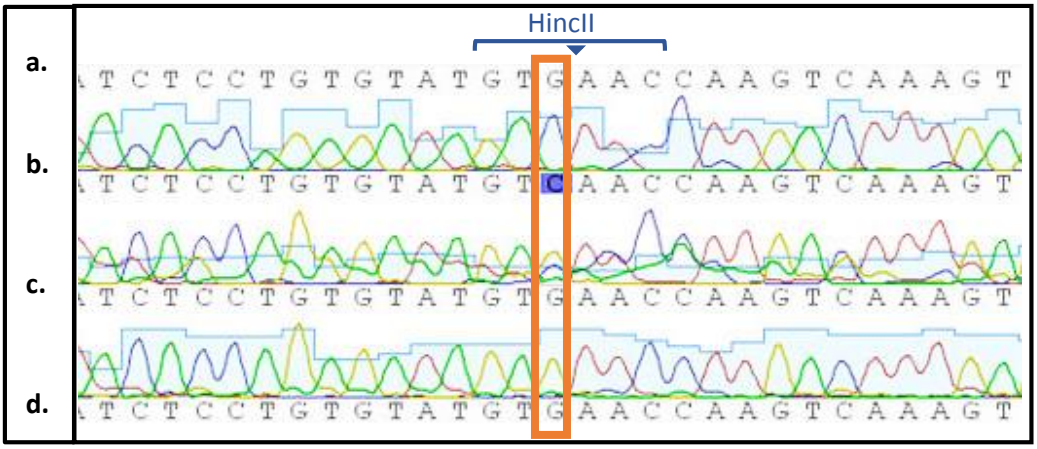


Figure 4.10: Sequence analysis of the *HTR1B* SNP site (rs6296): (a) Reference sequence, (b) electropherogram of a homozygous C individuals (participant A6 in Figure 4.9), (c) electropherogram of a heterozygous GC individuals (participant A15 in Figure 4.9), and (d) electropherogram of a homozygous G individuals (participant A1 in Figure 4.9).

[5] Lesser fluorescence of the fragments may occur in the event of less concentrated DNA in the PCR reaction or degradation of extracted DNA prior to PCR, this is caused by less GelRed binding to the DNA.

The *HTR1B* polymorphism has been associated directly with ADHD in some studies (Guimarães *et al.*, 2009; Quist *et al.*, 2003; Smoller *et al.*, 2006), this study did not find any direct correlations, similar to Ickowicz *et al.* (2007) and Odendaal (2012).

### 4.3.4 *HTR2A*

The region of the *HTR2A* gene containing the SNP rs6311 was successfully amplified and digested with the appropriate restriction enzyme in 44 individuals. Prior to digestion, the amplicon length of this region is 468 bp. Amplicon with an A allele at the SNP site is not digested and thus remains 468 bp in length. Amplicon with a G allele present is digested into two fragments of 224 bp and 244 bp each (Figure 4.11). In the event of heterozygotes, three fragments can be seen of 468 bp, 244 bp, and 224 bp each (Nakamura *et al.*, 1999).

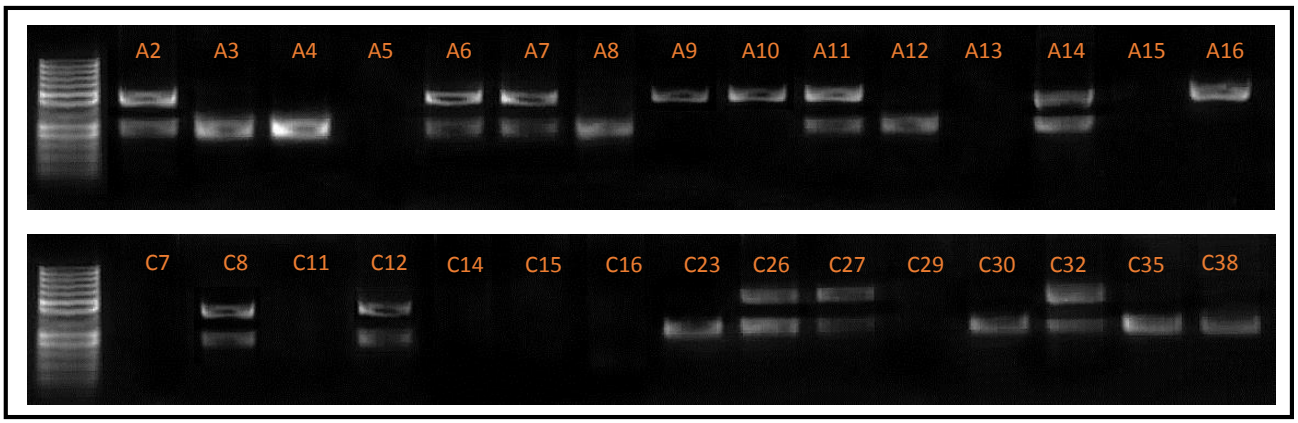


Figure 4.11: Image of a 2% agarose gel showing the digested *HTR2A* rs6311 promotor region for samples of the Affected Cohort in the top image and the Unaffected Cohort in the bottom image (as indicated by the numbers in each lane, with the 50 bp O'GeneRuler DNA ladder (Thermo Scientific) in the first lane of the top and bottom images). [6]

Genotype frequencies were relatively similar across both the Affected and Unaffected Cohorts, however, the Affected Cohort showed a slightly higher frequency of the GG genotype. There appears to be no bias of specific genotypes and alleles when considering ADHD as a

[6] Lesser fluorescence of the fragments may occur in the event of less concentrated DNA in the PCR reaction or degradation of extracted DNA prior to PCR, this is caused by less GelRed binding to the DNA.

whole. Genotype frequencies were slightly different to the results of the 1000 genomes project (Cunningham *et al.*, 2015) (GG=32%; GA=48%; AA=20%) (Table 4.5), with a slight increase for the GG genotype in both the Affected and Unaffected Cohorts (Cunningham *et al.*, 2015). However, the Unaffected Cohort showed a similar distribution in terms of allelic frequencies (G=56%; A=44%). The *HTR2A* SNP was in equilibrium in the sample group according to the $\chi^2$ statistic ($\chi^2$=010138) (Table 4.5).

Table 4.5: Genotype and allele frequencies for each polymorphism (split by cohort), and information for the calculation of Hardy-Weinberg equilibrium (observed and expected frequencies, $\chi^2$ statistic and result of the calculation).

| | | Frequencies | | | | Hardy-Weinberg Calculation | | | |
|---|---|---|---|---|---|---|---|---|---|
| Gene | Genotype/ Allele | Affected Cohort | | Unaffected Cohort | | Observed Frequencies | Expected Frequencies (for HWE) | $\chi^2$ statistic | Result |
| | | n | % | n | % | % | % | | |
| *HTR1B* (rs6296) | GG | 12 | 67% | 19 | 56% | 66% | 62% | 2.658641 | Population in HWE |
| | GC | 5 | 28% | 7 | 21% | 26% | 33% | | |
| | CC | 1 | 6% | 3 | 9% | 9% | 5% | | |
| | G | 29 | 81% | 45 | 66% | | | | |
| | C | 7 | 19% | 13 | 19% | | | | |
| *HTR2A* (rs6311) | GG | 8 | 44% | 13 | 38% | 48% | 48% | 0.010138 | Population in HWE |
| | GA | 7 | 39% | 12 | 35% | 43% | 43% | | |
| | AA | 2 | 11% | 2 | 6% | 9% | 9% | | |
| | G | 23 | 64% | 38 | 56% | | | | |
| | A | 11 | 31% | 16 | 24% | | | | |
| *5-HTT* SNP (rs25531) | AA | 6 | 33% | 15 | 44% | 81% | 82% | 0.294251 | Population in HWE |
| | AG | 4 | 22% | 1 | 3% | 19% | 17% | | |
| | GG | 0 | 0% | 0 | 0% | 0% | 1% | | |
| | A | 16 | 44% | 31 | 46% | | | | |
| | G | 4 | 11% | 1 | 1% | | | | |
| *5-HTTLPR* | SS | 8 | 44% | 4 | 12% | 41% | 34% | 2.425726 | Population in HWE |
| | SL | 7 | 39% | 3 | 9% | 35% | 49% | | |
| | LL | 0 | 0% | 7 | 21% | 24% | 17% | | |
| | S | 23 | 64% | 11 | 16% | | | | |
| | L | 7 | 19% | 17 | 25% | | | | |

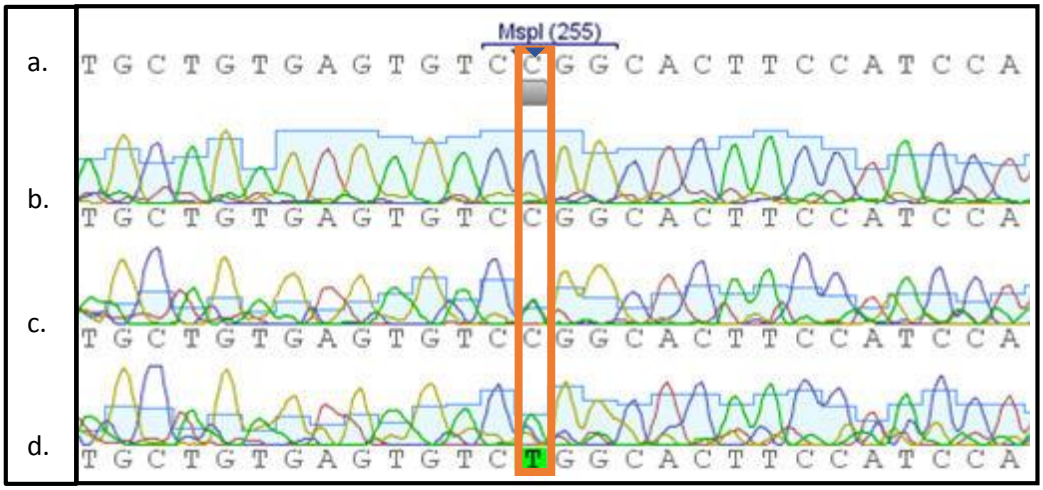


Figure 4.12: Sequence analysis of the *HTR2A* SNP site (rs6311) (forward strand): (a) Reference sequence, (b) electropherogram of a homozygous C individuals (participant A4 in Figure 4.11), (c) electropherogram of a heterozygous TC individuals (participant C12 in Figure 4.11), and (d) electropherogram of a homozygous T individuals (participant A16 in Figure 4.11).

Upon reshuffling the ADHD diagnosis variable (diagnoses reported by respondents) to allow the heterozygote to be coded as the highest ranking of the variable (GA=3), a linear regression established that *HTR2A* heterozygous (GA) genotype could significantly predict hyperactivity diagnoses (made by medical professionals, psychologists, psychiatrists or self-diagnosis) (criterion variable) [$F(1, 15)=5.805$, $p<0.05$], and hyperactivity diagnoses accounted for 28% of the explained variability in *HTR2A* heterozygous genotype.

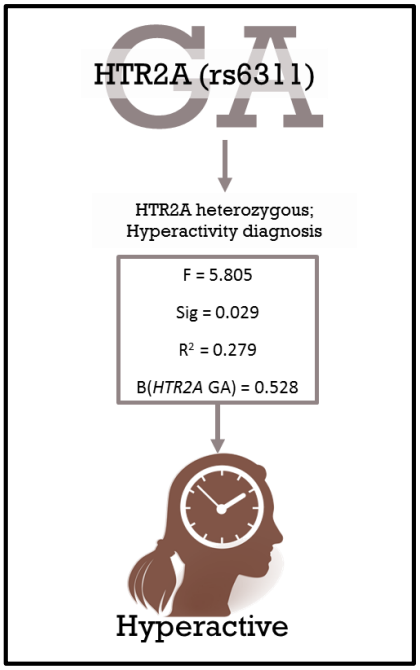


Figure 4.13: A visual representation of a linear regression testing the validity of the hypothesis where hyperactivity diagnosis, as the criterion, is influenced by the *HTR2A* genotypes, as the predictor.

### 4.3.5 *SLC6A4*

Two polymorphisms were assessed in the *SLC6A4* gene. Results of these are discussed in turn.

#### *a. 5-HTTLPR*

The promotor region of the *SLC6A4* gene contains the *5-HTTLPR* region with a VNTR implicated in ADHD. It consists of a repeat region of up to 528 bp. Two alleles are possible, namely the short allele (S allele) of 484 bp or the long allele (L allele) of 528 bp (Figure 4.14). A total of 29 samples were successfully amplified by PCR. Repetitive attempts at sequencing the *5-HTTLPR* gene region gave relatively unacceptable results. Due to limited resources, successful sequencing done in previous studies was used to confirm the amplification by the specific primers used (Malan, 2013). Genotyping could be done from the agarose (Figure 4.14).

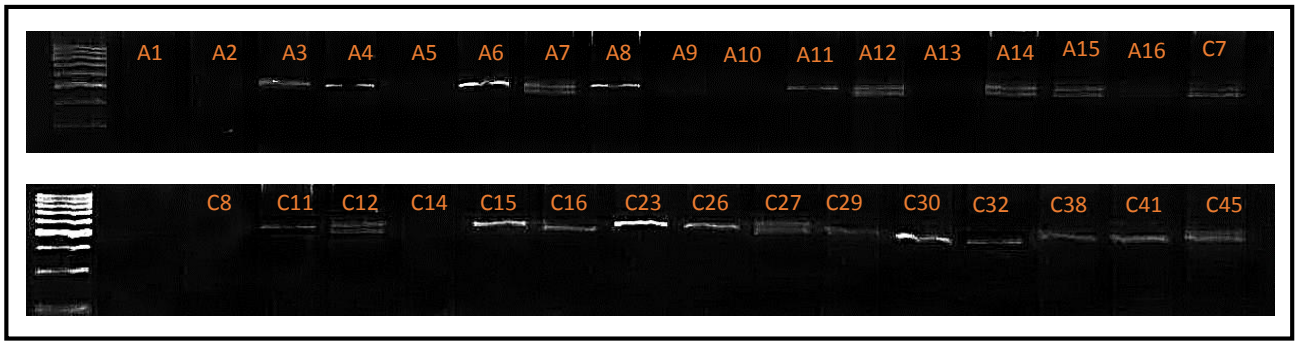


Figure 4.14: Image of a 3% agarose gel showing the digested *5-HTTLPR* promotor region for samples of the Affected Cohort in the top image and the Unaffected Cohort in the bottom image (as indicated by the numbers in each lane, with the 50 bp O'GeneRuler DNA ladder (Thermo Scientific) in the first lane of the top and bottom images). [7]

The strongest and most significant associations were between *5-HTTLPR* and ADHD. Genotype frequencies showed a clear distinction between the Affected and Unaffected Cohorts. The SS and SL genotypes were present to a much higher degree in the Affected Cohort compared to the Unaffected Cohort, whereas the LL genotype was not present at all in the Affected Cohort, yet it was the most prevalent in the Unaffected Cohort (Table 4.5). This confirms dominance of the S over the L allele (Siegel *et al.*, 2006). Allele frequencies reveal higher prevalence of the S allele in the Affected Cohort, as in a study by Landaas *et al.* (2010). The *5-HTTLPR* VNTR was in equilibrium in the sample group according to the $\chi^2$ statistic ($\chi^2$=2.425726) (Table 4.5).

Simple decision tree analysis showed a significant association between the presence of ADHD and the S allele (either in the homozygous or heterozygous form) (Figure 4.15). When considering ADHD, the presence of the S allele was predictable in 68.2% of cases. More complex decision tree analysis also showed this result with the combined type increasing in predictability to 16.7% and the inattentive type to 44.4% (Figure 4.17).

[7] Lesser fluorescence of the fragments may occur in the event of less concentrated DNA in the PCR reaction or degradation of extracted DNA prior to PCR, this is caused by less GelRed binding to the DNA.

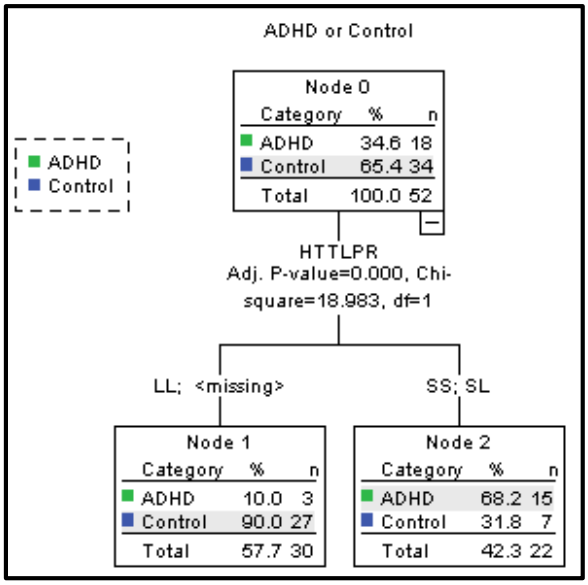


Figure 4.15: Visual representation of simple decision tree analysis focusing on the *5-HTTLPR* polymorphism.

Analysis of variance (ANOVA) of the *5-HTTLPR* VNTR showed a significant relationship to ADHD [$F(2, 26)=6.749$, $p<0.05$]. A logistic regression was performed to ascertain the effects of HTTLPR genotypes on the likelihood that participants have ADHD. The logistic regression model was statistically significant [$\chi^2(1) = 6.915$, $p<0.01$] (Figure 4.16). The model explained 28% (Nagelkerke $R^2$) of the variance in ADHD and correctly classified 62% of cases. Having the LL genotype of the HTTLPR gene was associated with an increased likelihood of exhibiting ADHD.

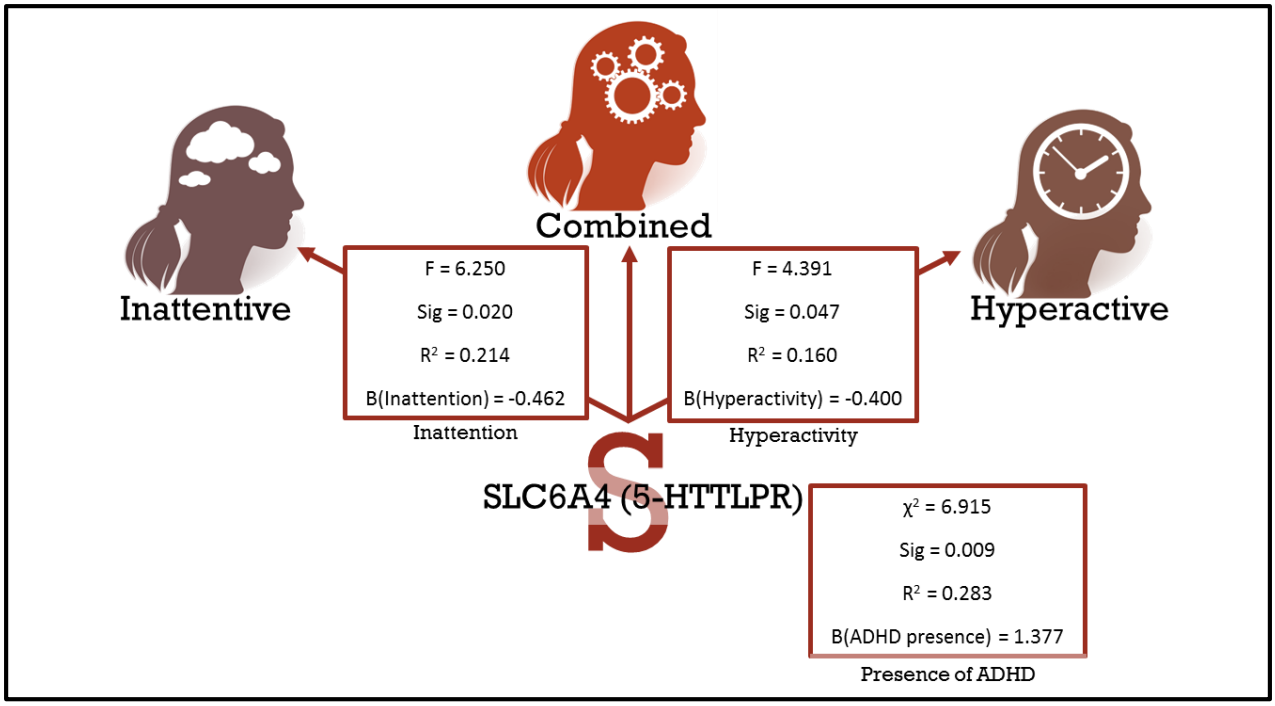


Figure 4.16: A visual representation of a multiple regression testing the validity of the hypotheses where ADHD presence, and inattentive and hyperactive scores (as measured by the ASRS), as the criterion variables, is influenced by the *5-HTTLPR* genotypes, as the predictor.

A multiple regression analysis supported this by significantly predictable regression for the association between *5-HTTLPR* (S allele) and inattention (criterion variable) [$F(1,23)=6.250$, $p<0.05$], as well as with hyperactivity (criterion variable) [$F(1,23)=4.391$, $p<0.05$] (Figure 4.16). These analyses accounted for 21% and 16% of the variation in the criterion variables, respectively. Considering the two major symptoms of ADHD, namely inattention and hyperactivity-impulsivity, associations were also present. Specifically, higher inattentive scores were associated with the SS genotype, and similarly high hyperactivity scores were associated with the SS genotype. Regression analysis further confirmed these results. Zoroglu *et al.* (2002) found similar associations with hyperactivity ratings, but not with inattention. Gadow *et al.* (2013) found worsened symptoms overall with the S allele, most prominent with hyperactivity, and Kiive and Harro (2013) found an association between the LL genotype and inattention.

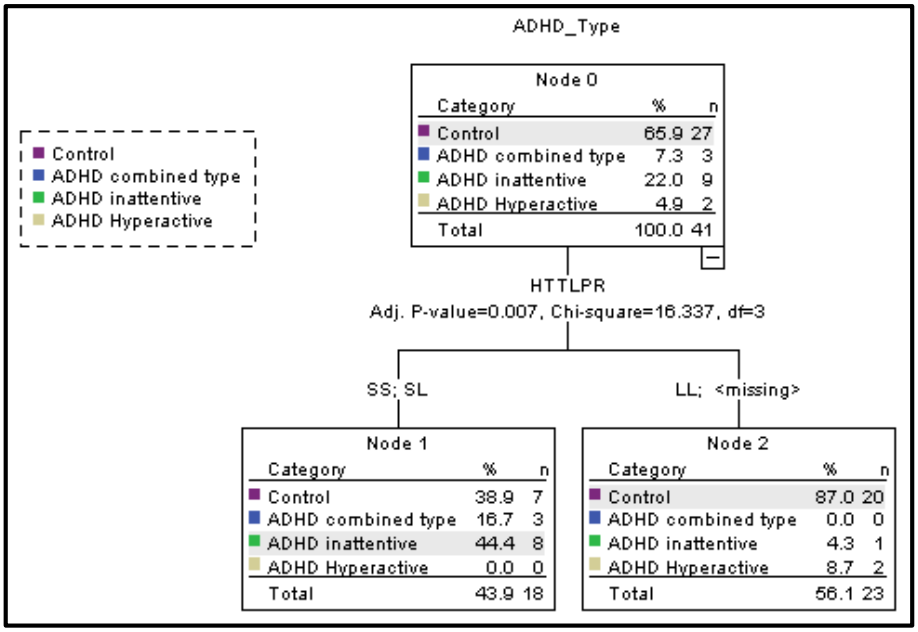


Figure 4.17: Visual representation of more complex decision tree analysis focusing on the *5-HTTLPR* polymorphism.

### *b. 5-HTT SNP*

The *SLC6A4* region also contains a regulatory SNP (rs25531) which is a G to T nucleic acid change. This region was successfully amplified and digested with the appropriate restriction enzyme in 26 individuals. Prior to digestion, the amplicon length of this region is 512 bp. Amplicon with an A allele at the SNP site is not digested and thus remains 512 bp in length. Amplicon with a G allele present is digested into two fragments of 403 bp and 109 bp each (Figure 4.18). In the event of heterozygotes three fragments are seen of 512 bp, 403 bp, and 109 bp each.

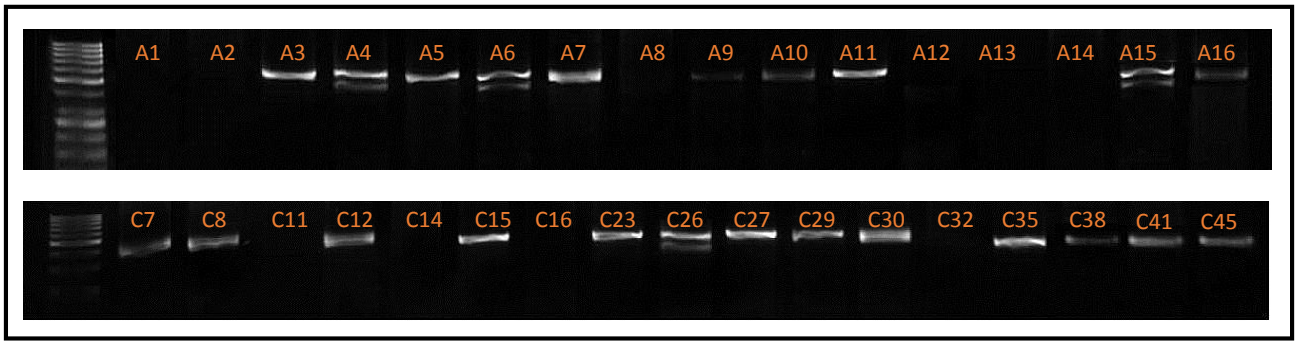


Figure 4.18: Image of a 3% agarose gel showing the digested *5-HTT* rs25531 promotor region for samples of the Affected Cohort in the top image and the Unaffected Cohort in the bottom image (as indicated by the numbers in each lane, with the 50 bp O'GeneRuler DNA ladder (ThermoScientific) in the first lane of the top and bottom images). [8]

Genotype frequencies were relatively similar across both the Affected and Unaffected Cohorts, however, the Affected Cohort showed a slightly higher frequency of the AG genotype. There also appears to be more favouring for the G allele in the Affected Cohort above the Unaffected Cohort. Although data was missing, genotype and allele frequencies were similar to the 1000 genomes project (AA=80%; AG=19%; GG=2%; A=89%; G=11%) (Table 4.5) (Cunningham *et al.*, 2015). The *5-HTT* SNP was in equilibrium in the sample group according to the $\chi^2$ statistic ($\chi^2$=0.294251) (Table 4.5).

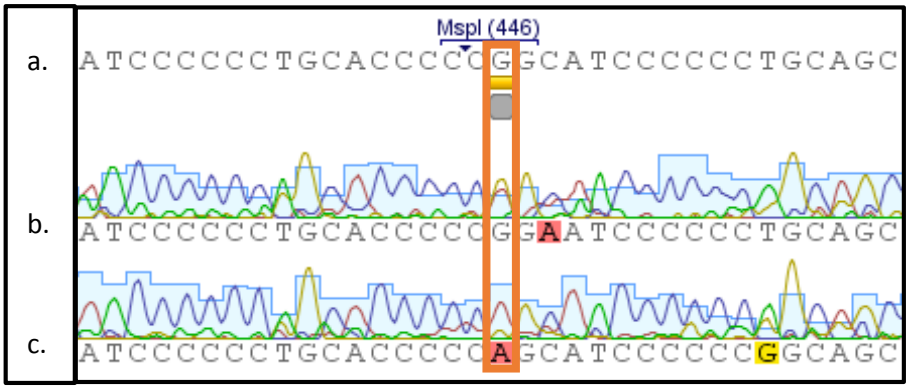


Figure 4.19: Sequence analysis of the *5-HTT* SNP site (rs25531): (a) Reference sequence, (b) electropherogram of a heterozygous AG individual (participant A6 in Figure 4.18), (c) electropherogram of a homozygous A individual (participant C45 in Figure 4.18). There were no homozygous G individuals in the sample group, due to the very small frequency with which this variant occurs within the population (2%).

[8] Lesser fluorescence of the fragments may occur in the event of less concentrated DNA in the PCR reaction or degradation of extracted DNA prior to PCR, this is caused by less GelRed binding to the DNA.

Analysis of the *SLC6A4* SNP showed significant correlations to the presence of ADHD. The AG genotype in particularly showed associations to the presence of ADHD regardless of type ($r$=-0.417; $p$<0.05). However, when considering types and symptoms of ADHD, no correlations were observed.

A linear regression was performed utilising the ASRS full score as the criterion and the *5-HTT* SNP genotypes as the predictor in order to determine if the *5-HTT* SNP could be predict ASRS full score. The analysis was found to be statistically significant [$F$(1,10)=6.166, $p$<0.05] indicating that the *5-HTT* SNP genotypes are good predictors of ASRS full score (Figure 4.20, a). This regression accounted for 32% of the variability, as indexed by the adjusted $R^2$ statistic. Additional investigation into symptom scores showed that the *5-HTT* SNP could be predict hyperactivity score (as measured by the ASRS). The analysis was found to be statistically significant [$F$(1,10)=6.337, $p$<0.05] indicating that the *5-HTT* SNP genotypes are good predictors of ASRS hyperactivity score (Figure 4.20, b). This regression accounted for 33% of the variability, as indexed by the adjusted $R^2$ statistic.

There is a definite association between ADHD and the heterozygous form (AG) of the *5-HTT* SNP. There was no correlation between specific types and the *5-HTT* SNP. However, regression analysis showed that full ADHD score and ADHD hyperactive score could be predicted by the *5-HTT* SNP genotypes. Gadow *et al.* (2013) also found an association to the heterozygous genotype, specifically to hyperactivity.

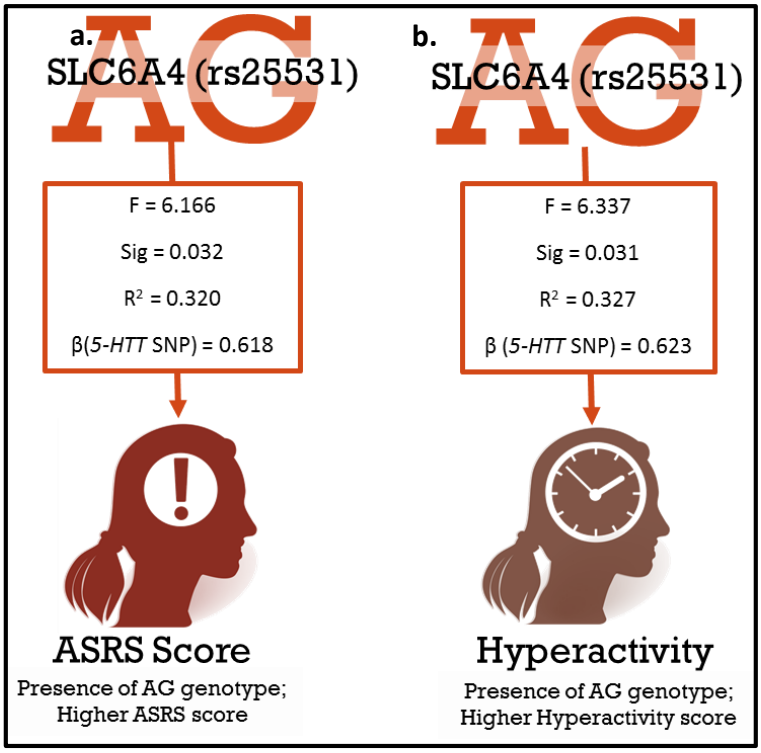


Figure 4.20: A visual representation of a linear regressions testing the validity of the hypotheses where (a) ASRS full score, as the criterion, is influenced by the *5-HTT SNP* genotype, as the predictor, and (b) ASRS hyperactivity score, as the criterion, is influenced by the *5-HTT SNP* genotype, as the predictor.

### 4.3.6 Gene combinations

A multiple regression was performed utilising the presence of inattention (as measured by the ASRS) as the criterion and the *5-HTTLPR* VNTR S allele, and *HTR1B* SNP genotypes as predictors in order to determine if the inattention could be predicted as a function of *5-HTTLPR* VNTR, and *HTR1B* SNP. The analysis was found to be statistically significant [$F(2, 21)=8.112$, $p<0.05$], indicating that the *5-HTTLPR* S allele and *HTR1B* GG genotype are good predictors of the inattention (Figure 4.21). This multiple regression accounted for 38% of the variability, as indexed by the adjusted $R^2$ statistic. The variable of *5-HTTLPR*, as indexed by its β value of -0.662, was shown to have the strongest association to inattention. Inattention is related to both *5-HTTLPR* and *HTR1B* polymorphisms. That is, higher inattention scores were associated both with the *5-HTTLPR* S allele and the *HTR1B* GG genotype. Banerjee, Banerjee,

Chatterjee, Sinha, and Nandagopal (2012) also noted an association between *HTR1B* and *SLC6A4* in individuals with ADHD. Smoller *et al.* (2006) also found an association between inattention and the *HTR1B* G allele.

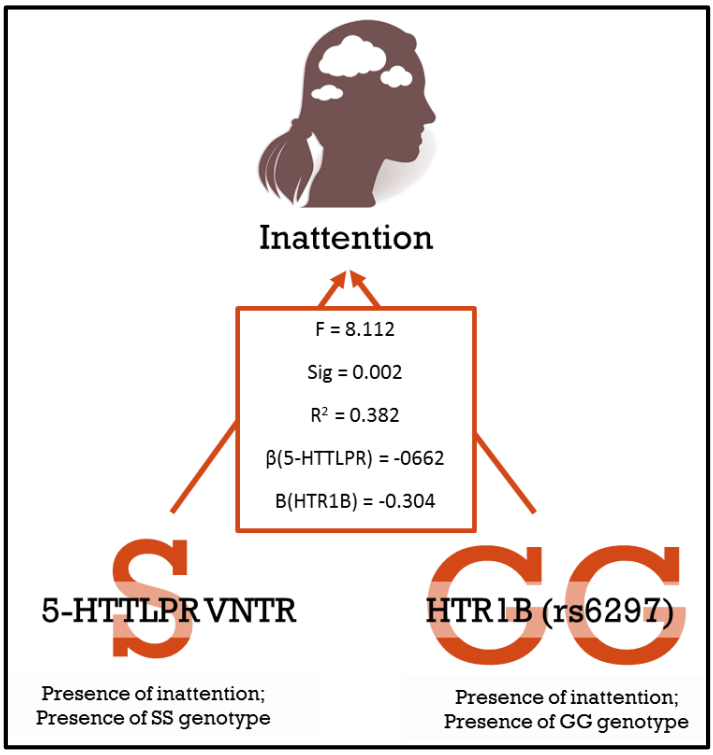


**Figure 4.21: A visual representation of a multiple regression testing the validity of the hypothesis where inattention score (as measured by the full inattention ASRS score), as the criterion, is influenced by the *HTR1B* and *5-HTTLPR* genotypes, as the predictors.**

Using the suggestion by Wendland *et al.* (2006), *5-HTTLPR* alleles with corresponding *5-HTT* SNP G alleles were assumed to have the same effect as the S allele. This rule applied to one case only and thus resulted in few changes to correlations. Correlations only differed in their significance levels, which became slightly weaker. Only one new correlation resulted between the reworked *5-HTTLPR* genotypes and results of previous diagnoses (by a medical practitioner, psychologist, psychiatrist or self-diagnosis). Results showed a moderate positive correlation potentially linking the SS genotype to diagnoses of combined type ADHD ($r$=0.526, $p$<0.05). However, regression analysis yielded non-significant results. Finally, while few changes resulted from the theory of L allele knockout by G allele *5-HTT* SNP, a new association was

brought to light with this change. In this instance previous ADHD diagnosis, specifically combined type diagnosis was associated with the SS allele. Again caution should be taken when interpreting these results, as regression analysis did not show significance. Kiive and Harro (2013) failed to find a significant distinction between the genotypes of these two polymorphisms when taken together.

## 4.4 Conclusions

Serotonin appears to be a significant modulator of ADHD. Direct associations reveal that previous diagnosis of hyperactivity and the *HTR2A* heterozygous genotype is related. The S allele of the *5-HTTLPR* polymorphism is responsible for both the presence and type of ADHD, as well as for the severity of inattentive and hyperactive symptoms. The heterozygous genotype of the *5-HTT* SNP is also responsible for hyperactivity, and inattention is predicted by both the S allele of *5-HTTLPR* and the GG genotype of *HTR1B*.

There is evidence to support some of these results, further study is crucial to ensure reproducibility. This includes associations with *5-HTTLPR*, inattention and hyperactivity symptoms, and the association between *5-HTTLPR*, *HTR1B,* and inattention. Also, controversial results need to be replicated to determine conclusive validity. As is the case with the *5-HTTLPR* S allele and ADHD association, and heterozygous association of the *5-HTT* SNP and ADHD. Finally, it is crucial to further study novel associations, as in the indirect association of ADHD and *HTR1B* via risky activity, and ADHD. Future studies should research the associations of other polymorphisms (not only restricted to the four studied here), within these serotonin receptor and transporter genes.

Although the modified salting out method has proven to be successful, limited quality genetic samples were still obtained. This may possibly due to external factors such as eating, drinking or smoking prior to giving saliva samples, which may degrade DNA.

# Chapter 5

# Attention and hyperactivity as a result of both genetic and environmental components

## Abstract

Attention-Deficit Hyperactivity Disorder shows significant heritability. Environmental influences also play a role in ADHD. Attention-Deficit Hyperactivity Disorder is a complex disorder, where genetics is the predominant cause of manifestation, and environment plays an important role in severity. This study considered the role of several serotonergic polymorphisms (within the *HTR1B*, *HTR2A* and *SLC6A4* genes), and potential environmental influences (including psychological and medical problems, poor sleep habits, severity of smoking, increased affinity for performing risky activities, and impairments in self-concept). Results showed associations in the *HTR1B*, *HTR2A* and *5-HTTLPR* genes, in combination with increased consequential psychological problems, medical problems, and sleep problems. In this study the polymorphism in *HTR2A* gene showed indirect association to ADHD through poor self-concept. The VNTR, *5-HTTLPR*, showed the strongest link to ADHD, this coupled with increased psychological and medical problems, severe smoking, and poor sleep patterns. Genetic and environmental combinations accounted for a large proportion of the variability in ADHD. Variability in ADHD can be accounted for by the *HTR1B* and *5-HTTLPR* polymorphisms coupled with psychological problems (37%), as well as with *HTR2A* and *5-HTTLPR* polymorphisms coupled with increased medical problems and poor sleep (33%).

**Keywords:** HTR2A, Psychological problems, Profile, Self-concept, Sleep.

## 5.1 Introduction: ADHD as a complex disorder

Although twin and adoption studies have found that genetics plays the largest role in ADHD, the specific genes and/or polymorphisms which genetic studies have assessed are not able to account for all of the genetic variation seen in twin and adoption studies (Gillis et al., 1992; Greven, Rijsdijk, Asherson, et al., 2011; Lehn et al., 2007; J. Nigg, Nikolas, & Burt, 2010; Nikolas et al., 2012). The discrepancy arises due to the complexity of ADHD as a disorder. Understanding what genes are important to the manifestation of ADHD is essential; it is also important to understand the interplay between genetics and environment (Hyde, Bogdan, & Hariri, 2011).

A number of studies have begun to look at the interaction between genetics and environment, and the implications of these interactions in psychological disorders such as ADHD (Altink et al., 2008; Burrows, McOmish, & Hannan, 2011; Charras, 2011; Daley, Sonuga-Barke, Thompson, & Chen, 2008; M. Das et al., 2011; Derks et al., 2008; Grizenko et al., 2012; Hyde et al., 2011; Larsson et al., 2004; J. Nigg et al., 2010; Nikolas & Burt, 2010; Nikolas, Friderici, Waldman, Jernigan, & Nigg, 2010; Nikolas et al., 2012; Peyrot et al., 2012; Plomp et al., 2009; Todd & Neuman, 2007b). The term "Gene-Environment Correlation" (GEC) refers to a phenomenon where environmental experiences combined with genetic factors cause variations in the phenotypic representation of a behavioural (or physiological) condition (Hyde *et al.*, 2011). That is, environmental influences may improve or worsen a phenotypic representation of disorders such as ADHD, if predisposing risk factors were already present.

Behavioural disorders are generally considered to be complex disorders where there is interaction between multiple genes as well as the environment (Burrows *et al.*, 2011). Studies of the Gene-Environment Interactions (GEI; in contrast to GEC, this occurs when a particular

environmental stimulus must be present along with already present predisposing genetic risk factors, to bring about the phenotypic representation of the condition) associated with ADHD have focussed predominantly on prenatal factors such as maternal stress, and smoking (Altink et al., 2008; Grizenko et al., 2012; Laucht et al., 2007; Todd & Neuman, 2007b). Retz *et al.* (2008) also found an interaction between maladjusted home environment and ADHD, mediated by the *5-HTT* gene, however, unlike Nikolas *et al.* (2010), this was found in the presence of at least one S allele (as discussed in Chapter 2).

This final chapter takes both the environmental factors studied in Chapter 3 and the genetic factors in Chapter 4 in combination to determine how all these factors work together to bring about variations in ADHD. To determine whether, in combination, these factors could provide a profile which may aid the diagnosis of ADHD.

## 5.2 Methods

Statistical analysis was performed using IBM® SPSS statistics v22 (IBM Corp, 2013) package. Bivariate correlations were performed to determine links between genetics and ADHD, and environmental factors and ADHD (as in Chapter 3 and 4). Partial correlations were then performed to determine the extent to which these genetic and environmental factors taken together correlated with ADHD. The SPSS software was also used to perform multiple regression analysis to further reveal connections between genetics, environment, and ADHD.

## 5.3 Results and Discussion[9]

As previously determined, correlations were found between ADHD and genetic components as well as between ADHD and environmental components (Chapters 3 and 4). Partial correlations revealed associations between these three factors (ADHD, genetics, and environment).

### 5.3.1 *HTR1B*

#### *a. Risky activity*

An indirect correlation was obtained between *HTR1B*, ADHD, and risky activity (as assessed by WFIRS-S) (i.e. while *HTR1B* and inattention are not directly correlated with each other, they are both correlated with risky activity). A Pearson Product Moment correlation explored the association between the *HTR1B* genotypes and risky activity ($\bar{x}$=4.8). This analysis was found to be statistically significant ($r$=0.618, p<0.05) indicating a strong positive correlation between the CC genotype of the *HTR1B* SNP and risky activity. The strength of this association, as indexed by the coefficient of determination (a measure of the proportion of variance in one factor which is explained by the known values of a second factor), was found to be 38.2%. Another Pearson Product Moment correlation explored the association between the ADHD as assessed by the ASRS ($\bar{x}$=6.66) and risky activity ($\bar{x}$=4.8). This analysis was found to be statistically significant ($r$=0.525, p<0.01) indicating a positive association between the score on the ASRS and level of risky activity. The strength of this association, as indexed by coefficient of determination, was found to be 27.6%. These associations were then subjected to a first-order partial correlation in order to explore the association between ADHD and risky activity,

[9] Details of statistical analysis can be found in Appendix 9.

controlling for the effects of the *HTR1B* gene. The first-order correlation was found to be statistically significant ($r$=0.795, p<0.01) indicating that an association between ADHD and risky activity exists regardless of the effects of the *HTR1B* SNP CC genotype, but that the association is strengthened when the SNP is taken into account.

A logistic regression established that *HTR1B* genotypes could significantly predict risky activity scores [$F$(1, 12)=7.4, $p$<0.05], and that *HTR1B* CC genotype accounted for 38% of the explained variability in risky activity scores. However, reshuffling the *HTR1B* genotypes (from GG=1, GC=2, CC=3 to CC=1, GG=2, GC=3) showed exactly the same results with the same significance and $F$ score. A second linear regression established that risky activity scores could significantly predict ADHD scores (ASRS full diagnosis) [$F$(1, 23)=8.745, $p$<0.05], and that risky activity scores accounted for 27.5% of the explained variability in ADHD scores (Figure 5.1).

A multiple regression was performed utilising the WFIRS risky activity score as the criterion, and the *HTR1B* CC genotype, and ASRS inattentive score as predictors in order to determine if the risky activity score could be predicted as a function of *HTR1B* genotype and inattention. The analysis was found to be statistically significant [$F$(2, 11)=6.373, $p$<0.05], indicating that *HTR1B* CC genotype and inattention are good predictors of risky activity (Figure 5.3). This multiple regression accounted for 54% of the variability, as indexed by the adjusted $R^2$ statistic. The variable of *HTR1B* CC genotype, as indexed by its β value of 0.594, was shown to have the strongest association to risky activity score. However, reshuffling the *HTR1B* genotypes (from GG=1, GC=2, CC=3 to CC=1, GG=2, GC=3) showed exactly the same results with the same significance and $F$ score.

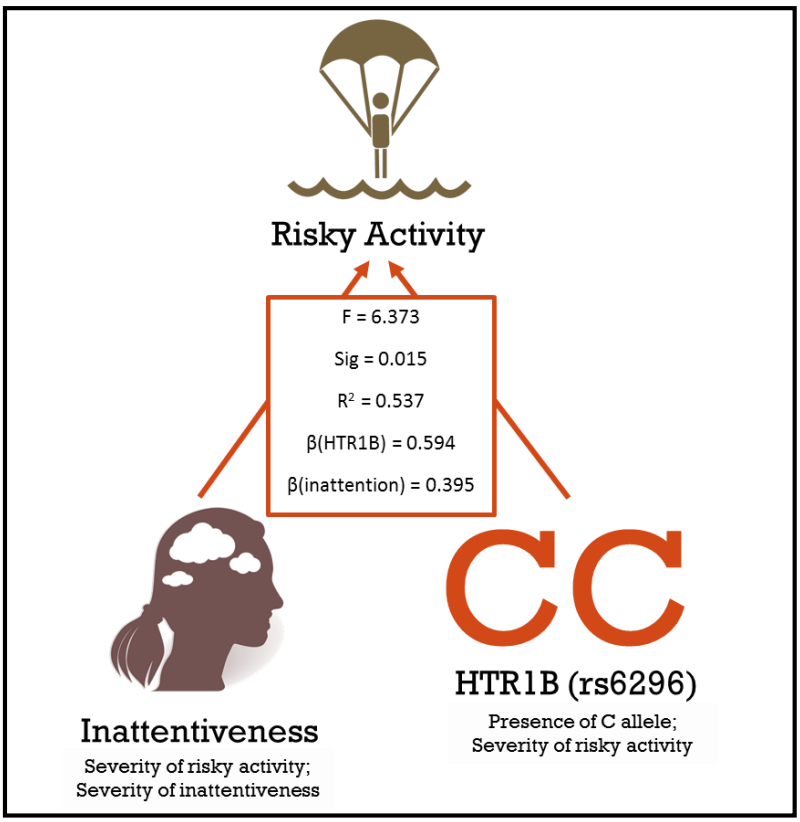


Figure 5.1: A visual representation of a multiple regression testing the validity of the hypothesis where the severity of risky activity, as the criterion, is influenced by several predictors (*HTR1B* CC genotype and inattention scores).

Multiple regression analysis of hyperactivity scores and inattentive scores are also shown to be significant predictors of risky activity scores [$F(1, 23)=8.745$, $p<0.01$] (Figure 5.2). This multiple regression accounted for 29% of the variability, as indexed by the adjusted $R^2$ statistic. The variable of inattention, as indexed by its β value of 0.395, was shown to have the strongest association to risky activity.

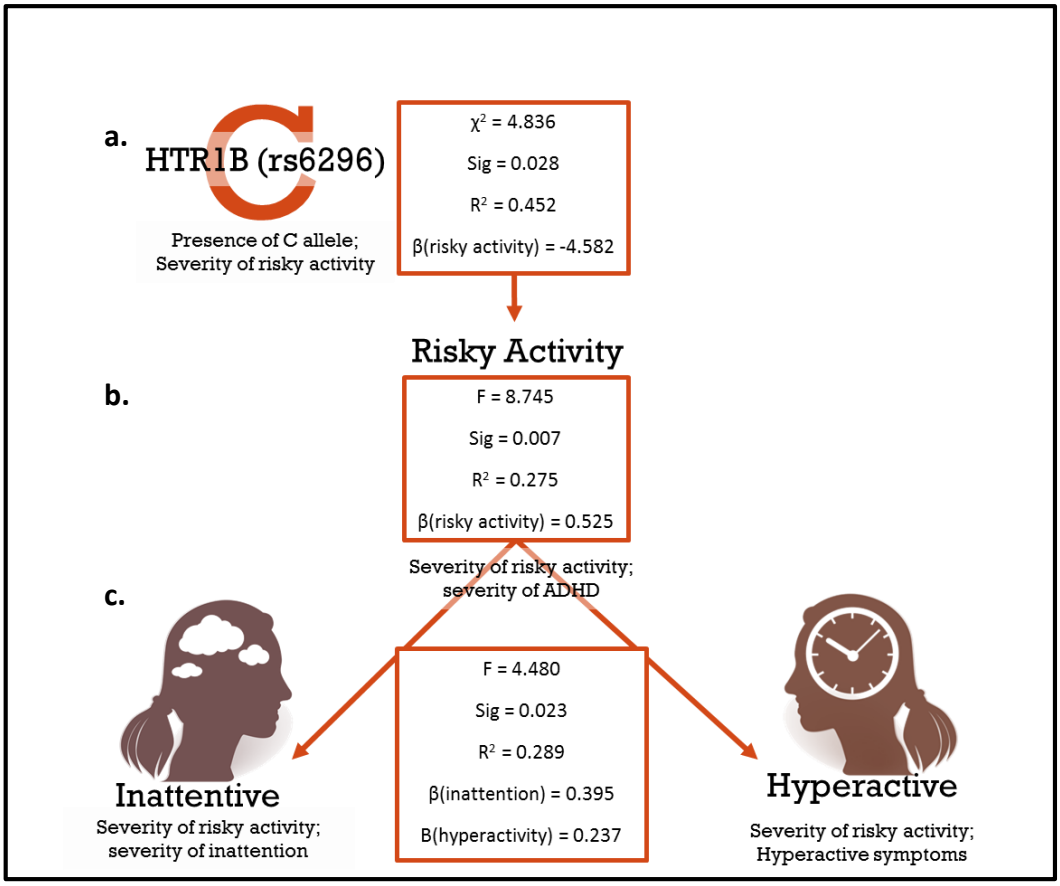


Figure 5.2: A visual representation of multiple regressions testing the validity of the hypothesis (a) where the severity of risky activity, as the criterion, is influenced by the *HTR1B* genotype, as the predictor, (b) where the severity of ADHD (as measured by ASRS), as the criterion, is influenced by the severity of risky activity, as the predictor, and (c) where the severity of risky activity, as the criterion, is influenced by the severity of inattentiveness and hyperactivity (as measured by ASRS), as the predictors.

These results for the *HTR1B* are inconclusive, because of the significance of the regression analysis preformed two different ways (ranking the CC and GC genotypes highest, respectively). Risky activity, however, does appear to show associations to ADHD, in aspects of both inattentiveness and hyperactivity, where high risky activity predicts high levels of inattention and hyperactivity. It seems plausible that difficulty in inhibition could affect both inattention (for example, by being unable to inhibit external stimuli from drawing focus away from the task at hand) and hyperactivity (for example, by reducing the ability to avoid fidgeting) and which results, more obviously, in "thrill seeking" behaviours. Although the precise genetic association of this could not be determined in this study.

*b. Psychological problems*

A multinomial logistic regression was performed to ascertain the effects of medical problems, psychological problems, developmental problems, learning disorders and the *HTR1B* polymorphism on the likelihood that participants have various types of ADHD. The logistic regression model was statistically significant [$\chi^2(18) = 36.111$, $p<0.01$]. The model explained 77% (Nagelkerke $R^2$) of the variance in ADHD type and correctly classified 78% of cases. Individuals with the *HTR1B* GG genotype and developmental problems were more likely to have ADHD combined type or inattentive type. (Figure 5.3).

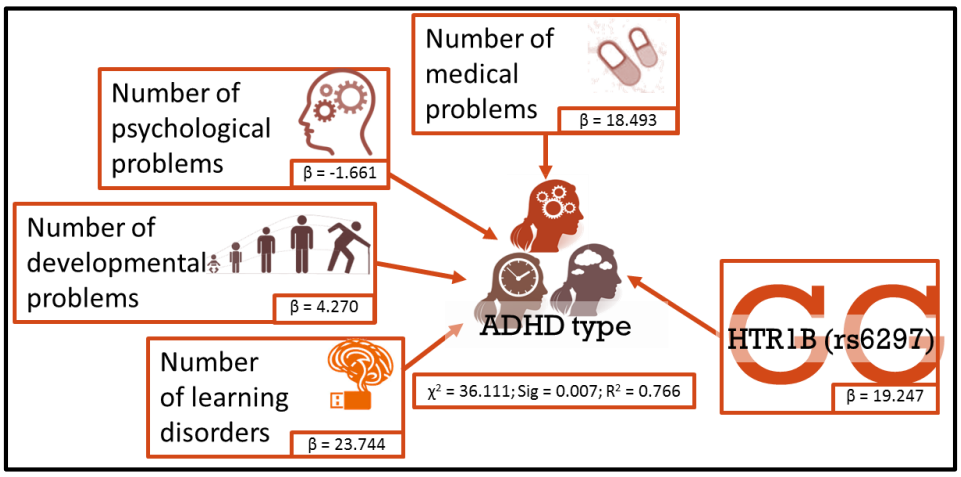


Figure 5.3: A visual representation of a multiple regression testing the validity of the hypothesis where ADHD type, as the criterion, is influenced by several predictors (including the *HTR1B* genotype).

### 5.3.2 *HTR2A*

*a. Self-concept*

A multiple regression was performed utilising the ASRS pre-diagnosis scores as the criterion, and the WFIRS presence of impaired self-concept, and *HTR2A* reshuffled genotypes (the heterozygous genotype was given the highest ranking) as predictors in order to determine

if the ASRS pre-diagnosis scores could be predicted as a function of self-concept and, *HTR2A* SNP genotypes. The analysis was found to be statistically significant [$F(2, 10)=8.643$, $p<0.05$] indicating that self-concept and *HTR2A* SNP AG genotype are good predictors of the ASRS pre-diagnosis scores (Figure 5.4, a). This multiple regression accounted for 56% of the variability, as indexed by the adjusted $R^2$ statistic. The variable of self-concept, as indexed by its β value of 0.778, was shown to have the strongest association to ASRS pre-diagnosis scores. These predictors (*HTR2A* reshuffled AG genotype and presence of self-concept) were also significantly able to predict inattention score (as measured by the full ASRS) [$F(2, 10)=5.164$, $p<0.05$]. This multiple regression accounted for 41% of the variability, as indexed by the adjusted $R^2$ statistic. The variable of self-concept, as indexed by its β value of 0.714, was shown to have the strongest association to ASRS inattention score (Figure 5.4, b).

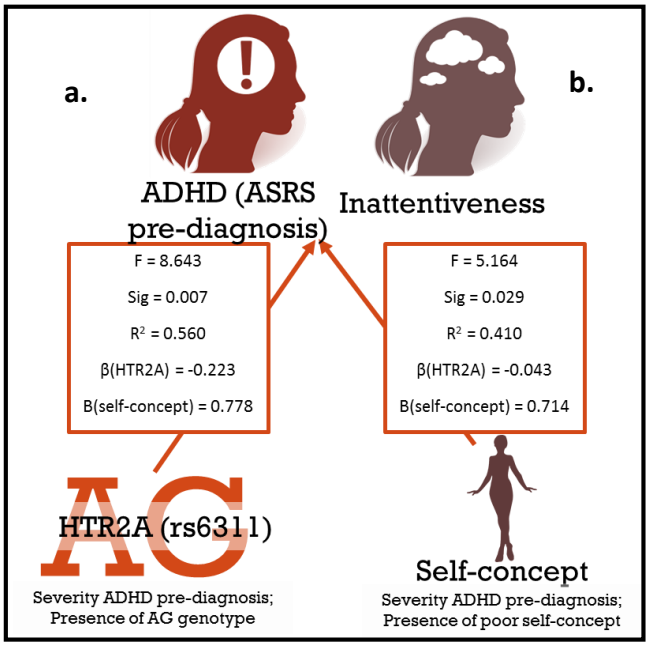


Figure 5.4: A visual representation of multiple regressions testing the validity of the hypothesis (a) where the ADHD pre-diagnosis score, as the criterion, is influenced by the *HTR2A* genotype, and presence of poor self-concept as the predictors, (b) where the inattention score (as measured by ASRS), as the criterion, is influenced by the *HTR2A* genotype, and presence of poor self-concept as the predictors.

The *HTR2A* polymorphism (rs6311) showed associations to impulsivity. The homozygous C genotype together with a poor self-concept are significant predictors of ADHD pre-diagnosis scores (measured by ASRS), as well as full inattention score. That is, individuals with a GG genotype and poor self-concept are likely to have high ADHD pre-diagnosis scores and high inattention scores, as measured by the ASRS. The *HTR2A* polymorphism may thus also have an influence on the high levels of depression accompanying the disorder. This is in contrast to a study by Pazvantoğlu *et al.* (2013) who found that the A allele was associated with ADHD.

### 5.3.3 *5-HTTLPR*

#### *a. Developmental and medical problems, severity of smoking, and quality of sleep*

A bivariate correlation between ADHD type and *5-HTTLPR* (S allele) showed significant results ($r$=-0.382; $p$<0.05). When controlling for developmental problems ($\bar{x}$=0.6), the correlation is slightly stronger, however, the significance is unchanging ($r$=-0.421; $p$<0.05). This reveals that ADHD type is equally correlated to *5-HTTLPR* S allele and developmental problems, as indicated by an unchanging significance value when controlling for developmental problems. A stronger, more significant correlation results when performing a partial correlation between ADHD type and *5-HTTLPR*, controlling for learning disorders ($\bar{x}$=0.08) ($r$=-0.456; $p$<0.05). This means that considering learning disorders significantly strengthens the correlation between ADHD and the *5-HTTLPR* S allele. Whilst controlling for medical problems ($\bar{x}$=1.12; $r$=-0.408) lowers the significance of the correlation between ADHD type and *5-HTTLPR*, it is still significant at the 95$^{th}$ percentile.

Partial correlations revealed associations between ADHD (especially ADHD-I and ADHD-HI), the *5-HTTLPR* S allele and increased developmental problems. Similar results were

obtained when learning disorders were considered. Practically speaking this means that the S allele of the *5-HTTLPR* polymorphism is significantly associated with ADHD, particularly in the homozygous form in hyperactive type individuals, especially when multiple learning disorders or developmental problems are present. Smoking and medical problems do not influence the fact that the *5-HTTLPR* S allele causes ADHD, however, ADHD is also correlated with smoking and medical problems on some level.

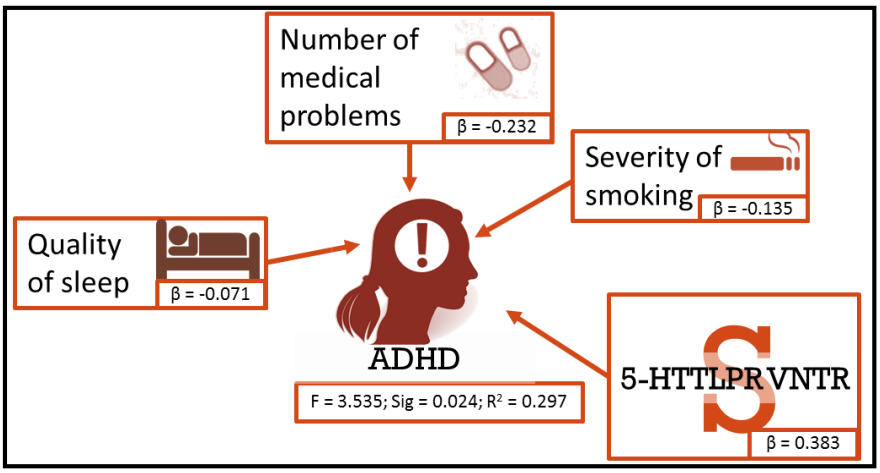


**Figure 5.5: A visual representation of a multiple regression testing the validity of the hypothesis where ADHD presence, as the criterion, is influenced by several predictors (including the *5-HTTLPR* allele).**

A multiple regression performed using the *5-HTTLPR* alleles as the primary contributor of ADHD revealed secondary influences from smoking, sleep, and medical problems. This analysis was found to be statistically significant [$F(4, 20)=3.535$, $p<0.05$], indicating that *5-HTTLPR* genotypes, smoking, sleep, and medical problems are good predictors of ADHD presence (Figure 5.6). This multiple regression accounted for 30% of the variability, as indexed by the adjusted $R^2$ statistics. The variable for *5-HTTLPR* allele, as indexed by its β value of 0.383, was shown to have the strongest association to ADHD presence (Figure 5.5).

Multiple regression analysis also revealed that the *5-HTTLPR* S allele, developmental problems, severe smoking, and exposure to hypoxic conditions were strong predictors of ADHD

[$F(4, 20)=3.116$, $p<0.05$] (Figure 5.6). This multiple regression accounted for 26% of the variability, as indexed by the adjusted $R^2$ statistics. The variable for *5-HTTLPR* S allele, as indexed by its β value of 0.393, was shown to have the strongest association to ADHD presence.

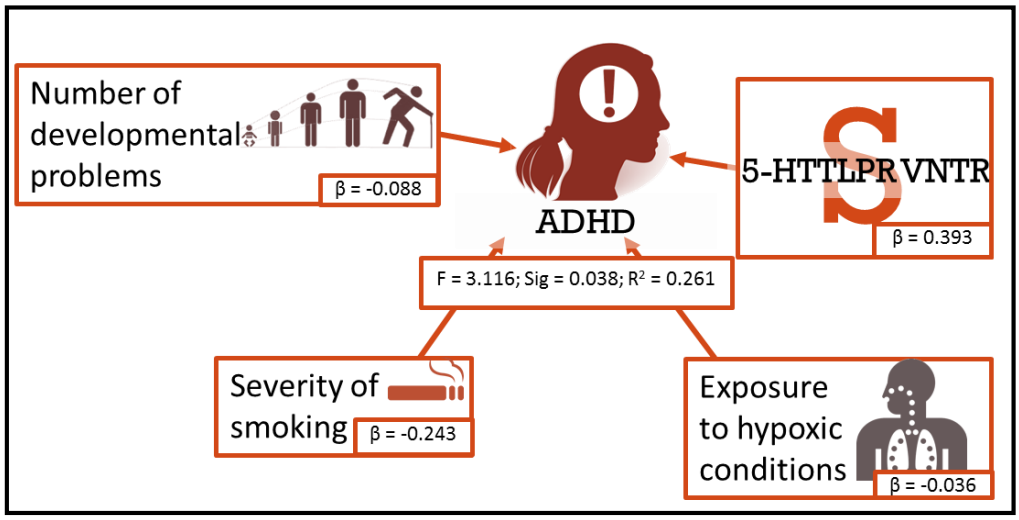


**Figure 5.6: A visual representation of a multiple regression testing the validity of the hypothesis where ADHD presence, as the criterion, is influenced by several predictors (including the *5-HTTLPR* alleles).**

Collectively, the *5-HTTLPR* S allele is the primary cause of ADHD, however, environment also plays a role in the form of smoking, poor sleep, and increased prevalence of medical problems. Developmental problems appear to be a predictor of ADHD type when the *5-HTTLPR* S allele, severe smoking, or exposure to hypoxic conditions are present.

### *b. Psychological problems*

Additionally, psychological problems associated with ADHD appear to be caused by the presence of the S allele in the *5-HTTLPR* gene [$F(2, 22)=4.907$, $p<0.05$] (Figure 5.7). This multiple regression accounted for 25% of the variability, as indexed by the adjusted $R^2$ statistics. The variable for *5-HTTLPR* S allele, as indexed by its β value of 0.546, was shown to have the strongest association to ADHD type (Figure 5.7). This, however, was non-significant when included with other environmental aspects associated with ADHD (Appendix 9).

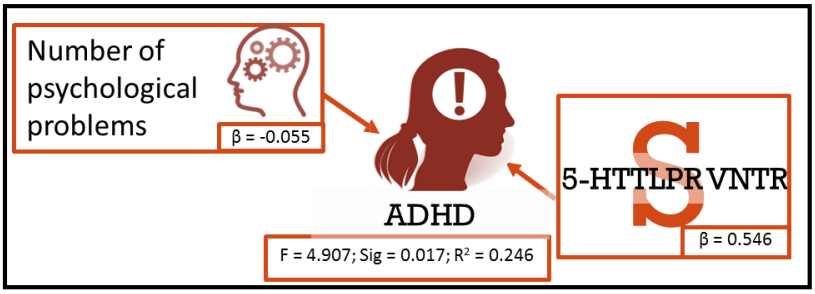


Figure 5.7: A visual representation of a multiple regression testing the validity of the hypothesis where ADHD type, as the criterion, is influenced by number of psychological problems and *5-HTTLPR* genotype, as predictors.

An increase in the number of psychological problems, along with the *5-HTT*LPR S allele appears to be common in ADHD individuals. The combination of these two components may show a predictive value for the presence of ADHD. This may point to *5-HTTLPR* having a greater effect on poor psychological well-being associated with ADHD, rather than difficulty in behaviour control and focus maintenance.

### 5.3.4 *5-HTT* SNP

While the SNP in the serotonin transporter gene did not show significant associations to ADHD as a whole, or the inattentive type, it did show associations to hyperactivity score.

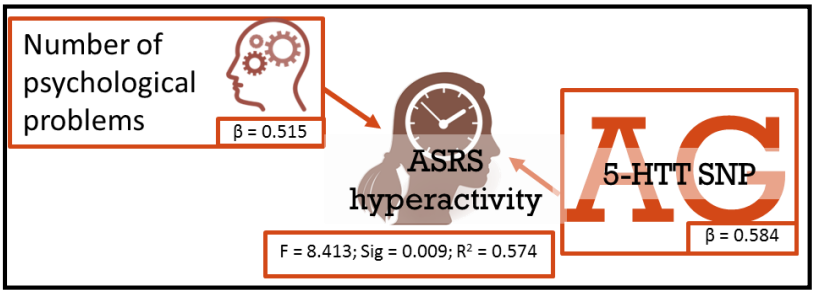


Figure 5.8: A visual representation of a multiple regression testing the validity of the hypothesis where hyperactivity score, as the criterion, is influenced by several number of psychological problems, and *5-HTT* SNP genotype, as predictors.

A multiple regression performed using the *5-HTT* SNP genotypes as the primary contributor of ASRS hyperactivity score revealed secondary influences from psychological problems [$F(2, 9)=8.413$, $p<0.05$]. That is, the *5-HTT* SNP AG genotype and number of

psychological problems present are good predictors of ASRS hyperactivity scores (Figure 5.8). Interestingly, this accounted for 57% of the variability, as indexed by the adjusted $R^2$ statistics. The variable with the strongest association to ASRS hyperactivity score was the *5-HTT* AG genotype (β = 0.584).

Due to the small sample size of the ADHD-HI group, hyperactivity scores were assessed to reveal a connection of the genes and environmental factors with hyperactivity. Analysis showed that higher hyperactivity scores were predicted by *5-HTT* SNP AG genotype, and an increase in prevalence of psychological problems (Figure 5.13, d). This SNP does not show associations with ADHD as a whole, or inattention. This may be indicative of the symptoms of hyperactivity being under different genetic control than inattention.

### 5.3.5 Gene combinations

The type of ADHD present may also be predicted by both the *5-HTTLPR* and *HTR1B* genotypes considered together, as well as with psychological, and medical problems (Figure 5.10) [$F(4, 19)= 4.015$, $p<0.05$]. This multiple regression accounted for 34% of the variability, as indexed by the adjusted $R^2$ statistic. The variable for *5-HTTLPR* genotype, as indexed by its β value of -0.591, was shown to have the strongest association to ADHD type (Figure 5.9).

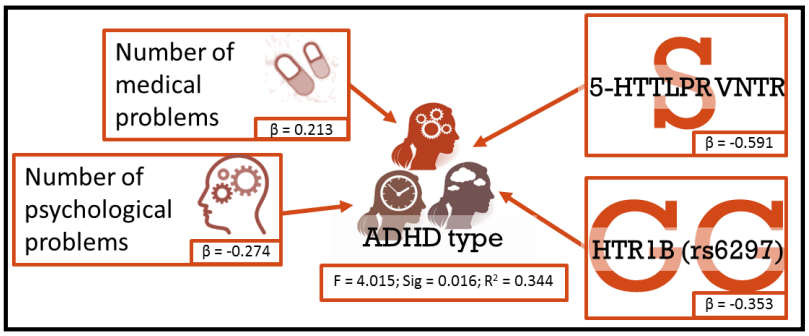


Figure 5.9: A visual representation of a multiple regression testing the validity of the hypothesis where ADHD type, as the criterion, is influenced by several predictors (including the *5-HTTLPR* and *HTR1B* genotypes).

When assessing the various types of ADHD, only inattention was revealed to be predicted by the combination of the *5-HTTLPR* S allele, *HTR1B* GG genotype and an increased number of medical problems [$F(3, 20)=5.422$, $p<0.05$] (Figure 5.10). These variables accounted for 37% of the variability seen in the inattentive type ADHD. The *5-HTTLPR* S allele accounted for most of the variability seen in the phenotype (β=-0.689) (Figure 5.10).

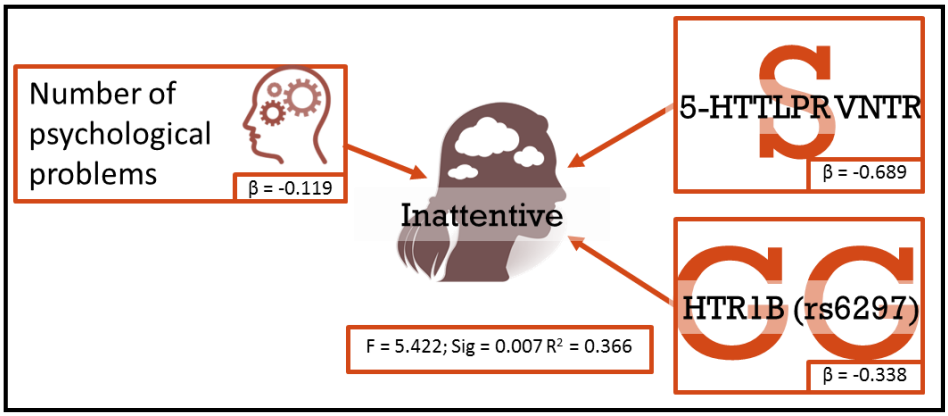


**Figure 5.10: A visual representation of a multiple regression testing the validity of the hypothesis where inattention score, as the criterion, is influenced by several predictors (including the *5-HTTLPR* and *HTR1B* genotypes).**

When assessing both the *HTR1B* and *5-HTTLPR* polymorphisms together in relation to ADHD, it appears that an increase in prevalence of psychological problems and show predictive value in revealing whether ADHD is present (Figure 5.13, a). The inattentive type of ADHD revealed a similar connection to the *HTR1B* GG genotype and *5-HTTLPR* S allele, as well as to psychological problems, however, only when looking at the presence of psychological problems rather than the number of psychological problems present (Figure 5.13, b).

The inattentive type ADHD was revealed to be predicted by the combination of the *5-HTTLPR* S allele, *HTR2A* AG genotype, an increased number of medical problems, and poorer quality sleep [$F(4, 17)=3.633$, $p<0.05$] (Figure 5.11). These variables accounted for 33% of the variability seen in the inattentive type ADHD. The *5-HTTLPR* genotype accounted for most of

the variability seen in the phenotype (β=-0.615). This shows an association between the inattentive type and the combination of *5-HTTLPR* S allele, *HTR2A* AG genotype, and increased medical problems (Figure 5.13, a). While this 33% may seem small, it shows that these three factors account for more than a quarter of the variability of ADHD. Given that ADHD is such a complex disorder, this 33% is a significant leap in understanding the contribution of genetic and environmental factors to ADHD.

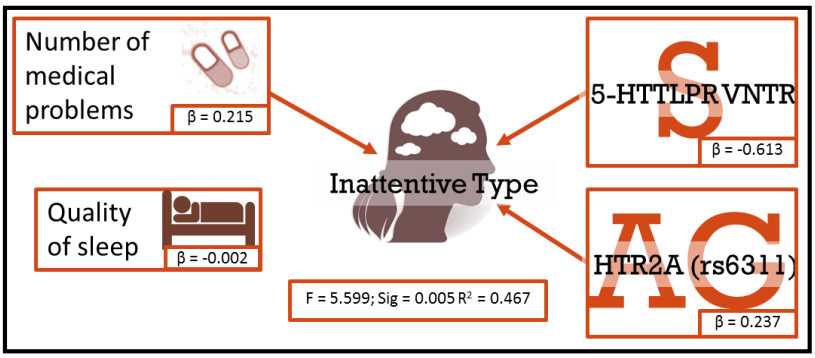


Figure 5.11: A visual representation of a multiple regression testing the validity of the hypothesis where inattentive type ADHD (reshuffled type variable), as the criterion, is influenced by several predictors (including the *5-HTTLPR* and *HTR2A* genotypes).

### 5.3.6 Combined type

Combined type ADHD showed no associations with any of the genes when entered into a multiple regression analysis (Figure 5.13, c) (Appendix 9), however, it did appear to be explained by environmental factors [$F(6, 46)=5.007$; $p<0.05$] (Figure 5.10). Associations were found with the number of medical and psychological problems present, as well as exposure to hypoxic conditions, and severity of smoking. This accounted for 31.6% of the variation found in combined type ADHD, as determined by the $R^2$ statistic, and was most significantly influenced by the number of medical problems present (β = 0.334).

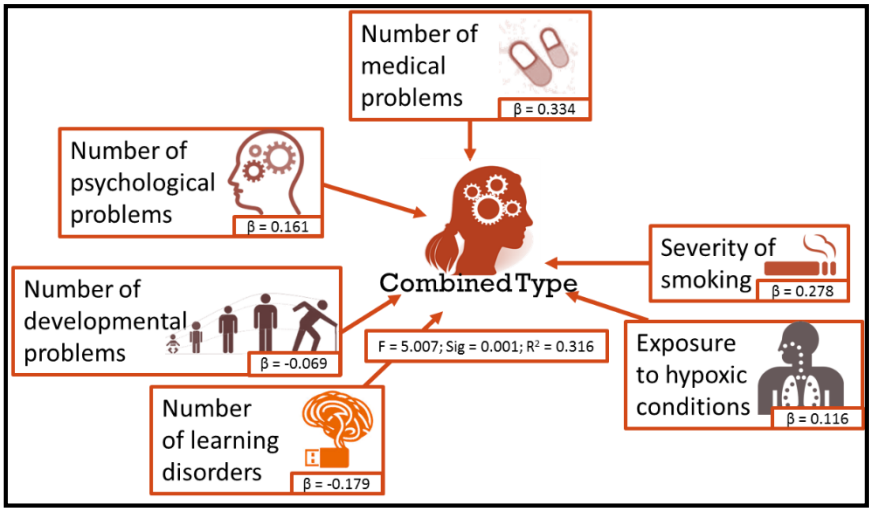


Figure 5.12: A visual representation of a multiple regression testing the validity of the hypothesis where the presence of ADHD-C, as the criterion, is influenced by several predictors.

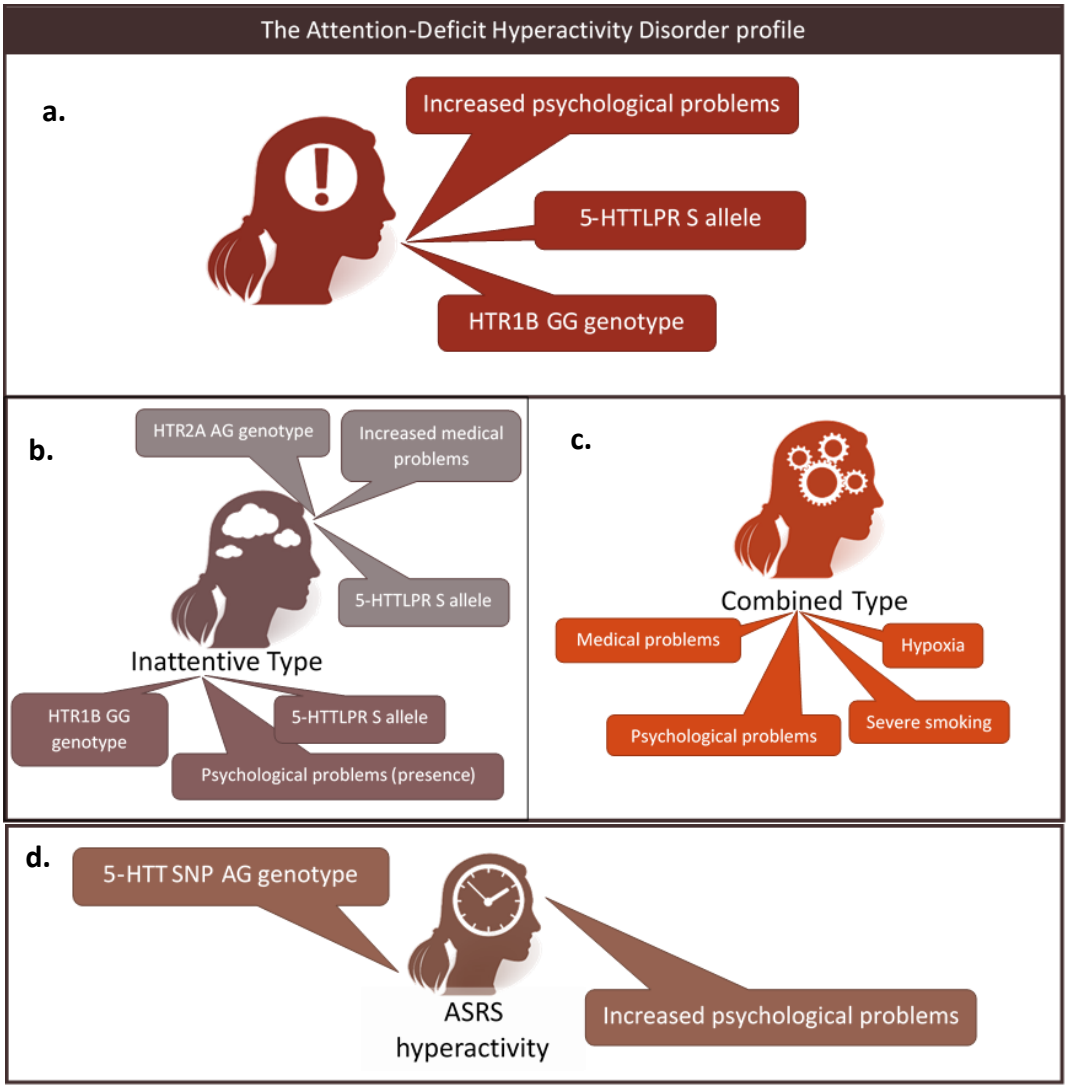


Figure 5.13: Profile of each type of ADHD, based on the results found in this study.

## 5.4 Conclusions

It is clear that ADHD is a complex disorder with multiple influencing factors. This disorder is predominantly genetic in nature, which translate to neurochemical imbalances. Studying all of the environmental influences will aid in understanding ADHD on an individual level, and allowing for a profile to be determine of what exactly constitutes an individual with ADHD. By providing evidence of the large role that environmental factors play in the manifestation on ADHD, this study motivates a change from a purely medication-based treatment regime, to one which focuses on environmental factors as well. The implication of serotonin in the manifestation of ADHD suggests that clinicians could attempt to use a serotonin-based medication approach to treat ADHD, as an alternative to Methylphenidate. Further, it is important that clinicians in contact with pregnant mothers, especially those with a familial history of ADHD, should urge them to consider the serious effects which environmental factors (such as both direct and indirect nicotine exposure and hypoxic conditions) could have on their unborn child.

This study has provided progress into determining this desired profile which could be used to better diagnose individuals with ADHD. Results have revealed significant patterns in the *HTR1B*, *HTR2A,* and *SLC6A4* genes, and this in combination with increased consequential psychological and medical problems may prove to be essential for diagnostic processes in the future.

Risk genotypes associated with ADHD include the *HTR1B* GG genotype, the *HTR2A* AG genotype, and the *SLC6A4 5-HTT* SNP AG genotype. All of these genes show additive effects. The *SLC6A4 5-HTTLPR* S allele is the risk allele in ADHD and shows an interactive effect, where the S allele is dominant.

As with any study, there have been several limitations. The most significant limitation is small sample size. Because adult ADHD has only recently been considered plausible, most adults with ADHD are unaware of the fact that they have the disorder. For this reason medical professionals are not often consulted by adults with ADHD, thus limiting the availability of contacts. Finding adults with pure hyperactivity proved more challenging than anticipated. This may be due to adult individuals having developed means of controlling their hyperactive symptoms over the years using strict structural regimes, or by seeking out environments in which hyperactive symptoms may be beneficial. Challenges were also experienced in contacting individuals for re-examination using the DIVA semi-structured interview, perhaps due to lack of interest from participants.

This study could be replicated in future, but would need to include a larger sample population, particularly of those individuals with ADHD-H. Given the effectiveness of the multi-factorial approach taken in this study, it would be advisable that future research into ADHD consider implementing such an approach. Future research may also consider looking into the epigenetic effects of prenatal maternal stress and both maternal and paternal smoking. It may also be interesting to perform expression analysis of the *HTR1B* and *5-HTTLPR* genes to determine the effects of certain alleles on individuals with ADHD compared to controls. More polymorphisms in these genes need to be assessed to determine whether other polymorphisms which influence expression similarly are also influential in bringing about the ADHD phenotype. Additional polymorphisms, both in the serotonergic system, and other neurotransmitter pathways, should be explored to determine to what extent these pathways play a role in ADHD.

# Chapter 6

# Summary

Attention-Deficit Hyperactivity Disorder is a neurodevelopmental disorder characterised by symptoms of inattention, hyperactivity, and impulsivity. This disorder has been increasingly diagnosed in children and adults since the early 1990s. Genetics has been largely implicated in the aetiology of ADHD, with environment influencing the severity of the condition.

The purpose of this research was to study the influence of polymorphisms in the serotonin system on ADHD, and to investigate the extent to which certain environmental factors affect the severity of the condition. In total, 74 individuals took part in this study by completing an online self-report survey, a semi-structured interview, and/or providing genetic material in the form of saliva (52 individuals in total). Of these, a sub-set of comparative participants comprised of 45 individuals, and a sub-set of participants previously diagnosed with ADHD comprised of 29 individuals.

Environmental analysis involved the assessment of medical, psychological, and developmental problems, learning disorders, sleep problems, nicotine dependence, and exposure to oxygen deprived conditions. Impairments in various other aspects were also assessed, including life skills, social concept, work or education, family life, and risky activities. Molecular analysis focussed on three genes in the serotonin system. These genes are responsible for various aspects of the functioning of the system. These genes encode for two serotonin receptors (*HTR1B* and *HTR2A*) and the serotonin transporter (*SLC6A4*). Three single nucleotide polymorphisms (SNPs) were genotyped using restriction enzyme digestion and confirmatory sequencing. A single variable number of tandem repeats (VNTR) in the *SLC6A4* gene was also assessed.

Results of environmental analysis alone revealed that exposure to hypoxic conditions and/or second-hand nicotine inhalation worsen inattentive and hyperactive symptoms of ADHD. Aspects found to be present alongside ADHD were increased psychological, medical and learning problems, and high nicotine dependence. The most significant impairments in life functioning in ADHD individuals arose in familial, social, and school or work environments, as well as significant impairments in self-concept and an increased affinity for risky behaviours. Exercise was found to have a positive self-reported effect on ADHD symptoms.

Molecular analysis showed that the serotonin system plays a significant role in modulating ADHD. The *HTR2A* (rs6311) SNP in heterozygous form is linked to high levels of hyperactivity. The heterozygous form of the *5-HTT* SNP (located in the *SLC6A4* gene) was indicative of the presence of ADHD. The GG genotype of the SNP *HTR1B* (rs6296) showed significant associations with inattention score. The S allele of VNTR in the *SLC6A4* gene showed the strongest association to ADHD in terms of type of ADHD (mainly inattentive), presence of ADHD, and severity of inattention and hyperactivity symptoms.

Molecular and environmental components taken together reveal an indirect association between the *HTR1B* (rs6296) GG genotype and increased psychological problems. The *HTR2A* polymorphism (AG genotype), on the other hand, is associated with poor self-perception. This polymorphism, coupled with the *5-HTTLPR* S allele, and medical problems shows significant associations with inattentive type ADHD. The *5-HTTLPR* VNTR showed the strongest association to ADHD, even when coupled with environmental influences. The S allele of this VNTR, along with increased medical and psychological problems show significant correlations to ADHD.

This study also shows that methods of measurement, while different, produce similar quantifiable information, however, may produce differing resulting diagnoses and should thus be viewed in context for study purposes.

In concluding, this study provides a potential profile for the diagnosis of ADHD, in terms of both environmental and genetic components. The research also implicates the importance of the serotonin system as an integral modulator of the presence and severity of ADHD and its symptoms.

Keywords: Adult ADHD Self-Report Scale, Attention-Deficit Hyperactivity Disorder, Environment, HTR2A, HTR1B, Hyperactivity, Impulsivity, Inattention, Serotonin, SLC6A4, Weiss Functional Impairment Rating Scale.

Aandag-afleibaarheid en hiperaktiwiteit sindroom, bekend as "*ADHD*", is 'n neuro-ontwikkelende afwyking gekaraktiriseer deur 'n gebrek aan aandag, gepaardgaande met hiperaktiwiteit en impulsiwitieit. Hierdie afwyking word al hoe meer in kinders en volwassenes gediagnoseer van die vroeë 1990s. Genetika is meestal betrokke by die ontwikkeling van *ADHD*, met omgewingsfaktore wat die toestand vererger.

Die doel van hierdie navorsing is om die uitwerking wat polimorfismes in die serotonienstelsel op *ADHD* het, te ondersoek, asook om te bepaal in hoe 'n mate omgewingsfaktore die intensiteit van die afwyking bepaal. In total het 74 individue deelgeneem aan hierdie studie deur 'n aanlyn self-verslag opname te voltooi , aan 'n semi-gestruktureerde onderhoud deel te neem en/of genetiese material in die vorm van sputum te verskaf (52 individue in totaal). Van hierdie 74 individue, het 45 'n sub-groep van vergelykende deelnemers gevorm, en die orige 29 was 'n sub-groep van deelnemers wat voorheen met *ADHD* gediagnoseer was.

Daar was onder andere vir mediese, psigologiese- en ontwikkelingsprobleme, leer en slaap versteurings, nikotien afhanklikheid, en suurstof-gebreks toestande, as omgewingsinvloede getoets. Agterstande in verskeie ander aspekte, onder andere lewensvaardighede, sosiale konsepte, werk of geleerdheid, familie lewe, en deelname aan gevaarlike aktiwiteite, was ook geassesseer. Die molekulêre analises het op drie gene gefokus wat deel vorm van die serotonienstelsel. Die gene is verantwoordelik vir verskeie funksionele aspekte van die serotonienstelsel. Hierdie gene kodeer twee serotonien reseptore (*HTR1B* en *HTR2A*) en die serotonien transporter (*SLC6A4*). Drie enkelnukleotied polimorfismes ("SNP") was gegenotipeer met behulp van beperkingsensieme en bevestigende nukleotiedvolgorde

bepaling. ‘n Enkele veranderlike aantal tandem herhalings (“VNTR”) in die *SLC6A4* geen was ook geassesseer.

Resultate van die analisering, van slegs die omgewingsinvloede, het aangedui dat blootstelling tot hipoksiese omstandighede en/of tweedehandse nikotien inaseming vererger aandagsgebrek en hiperaktiwiteit simptome van *ADHD* kan vererger. Ander aspekte wat saam met *ADHD* voorgekom het sluit verhoogte psigologiese-, mediese- en leerprobleme, asook nikotien afhanklikheid in. Die mees beduidende leefbeperkings van individue met *ADHD,* is familie, sosiale, en skool- of werksomgewings, asook beduidende beperkings in self-konsep en ‘n verhoogde geneigdheid vir waaghalsige gedrag. Daar is bevind dat fisieke aktiwiteit ‘n positiewe uitwerking op *ADHD* simptome het.

Die molekulêre analise het getoon dat die serotonienstelsel ‘n groot rol in die modulering van *ADHD* speel. Die *HTR2A* (rs6311) *SNP* se heterosigotiese vorm is geassosieer met hoë vlakke van hiperaktiwiteit. Die heterosigotiese vorm van die *5-HTT SNP* (gevind in die *SLC6A4* geen) dui op die voorkoms van *ADHD*. Die GG-genotipe van die *HTR1B* (rs6296) *SNP* het sterk geassosieer met aandagsgebrekkigheid. Die S-alleel van die *VNTR* in die *SLC6A4* geen het die strekste assosiasie met *ADHD* getoon in terme van die tipe *ADHD* (hoofsaaklik aandagsgebrekkigheid), *ADHD* teenwoordigheid, en die graad van aandagsgebrekkigheid en hiperaktiwiteit.

Molekulêre- en omgewingskomponente toon oor die algemeen ‘n indirekte assosiasie met die *HTR1B* (rs6296) GG-genotipe en meer psigologiese probleme. Aan die ander kant word die *HTR2A* polimorfisme (AG-genotipe) geassossieer met swak self-persepsie. Hierdie polimorfisme, tesame met die *5-HTTLPR* S-alleel, asook die mediese probleme, het beduidende assosiasies met ADHD-impulsiwiteit gehad. Die *5-HTTLPR VNTR* toon die sterkste assosiasie

met *ADHD*, selfs wanneer dit met omgewingsfaktore gekoppel word. Die S-alleel van die *VNTR*, saam met verhoogte mediese- en psigologiese probleme, korreleer betekenisvol met *ADHD*.

Hierdie studie toon ook dat verskillende maatstawwe soortgelyke kwantifiseerbare inligting genereer, alhoewel dit tot verskillende diagnoses mag lei. Dit moet binne die studie konteks geïnterpreteer word.

Ter afsluiting: die studie verskaf ‘n moontlike profiel vir die diagnose van *ADHD*, beide in terme van omgewings- en genetiese komponente. Die navorsing beklemtoon die belang van die serotonienstelsel as ‘n integrale modulator van die teenwoordigheid en die graad van *ADHD* simptome.

Sleutelwoorde: Aandag-Afleibaarheid en Hiperaktiwiteits Sindroom, Aandagsgebrekkigheid, Hiperaktiwiteit, HTR2A, HTR1B, Impulsiwiteit, Omgewing, Serotonien SLC6A4, Volwassene ADHD Self-Verslag Skaal, Weiss Funksionele Gebrek Gradering Skaal.

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# Appendix 1

Ethical approval

UNIVERSITY OF THE FREE STATE
UNIVERSITEIT VAN DIE VRYSTAAT
YUNIVESITHI YA FREISTATA
UFS UV

Research Division
Internal Post Box G40
☎(051) 4052812
Fax (051) 4444359

E-mail address: StraussHS@ufs.ac.za

Ms H Strauss/hv

2013-07-25

REC Reference nr 230408-011
IRB nr 00006240

Ms J MANSFIELD
DEPT OF GENETICS
FACULTY OF NATURAL & AGRICULTURAL SCIENCES
UFS

Dear Ms Mansfield

**ECUFS 95/2013**
**PROJECT TITLE AND UMBRELLA STUDY: THE ETIOLOGY AND TREATMENT EFFICACY OF ATTENTION AND HYPERACTIVITY RELATED DISORDERS IN A SOUTH AFRICAN POPULATION**

**ECUFS 95/2013A**
**MS J MANSFIELD DEPT OF GENETICS**
**PROJECT TITLE: THE ETIOLOGY OF THE SEVERITY AND PRESENCE OF ATTENTION AND HYPERACTIVITY RELATED DISORDERS IN A POPULATION FROM SOUTH AFRICA.**

**ECUFS 95/2013B**
**MS HS POSTHUMUS DEPT OF GENETICS**
**PROJECT TITLE: GENETIC VARIANTS INVOLVED IN THE ETIOLOGY AND METABOLISATION OF MEDICINE USED IN TREATING ADULT ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.**

- You are hereby kindly informed that the Ethics Committee reviewed the above research project and it was presented at the meeting on 23 July 2013. Before the Ethics Committee may grant final approval for this project, the following condition(s) has/have to be met:

  a) ***A signed approval letter from the study leader(s) to indicate that the studies have been approved.***

  b) ***Signed letter from the statistician indicating that the methodology has been approved.***

- Committee guidance documents: Declaration of Helsinki, ICH, GCP and MRC Guidelines on Bio Medical Research. Clinical Trial Guidelines 2000 Department of Health RSA; Ethics in Health Research: Principles Structure and Processes Department of Health RSA 2004; Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa, Second Edition (2006); the Constitution of the Ethics Committee of the Faculty of Health Sciences and the Guidelines of the SA Medicines Control Council as well as Laws and Regulations with regard to the Control of Medicines.

- Any amendment, extension or other modifications to the protocol must be submitted to the Ethics Committee for approval.

- The Committee must be informed of any serious adverse event and/or termination of the study.

- Research may not be conducted before the condition(s) has/have been met. Thus, this letter only serves as conditional approval.
- All relevant documents e.g. signed permission letters from the authorities, institutions, changes to the protocol, questionnaires etc. have to be submitted to the Ethics Committee before the study may be conducted (if applicable).
- A progress report should be submitted within one year of approval of long term studies and a final report at completion of both short term and long term studies.
- Kindly refer to the ETOVS/ECUFS reference number in correspondence to the Ethics Committee secretariat.

Yours faithfully

.....
**PROF WH KRUGER**
**CHAIR: ETHICS COMMITTEE**

**Cc** **Ms HS Posthumus**

# Appendix 2

## Self-report questionnaire

# Appendix 1.1: Information and consent forms

## Participant information

Dear participant,

The aim of this study is to determine whether certain genes (the physical components we inherited from our parents) can be linked to Attention Deficit/Hyperactivity Disorder (ADHD) in people, whether these genes affect treatment response and whether there is a link between environmental factors and ADHD. You will only be asked to complete a questionnaire, and a DNA sample may be taken from you by means of a saliva sample. Since we need to link your DNA sample to your questionnaire, we do require your name. We can assure you, however, that your personal details will be treated with the strictest confidence. We will not require more than 30 minutes of your time. Furthermore, the information we collect will only be used to research ADHD, and we will not give it to any other person. We will not use your DNA for any other test! The results of this study will be published in a scientific journal without any reference to you. Feel assured that your anonymity will be kept! You will not be hurt physically or emotionally if you take part in this study. However, you are free to stop participating at any time, and doing so will have no negative effect on you in any way. Participating in this study will not cost you any money. Similarly, you will also not receive any money or any other compensation if you participate in this study. Ethical approval has been obtained for this study from the Medical Faculty ethical board at the University of the Free State. Reference number: Ecufs 95/2013.If you have any uncertainties or questions, please feel free to contact us (find our details at the very top of the page). If you are willing to participate, please mark the appropriate box below and complete the questionnaire. Please note that this questionnaire should be completed in its entirety before exiting. In the event that you exit before completion, the data will not be submitted for the research. Thank you for your participation!

1. I would like to participate
2. I would not like to participate

## Consent for taking part in study

I hereby agree to participate in the previously mentioned study on ADHD.I understand that my participation in the study is completely voluntary and that I can withdraw from the study at any time. I also understand that participating or withdrawing from the study will hold no negative consequences for me. I understand that I will receive no compensation in the form of money for participating in this study, nor do I need to pay anything to participate. I further understand that the data gathered in this study may be published in a scientific journal, but should this happen, I will remain completely anonymous.

1. I agree to take part
2. I do not agree to take part

## Consent for the Handling of Genetic Material

I hereby understand that providing my genetic material in the form of a saliva sample will hold no negative effects for me. I further understand that my genetic material will be handled only by the researchers (J. Mansfield and H. Posthumus) and that it will not be used for any other purpose than the afore mentioned study. I understand that this genetic material will need to be stored for the duration of two years while the study is being completed and will thereafter be disposed of. I recognise that I will be handing my genetic information over to the researchers and I trust that it will be handled with the utmost care and secrecy.

1. I agree to provide a DNA sample
2. I do not agree to provide a DNA sample

## Appendix 1.2: Demographic information as suggested by CADDRA (2011)

### Identifying Information

### Personal Identifiers

Name and surname:

Age:

Gender:
1. Male
2. Female

Ethnic origin:
1. Caucasian
2. Asian
3. African
4. Mixed Ancestry
5. Indian
6. Other

Home language:
1. English
2. Afrikaans
3. Sesotho
4. Zulu
5. Xhosa
6. Other

Status:
1. Single
2. Married
3. Widowed
4. Separated
5. Divorced

Number of step children (if applicable):

I have been diagnosed with:
1. ADHD Combined type (Attention deficit, Hyperactivity and Impulsivity)
2. ADHD - Predominantly Inattentive (also called ADD)
3. ADHD - Predominantly Hyperactive or Impulsive

This diagnosis was made by:
1. My personal doctor (GP)
2. Psychologist
3. Psychiatrist
4. Pediatrician
5. Other professional medical specialist
6. Self-diagnosis

The diagnosis was made by:
1. My personal doctor (GP)
2. Psychologist

3. Psychiatrist
4. Pediatrician
5. Other professional medical specialist
6. Self-diagnosis

## Education

Grade (last completed):

1. Completed Primary School
2. Completed Grade 9
3. Matriculated from High School
4. Completed Undergraduate Studies
5. Completed Postgraduate Studies

Current occupation:

1. Student
2. Unemployed
3. Disability
4. Other

Please specify your current occupation:

## Contact Information

(Please note that personal details will only be used in the event that we need to contact you and will not be revealed to any other persons)

Phone number:

E-mail Address:

## Medical and Psychological Information

Please only select conditions which have been diagnosed by a medical professional (doctor, psychologist, psychiatrist, pediatrician)

Medical Information (see below for a detailed description of each condition):

1. Enlarged tonsils
2. Stigmata of FAS/FAE
3. History of anoxia or perinatal
4. complications
5. Growth delay
6. Myotonic dystrophy
7. Anaemia
8. Traumatic brain injury
9. Hearing or visual problems
10. Neurofibromatosis
11. Injuries
12. Thyroid disorder
13. Diabetes
14. Developmental delays
15. Coordination problems
16. Sleep apnoea
17. Seizures
18. Medical complications of drug/alcohol use
19. *In utero* exposure to nicotine, alcohol or drugs

20. Cerebral palsy
21. Enuresis
22. Asthma
23. Lead poisoning
24. Not applicable

Medical Information:

*In utero* exposure to nicotine, alcohol or drugs: Exposure to nicotine, alcohol or drugs whilst in the womb Stigmata of FAS or FAE: Similar features which usually occur due to fetal alcohol syndrome or fetal alcohol exposure without actual exposure to alcohol in the uterus (e.g. mental retardation, shortened height etc.)
History of anoxia or perinatal complications: Total depletion of oxygen at any time or complications during the birth process
Hearing or visual problems: Difficulties with blindness or deafness
Developmental delays: Not meeting the required marks of development (such as sitting up or walking) within the required time
Coordination problems: Problems with combining a number of body movements (usually combining direction and force) to bring about a specific action
Cerebral palsy: any of a number of motor conditions causing physical disability in human development, especially in terms of body movement
Lead poisoning: Exposure to high levels of lead
Neurofibromatosis: A genetic disorder of the nervous system which affects how nerve cells form and grow
Myotonic dystrophy: a genetic disease characterised by wasting of the muscles, cataracts, heart conduction defects, endocrine changes and myotonia
Thyroid disorder: Imbalance in the production of thyroid hormones. Characterised by excessive weight gain or weight loss, muscle weakness and insomnia.
Diabetes: Increased blood sugar due to low levels of insulin
Growth delay: Not reaching the required levels of growth and development at the expected time during childhood
Anaemia: Low iron levels due to a decreased number of red blood cells or haemoglobin
Traumatic brain injury: A traumatic accident which may have caused physical injury to the brain (e.g. a car accident or concussion)
Seizures: Abnormal excessive brain activity causing wild thrashing movements or a brief loss of awareness
Enuresis: A repeated inability to control urination
Injuries: Any significant injuries which caused distress, especially very serious injuries
Sleep apnoea: A sleep disorder characterised by pauses in breathing or very low breathing during sleep
Medical complications of drug/alcohol use: Any medical conditions or problems that may have occurred as a direct result of taking drugs or drinking alcohol
Enlarged tonsils: Swollen tonsils
Asthma: An inflammatory disease of the airways characterised by wheezing, coughing, chest tightness and shortness of breath

Please indicate any other genetic condition(s) which you have been diagnosed with (by a medical professional):

Please indicate any other medical condition(s) (if applicable) which you have been diagnosed with (by a medical professional):

Psychological Information (This refers to conditions only diagnosed by either a psychologist or psychiatrist. This includes conditions diagnosed anytime throughout life, even if experienced only for a short period of time. See below for a description of each).

1. Tourettes or tics
2. Anxiety disorder
3. Autism spectrum disorder
4. Learning disorder
5. Conduct disorder
6. Depression
7. Sleep disorders
8. Bipolar disorder
9. Suicidal Attempts
10. Oppositional defiant disorder
11. Violent gestures towards others
12. Not applicable

Psychological information

Tourettes or tics: A disorder marked by involuntary vocalisations or movements
Sleep disorders: An umbrella term for any significant departure from the normal sleep-waking cycle
Anxiety: An unpleasant emotional state with qualities of apprehension, dread, distress and uneasiness; Distinct from fear in that it is objectless
Depression: Extreme feelings of inadequacy, feelings of despondency, decreased activity or reactivity, pessimism, sadness, etc.
Bipolar disorder: A major mood disorder in which manic and depressive episodes occur, or only manic episodes
Autism spectrum disorder: A tendency to be self-absorbed to the extent that one's thoughts, feelings and desires are governed by one's internal apprehension of the world. Usually accompanied by severe cognitive deficits, deficits in social functioning and language skills
Conduct disorder: A behavioural disorder in which a person repetitively and persistently violates the rights, privileges and privacy of others
Learning disorder: Dyslexia, dysgraphia, dyscalulia or dyssemia
Suicidal Attempts: An attempt at taking one's own life Violent gestures towards others: Acting out physically and inappropriately especially when provoked by others
Oppositional defiant disorder: A developmental disorder marked by defiant, hostile and negativistic behaviour

Please indicate any other psychological conditions (diagnosed by a psychologist or psychiatrist):

Have you ever been treated for any diagnosed psychological conditions?
1. Yes
2. No

Have you had any previous psychological or psychiatric evaluation or hospitalization?
1. Yes
2. No

## Developmental History

### Developmental Difficulties

Did you experience any difficulties with the following as a child? Mark even if the symptoms were temporary.

Difficulties in gross motor control (crawl, walk, gym, sports):
1. Yes
2. No

Difficulties in fine motor skills (tracing, shoe laces, writing):
1. Yes
2. No

Language difficulties (first language, first words, full sentences, stuttering):
1. Yes
2. No

Odd behaviours noted (rocking, flapping, no eye contact, odd play, head banging, etc.):
1. Yes
2. No

Mood/Temperament when you were a child:
1. Difficult/Hyperactive
2. Easy/Calm

## Learning Difficulties

(this includes only conditions diagnosed by a medical professional, including doctors, psychologists, psychiatrists, pediatricians, speech therapist or remedial therapist)

Presence of Learning Disorder:

1. Dyslexia
2. Dysorthographia
3. Dyscalculia
4. Dysphasia
5. Not Applicable
6. Other

Please mention the presence of any other learning disorders:

### Learning disorders

Dyslexia: A learning disorder characterised by a difficulty in reading
Dysgraphia: An inability to write properly or to express oneself through writing. It manifests in multiple ways, including, an inability to write numbers, and inability to write lower case letters, an inability to write vowels or the correct spelling of regular words, but not irregular ones, etc.
Dyscalculia: A learning disability in which a child of normal or above normal intelligence experiences inordinate difficulty in learning standard arithmetic
Dysphasia: A language disorder in which the individual may experience difficulty communicating verbally, but not comprehending spoken words, or may have difficulty with both

## Environmental Components

Exposure to smoking (This includes all nicotine based products like cigarettes, tobacco pipes and snuff)

Are you or have you ever been a habitual smoker?

1. Yes
2. No

On average, how many times per day do you need nicotine based products?

Do you find it difficult to refrain from smoking in places where smoking is not allowed (e.g. hospitals, government offices, cinemas, libraries, etc.)?

1. Yes
2. No
3. Not applicable

Is the number of cigarettes you smoke per day often influenced by other factors (i.e. how you're feeling, what you're doing, etc.)?

1. Yes
2. No
3. Not applicable

After not smoking for a while, do you feel you need to smoke to relieve feelings of restlessness and irritability?

1. Yes
2. No
3. Not applicable

Have you tried to stop smoking only to relapse?

1. Yes
2. No
3. Not applicable

How many times have you attempted to stop smoking?

1. 1-2 times
2. 3-4 times
3. 4-5 times
4. 6 times or more
5. Not applicable

What were the most likely causes of relapse?

1. Low self-control
2. Influence from other smokers
3. Limited cessation methods
4. Little family or social support
5. Not applicable
6. Other

What other experiences may have caused you to relapse?

Have you often been exposed to second hand cigarette smoke, especially as a child?

1. Yes
2. No

## Discipline

Was discipline strongly enforced in your home when you were a child?

1. Yes
2. No

Which parent enforced discipline?

1. Mother
2. Father
3. Both
4. Neither

Were you often punished for being naughty?

1. Yes
2. No

Do you feel the punishment was unfair?

1. Yes
2. No

## Hypoxia and Anoxia (Oxygen deprivation)

Have you ever experienced difficulty in breathing due to altitude, or altitude sickness?

1. Yes
2. No

Do you experience sleep apnoea (stop breathing when sleeping)?

1. Yes
2. No

Have you ever had respiratory failure?

1. Yes
2. No

Have you ever lived in an area with much air pollution?

1. Yes
2. No

Were you born premature?

1. Yes
2. No

## Functioning and lifestyle evaluation

### Nutrition

How many days a week (on average) do you eat a nutritional meal (i.e. not fast food)?

1. 0
2. 1
3. 2
4. 3
5. 4
6. 5
7. 6
8. 7

How often do you eat foods high in sugar (e.g. sweets or sugary fruit)?

1. Never
2. 1-2 times a week
3. 3-5 times a week
4. Almost every day

How often do you eat foods high in additives (like MSG in crisps, artificial sweeteners in diet foods, refined sugars in candy or sodas and artificial flavourants) and artificial colourants?

1. Never
2. 1-2 times a week
3. 3-5 times a week
4. Almost every day

### Self-care and personal hygiene

How often do you make time for personal hygiene (e.g. bathing)?

1. Never
2. 1-2 times a week
3. 3-5 times a week
4. Almost every day

How often do you make time for self-care (e.g. doing your nails, having your hair done,shaving)?

1. Never
2. 1-2 times a week
3. 3-5 times a week
4. Almost every day

### Leisure

How often do you make time for leisure activities (e.g. relaxing, watching movies, hobbies)?

1. Never
2. 1-2 times a week
3. 3-5 times a week
4. Almost every day

## Sleeping habits: Sleep Routine and Quality of Sleep

On average, how many hours of sleep do you get per night (without any sleep aid)?

1. Less than 4 hours
2. 4-6 hours
3. 6-8 hours
4. 8-10 hours
5. 10-12 hours
6. Over 12 hours

Do you dream regularly?

1. Yes
2. No

On average, how many hours of sleep do you get per night (without any sleep aid)?

1. Less than 4 hours
2. 4-6 hours
3. 6-8 hours
4. 8-10 hours
5. 10-12 hours
6. Over 12 hours

Do you dream regularly?

1. Yes
2. No

Do you experience any of the sleep problems mentioned below?

| | Yes | No |
|---|---|---|
| Difficulty falling asleep | ❑ | ❑ |
| Difficulty keeping regular sleep pattern | ❑ | ❑ |
| Excessive daytime sleepiness | ❑ | ❑ |
| Snoring | ❑ | ❑ |
| Restless leg syndrome | ❑ | ❑ |

## Exercise

On average, how many days per week do you exercise?

1. 0
2. 1
3. 2
4. 3
5. 4
6. 5
7. 6
8. 7

On average, how many hours per day do you exercise?

1. None
2. 1-2
3. 3-4
4. 5-6
5. Over 6

What type of exercise do you do?

1. Gym
2. Rugby/Cricket/Soccer
3. Dancing

4. Golf
5. Yoga or Pilates
6. Swimming
7. Not applicable
8. Other _____

Level of exercise: Indicate how physically taxing the exercise that you do is

1. Become out of breath
2. Work up a light sweat
3. Sweat profusely
4. Not applicable

Do you feel as though exercise provides relief from your ADHD symptoms?

1. Yes
2. No
3. Not applicable

## Demographic Information

### Biological Family (Answer if applicable)

Indicate the current occupation of biological mother:

Indicate the current occupation of biological father:

Indicate the current occupation of spouse or partner:

Indicate your Mothers highest level of education:

1. Completed Primary School
2. Completed Grade 9
3. Matriculated from High School
4. Completed Undergraduate Studies
5. Completed Postgraduate Studies

Indicate your Fathers highest level of education:

1. Completed Primary School
2. Completed Grade 9
3. Matriculated from High School
4. Completed Undergraduate Studies
5. Completed Postgraduate Studies

Indicate your Spouse or Partners highest level of education:

1. Completed Primary School
2. Completed Grade 9
3. Matriculated from High School
4. Completed Undergraduate Studies
5. Completed Postgraduate Studies

Are you adopted?

1. Yes
2. No
3. Unsure

Age of Adoption:

How many siblings do you have?

1. 1
2. 2
3. 3
4. 4
5. 5
6. 6
7. 7
8. 8
9. 9
10. 10
11. 11+

Indicate the current occupation of your Stepmother:

Indicate the current occupation of your Stepfather:

Indicate the current occupation of your Guardian:

Indicate your Stepmothers highest level of education:

1. Completed Primary School
2. Completed Grade 9
3. Matriculated from High School
4. Completed Undergraduate Studies
5. Completed Postgraduate Studies

Indicate your Stepfathers highest level of education:

1. Completed Primary School
2. Completed Grade 9
3. Matriculated from High School
4. Completed Undergraduate Studies
5. Completed Postgraduate Studies

Indicate your Guardians highest level of education:

1. Completed Primary School
2. Completed Grade 9
3. Matriculated from High School
4. Completed Undergraduate Studies
5. Completed Postgraduate Studies

How many step-siblings do you have?

1. 0
2. 1
3. 2
4. 3
5. 4
6. 5
7. 6
8. 7
9. 8
10. 9
11. 10
12. 11+

## Family history of health or personal and psychological conditions in first degree relatives

(Any conditions listed below should have been diagnosed by a medical professional)

Has anyone in your biological family experienced any of the following Health or Personal Conditions?

1. Pregnancy Problems
2. Legal Convictions
3. Epilepsy
4. Alcohol/Drug Problems
5. Congenital Disorders
6. Not applicable

Has anyone in your biological family experienced any of the following Psychological conditions?

1. ADHD (confirmed)
2. ADHD (probable)
3. Tourettes or Tics
4. Depression
5. Sleep Disorders
6. Bipolar
7. Suicide
8. Anxiety
9. Psychosis
10. Mental Retardation
11. Learning Disorders
12. Personality Disorder
13. Autism Spectrum Disorders
14. Not applicable

### Family history of health or personal and psychological conditions in first degree relatives

Pregnancy Problems: Complications during the birth process
Epilepsy: A diverse set of neurological disorders characterised by seizures
Congenital Disorders: A condition existing at or before birth or in the first month of life
ADHD: Attention Deficit Hyperactivity Disorder, this may include Attention Deficit Disorder, Impulsivity and Hyperactivity or Combined type inattention, impulsivity and hyperactivity
Personality Disorders: A group of mental illnesses characterised by patterns of thoughts and behaviours that are unhealthy and inflexible
Suicide: The act of intentionally taking one's own life
Mental Retardation: A disorder appearing before adulthood, characterised by significantly impaired cognitive functioning and deficits in two or more adaptive behaviours
Depression: Extreme feelings of inadequacy, feelings of despondency, decreased activity or reactivity, pessimism, sadness, etc.
Bipolar disorder: A major mood disorder in which manic and depressive episodes occur, or only manic episodes
Autism spectrum disorder: A tendency to be self-absorbed to the extent that one's thoughts, feelings and desires are governed by one's internal apprehension of the world. Usually accompanied by severe cognitive deficits, deficits in social functioning and language skills
Tourettes or tics: A disorder marked by involuntary vocalisations or movements
Sleep disorders: An umbrella term for any significant departure from the normal sleep-waking cycle
Anxiety: An unpleasant emotional state with qualities of apprehension, dread, distress and uneasiness; Distinct from fear in that it is objectless
Psychosis: An abnormal condition of the mind characterised by a loss of contact with reality
Learning disorder: Dyslexia, dysgraphia, dyscalulia or Dysphasia

## Environmental Components

### Exposure to smoking

Does your mother smoke or has she ever smoked?

1. Yes
2. No

How long has/did your mother smoke for?

Does your father smoke or has he ever smoked?

1. Yes
2. No

How long has/did your father smoke for?

Do any of your other family members smoke?

1. Yes
2. No

Was your family particular about not exposing you to second hand smoke, especially while your mother was pregnant with you and during the first few years of life?

1. Yes
2. No

## Parental Trauma

(Trauma may include, but is not limited to, car accidents, surgery, a tragic death of a close friend or family member, physical, sexual or emotional abuse, witnessing a disturbing event, mass violence such as war, the break up of a serious relationship, an exceptionally humiliating or disappointing experience and the discovery of a serious life threatening or debilitating condition)

Have your parents experienced any traumatic events in the past?

1. Yes
2. No

How long ago did this traumatic event take place?

## Appendix 1.3: Adult ADHD Self-Report Scale (ASRS V1.1) Symptom Checklist (Adler, Kessler, & Spencer, 2003)

### Part A

Please answer the questions below, rating yourself on each of the criteria shown using the scale. As you answer each question, indicate that which best describes how you have felt and conducted yourself over the past 6 months.

| | Never | Rarely | Sometimes | Often | Very often |
|---|---|---|---|---|---|
| How often do you have trouble wrapping up the final details of a project, once the challenging parts have been done? | ❑ | ❑ | ❑ | ❑ | ❑ |
| How often do you have difficulty getting things in order when you have to do a task that requires organisation? | ❑ | ❑ | ❑ | ❑ | ❑ |
| How often do you have problems remembering appointments or obligations? | ❑ | ❑ | ❑ | ❑ | ❑ |
| When you have a task that requires a lot of thought, how often do you avoid it or delay getting started? | ❑ | ❑ | ❑ | ❑ | ❑ |
| How often do you fidget or squirm with your hands or feet when you have to sit down for a long time? | ❑ | ❑ | ❑ | ❑ | ❑ |
| How often do you feel overly active and compelled to do things, like you were driven by a motor? | ❑ | ❑ | ❑ | ❑ | ❑ |

### Part B

Please answer the questions below, rating yourself on each of the criteria shown using the scale. As you answer each question, indicate that which best describes how you have felt and conducted yourself over the past 6 months.

| | Never | Rarely | Sometimes | Often | Very often |
|---|---|---|---|---|---|
| How often do you make careless mistakes when you have to work on a boring or difficult project? | ❑ | ❑ | ❑ | ❑ | ❑ |
| How often do you have difficulty keeping your attention when you are doing boring or repetitive work? | ❑ | ❑ | ❑ | ❑ | ❑ |
| How often do you have difficulty concentrating on what people say to you, even when they are speaking to you directly? | ❑ | ❑ | ❑ | ❑ | ❑ |
| How often do you misplace or have difficulty finding things at home or at work? | ❑ | ❑ | ❑ | ❑ | ❑ |
| How often are you distracted by activity or noise around you? | ❑ | ❑ | ❑ | ❑ | ❑ |
| How often do you leave your seat in meetings or in other situations in which you are expected to stay seated? | ❑ | ❑ | ❑ | ❑ | ❑ |
| How often do you feel restless or fidgety? | ❑ | ❑ | ❑ | ❑ | ❑ |
| How often do you have difficulty unwinding and relaxing when you have time to yourself? | ❑ | ❑ | ❑ | ❑ | ❑ |
| How often do you find yourself talking too much when you are in social situations? | ❑ | ❑ | ❑ | ❑ | ❑ |
| When you're in a conversation, how often do you find yourself finishing the sentences of the people you are talking to, before they can finish it themselves? | ❑ | ❑ | ❑ | ❑ | ❑ |
| How often do you have difficulty waiting your turn in situations when turn taking is required? | ❑ | ❑ | ❑ | ❑ | ❑ |
| How often do you interrupt others when they are busy? | ❑ | ❑ | ❑ | ❑ | ❑ |

## Appendix 1.4: Weiss Functional Impairment Rating Scale (WFIRS) (Weiss, 2000)

Please indicate by means of the scale provided how much impairment you have experienced in each of the 6 areas of your life.

### A. Family

| | Never or not at all | Sometimes or somewhat | Often or much | Very often or very much | Not Applicable |
|---|---|---|---|---|---|
| Having problems with brothers & sisters | ❑ | ❑ | ❑ | ❑ | ❑ |
| Causing problems between parents | ❑ | ❑ | ❑ | ❑ | ❑ |
| Takes time away from family members' work or activities | ❑ | ❑ | ❑ | ❑ | ❑ |
| Causing fighting in the family | ❑ | ❑ | ❑ | ❑ | ❑ |
| Isolating the family from friends and social activities | ❑ | ❑ | ❑ | ❑ | ❑ |
| Makes it hard for the family to have fun together | ❑ | ❑ | ❑ | ❑ | ❑ |
| Made parenting difficult when you were a child | ❑ | ❑ | ❑ | ❑ | ❑ |
| Makes it hard to give fair attention to all family members | ❑ | ❑ | ❑ | ❑ | ❑ |
| Provoke others to hit or scream at you, especially during childhood | ❑ | ❑ | ❑ | ❑ | ❑ |
| Costs the family more money, especially during childhood | ❑ | ❑ | ❑ | ❑ | ❑ |

### B. School/Work

#### Learning/Job performance

| | Never or not at all | Sometimes or somewhat | Often or much | Very often or very much | Not Applicable |
|---|---|---|---|---|---|
| Difficulty keeping up with schoolwork/work required of job | ❑ | ❑ | ❑ | ❑ | ❑ |
| Needs extra help at school/work | ❑ | ❑ | ❑ | ❑ | ❑ |
| Needs tutoring at school or extensive explanations of requirements for work | ❑ | ❑ | ❑ | ❑ | ❑ |
| Receive grades that are not as good as your ability or not performing to the best of your ability at work | ❑ | ❑ | ❑ | ❑ | ❑ |

#### Behaviour

| | Never or not at all | Sometimes or somewhat | Often or much | Very often or very much | Not Applicable |
|---|---|---|---|---|---|
| Causes problems for the teacher in the classroom/employer | ❑ | ❑ | ❑ | ❑ | ❑ |
| Receives "time-out" or removal from the classroom/suspensions from work | ❑ | ❑ | ❑ | ❑ | ❑ |
| Having problems in the school yard/communal work area | ❑ | ❑ | ❑ | ❑ | ❑ |
| Receives detentions (during or after school)/warnings from employer | ❑ | ❑ | ❑ | ❑ | ❑ |
| Suspended or expelled from school/suspended or fired from work | ❑ | ❑ | ❑ | ❑ | ❑ |
| Misses classes or is late for school/misses work or is late for work | ❑ | ❑ | ❑ | ❑ | ❑ |

### C. Life skills

| | Never or not at all | Sometimes or somewhat | Often or much | Very often or very much | Not Applicable |
|---|---|---|---|---|---|
| Excessive use of TV, computer, or video games | ❑ | ❑ | ❑ | ❑ | ❑ |
| Disinterest in keeping clean, brushing teeth, brushing | ❑ | ❑ | ❑ | ❑ | ❑ |

| | | | | | |
|---|---|---|---|---|---|
| hair, bathing, etc. | | | | | |
| Problems getting ready for school/work | ❑ | ❑ | ❑ | ❑ | ❑ |
| Problems getting ready for bed | ❑ | ❑ | ❑ | ❑ | ❑ |
| Problems with sleeping | ❑ | ❑ | ❑ | ❑ | ❑ |
| Gets hurt or injured | ❑ | ❑ | ❑ | ❑ | ❑ |
| Avoids exercise | ❑ | ❑ | ❑ | ❑ | ❑ |
| Needs more medical care | ❑ | ❑ | ❑ | ❑ | ❑ |
| Has trouble taking medication, getting needles or visiting the doctor/dentist | ❑ | ❑ | ❑ | ❑ | ❑ |

## D. Self-concept

| | Never or not at all | Sometimes or somewhat | Often or much | Very often or very much | Not Applicable |
|---|---|---|---|---|---|
| Feel bad about self | ❑ | ❑ | ❑ | ❑ | ❑ |
| Feel you don't have enough fun | ❑ | ❑ | ❑ | ❑ | ❑ |
| Not happy with life | ❑ | ❑ | ❑ | ❑ | ❑ |

## E. Social activities

| | Never or not at all | Sometimes or somewhat | Often or much | Very often or very much | Not Applicable |
|---|---|---|---|---|---|
| Teases or bullies others | ❑ | ❑ | ❑ | ❑ | ❑ |
| Problems getting along with others | ❑ | ❑ | ❑ | ❑ | ❑ |
| Problems participating in after-school/after-work activities (sports, music, clubs) | ❑ | ❑ | ❑ | ❑ | ❑ |
| Problems making new friends | ❑ | ❑ | ❑ | ❑ | ❑ |
| Problems keeping friends | ❑ | ❑ | ❑ | ❑ | ❑ |
| Difficulty with parties (not invited, avoids them, misbehaves) | ❑ | ❑ | ❑ | ❑ | ❑ |

## F. Risky activities

| | Never or not at all | Sometimes or somewhat | Often or much | Very often or very much | Not Applicable |
|---|---|---|---|---|---|
| Easily led by others (peer pressure) | ❑ | ❑ | ❑ | ❑ | ❑ |
| Breaking or damaging things | ❑ | ❑ | ❑ | ❑ | ❑ |
| Doing things that are illegal | ❑ | ❑ | ❑ | ❑ | ❑ |
| Being involved with the police | ❑ | ❑ | ❑ | ❑ | ❑ |
| Smoking cigarettes | ❑ | ❑ | ❑ | ❑ | ❑ |
| Taking illegal drugs | ❑ | ❑ | ❑ | ❑ | ❑ |
| Doing dangerous things | ❑ | ❑ | ❑ | ❑ | ❑ |
| Causes injury to others | ❑ | ❑ | ❑ | ❑ | ❑ |
| Says mean or inappropriate things | ❑ | ❑ | ❑ | ❑ | ❑ |
| Sexually inappropriate behaviour | ❑ | ❑ | ❑ | ❑ | ❑ |

# Appendix 3

## Diagnostic interview for ADHD in adults (DIVA)

Diagnostisch Interview Voor ADHD bij volwassenen

## Introduction

According to the DSM-IV, ascertaining the diagnosis of ADHD in adults involves determining the presence of ADHD symptoms during both childhood and adulthood.

The main requirements for the diagnosis are that the onset of ADHD symptoms occurred during childhood and that this was followed by a lifelong persistence of the characteristic symptoms to the time of the current evaluation.

The symptoms need to be associated with significant clinical or psychosocial impairments that affect the individual in two or more life situations.

Because ADHD in adults is a lifelong condition that starts in childhood, it is necessary to evaluate the symptoms, course and level of associated impairment in childhood, using a retrospective interview for childhood behaviours.

Whenever possible the information should be gathered from the patient and supplemented by information from informants that knew the person as a child (usually parents or close relatives).

## The Diagnostic Interview for ADHD in Adults (DIVA)

The DIVA is based on the DSM-IV criteria and is the first structured Dutch interview for ADHD in adults. The DIVA has been developed by J.J.S. Kooij and M.H. Francken and is the successor of the earlier Semi-Structured Interview for ADHD in adults.

In order to simplify the evaluation of each of the 18 symptom criteria for ADHD, in childhood and adulthood, the interview provides a list of concrete and realistic examples, for both current and retrospective (childhood) behaviour.

The examples are based on the common descriptions provided by adult patients in clinical practice. Examples are also provided of the types of impairments that are commonly associated with the symptoms in five areas of everyday life: work and education; relationships and family life; social contacts; free time and hobbies; self-confidence and self-image.

Whenever possible the DIVA should be completed with adults in the presence of a partner and/or family member, to enable retrospective and collateral information to be ascertained at the same time. The DIVA usually takes around one and a half hours to complete.

The DIVA only asks about the core symptoms of ADHD required to make the DSM-IV diagnosis of ADHD, and does not ask about other co-occurring psychiatric symptoms, syndromes or disorders. However, comorbidity is commonly seen in both children and adults with ADHD, in around 75% of cases. For this reason, it is important to complete a general psychiatric assessment to enquire about commonly co-occurring symptoms, syndromes and disorders. The most common mental health problems that accompany ADHD include anxiety, depression, bipolar disorder, substance abuse disorders and addiction, sleep problems and personality disorders, and all these should be investigated. This is needed to understand the full range of symptoms experienced by the individual with ADHD; and also for the differential diagnosis, to exclude other major psychiatric disorders as the primary cause of 'ADHD symptoms' in adults.

## Instructions for performing the DIVA

The DIVA is divided into three parts that are each applied to both childhood and adulthood:

- The criteria for Attention Deficit (A1)
- The criteria for Hyperactivity-Impulsivity (A2)
- The Age of Onset and Impairment accounted for by ADHD symptoms

Start with the first set of DSM-IV criteria for attention deficit (A1), followed by the second set of criteria for hyperactivity/impulsivity (A2). Ask about each of the 18 criteria in turn. For each item take the following approach:

First ask about adulthood (symptoms present in the last 6-months or more) and then ask about the same symptom in childhood (symptoms between the ages of 5 to 12 years). Read each question fully and ask the person being interviewed whether they recognise this problem and to provide examples. Patients will often give the same

examples as those provided in the DIVA, which can then be ticked off as present. If they do not recognise the symptoms or you are not sure if their response is specific to the item in question, then use the examples, asking about each example in turn. For a problem behaviour or symptom to be scored as present, the problem should occur more frequently or at a more severe level than is usual in an age and IQ matched peer group, or to be closely associated with impairments. Tick off each of the examples that are described by the patient. If alternative examples that fit the criteria are given, make a note of these under "other". To score an item as present it is not necessary to score all the examples as present, rather the aim is for the investigator to obtain a clear picture of the presence or absence of each criterion. For each criterion, ask whether the partner or family member agrees with this or can give further examples of problems that relate to each item. As a rule, the partner would report on adulthood and the family member (usually parent or older relative) on childhood. The clinician has to use clinical judgement in order to determine the most accurate answer. If the answers conflict with one another, the rule of thumb is that the patient is usually the best informant.

The information received from the partner and family is mainly intended to supplement the information obtained from the patient and to obtain an accurate account of both current and childhood behaviour; the informant information is particularly useful for childhood since many patients have difficulty recalling their own behaviour retrospectively. Many people have a good recall for behaviour from around the age of 10-12 years of age, but have difficulty for the pre-school years.

For each criterion, the researcher should make a decision about the presence or absence in both stages of life, taking into account the information from all the parties involved. If collateral information cannot be obtained, the diagnosis should be based on the patient's recall alone. If school reports are available, these can help to give an idea of the symptoms that were noticed in the classroom during childhood and can be used to support the diagnosis. Symptoms are considered to be clinically relevant if they occurred to a more severe degree and/or more frequently than in the peer group or if they were impairing to the individual.

## Age of onset and impairment

The third section on Age of Onset and Impairment accounted for by the symptoms is an essential part of the diagnostic criteria. Find out whether the patient has always had the symptoms and, if so, whether any symptoms were present before 7-years of age. If the symptoms did not commence till later in life, record the age of onset.

Then ask about the examples for the different situations in which impairment can occur, first in adulthood then in childhood. Place a tick next to the examples that the patient recognises and indicate whether the impairment is reported for two or more domains of functioning. For the disorder to be present, it should cause impairment in at least two situations, such as work and education; relationships and family life; social contacts; free time and hobbies; self-confidence and self-image, and be at least moderately impairing.

## Summary of symptoms

In the Summary of Symptoms of Attention Deficit (A) and Hyperactivity-Impulsivity (HI), indicate which of the 18 symptom criteria are present in both stages of life; and sum the number of criteria for inattention and hyperactivity/impulsivity separately.

Finally, indicate on the Score Form whether six or more criteria are scored for each of the symptom domains of Attention Deficit (A) and Hyperactivity-Impulsivity (HI). For each domain, indicate whether there was evidence of a lifelong persistent course for the symptoms, whether the symptoms were associated with impairment, whether impairment occurred in at least two situations, and whether the symptoms might be better explained by another psychiatric disorder. Indicate the degree to which the collateral information, and if applicable school reports, support the diagnosis. Finally, conclude whether the diagnosis of ADHD can be made and which subtype (with DSM-IV code) applies.

## Explanation to be given beforehand to the patient

This interview will be used to ask about the presence of ADHD symptoms that you experienced during your childhood and adulthood. The questions are based on the official criteria for ADHD in the DSM-IV. For each question I will ask you whether you recognise the problem. To help you during the interview I will provide some examples of each symptom, that describe the way that children and adults often experience difficulties related to

each of the symptoms of ADHD. First of all, you will be asked the questions, then your partner and family members (if present) will be asked the same questions. Your partner will most likely have known you only since adulthood and will be asked questions about the period of your life that he or she knew you for; your family will have a better idea of your behaviour during childhood. Both stages of your life need to be investigated in order to be able to establish the diagnosis of ADHD.

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| |
|---|
| Name of the patient: |
| Date of birth: |

Sex:

| | |
|---|---|
| M | F |

| |
|---|
| Date of interview: |
| Name of researcher: |
| Patient number: |

## Part 1: Symptoms of attention-deficit (DSM-IV criterion A1)

**Instructions:** the symptoms in adulthood have to have been present for at least 6 months. The symptoms in childhood relate to the age of 5-12 years. For a symptom to be ascribed to ADHD it should have a chronic trait-like course and should not be episodic.

A1 Do you often fail to give close attention to detail, or do you make careless mistakes in your work or during other activities? And how was that during childhood?

| Examples during adulthood: | Examples during childhood: |
|---|---|
| ◯ Makes careless mistakes | ◯ Careless mistakes in schoolwork |
| ◯ Works slowly to avoid mistakes | ◯ Mistakes made by not reading questions properly |
| ◯ Does not read instructions carefully | ◯ Leaves questions unanswered by not reading them properly |
| ◯ Difficulty working in a detailed way | ◯ Leaves the reverse side of a test unanswered |
| ◯ Too much time needed to complete detailed tasks | ◯ Others comment about careless work |
| ◯ Gets easily bogged down by details | ◯ Not checking the answers in homework |
| ◯ Works too quickly and therefore makes mistakes | ◯ Too much time needed to complete detailed tasks |
| ◯ Other: | ◯ Other: |
| Symptom present: ❑ Yes / ❑ No | Symptom present: ❑ Yes / ❑ No |

A2 Do you often find it difficult to sustain your attention on tasks? And how was that during childhood?

| Examples during adulthood: | Examples during childhood: |
|---|---|
| ◯ Not able to keep attention on tasks for long*<br>◯ Quickly distracted by own thoughts or associations<br>◯ Finds it difficult to watch a film through to the end, or to read a book*<br>◯ Quickly becomes bored with things*<br>◯ Asks questions about subjects that have already been discussed<br>◯ Other:<br>*Unless the subject is found to be really interesting (e.g. computer or hobby)<br>Symptom present: ❑ Yes / ❑ No | ◯ Difficulty keeping attention on schoolwork<br>◯ Difficulty keeping attention on play*<br>◯ Easily distracted<br>◯ Difficulty concentrating*<br>◯ Needing structure to avoid becoming distracted<br>◯ Quickly becoming bored of activities*<br>◯ Other:<br>*Unless the subject is found to be really interesting (e.g. computer or hobby)<br>Symptom present: ❑ Yes / ❑ No |

A3 Does it often seem as though you are not listening when you are spoken to directly? And how was that during childhood?

| Examples during adulthood: | Examples during childhood: |
|---|---|
| ◯ Dreamy or preoccupied<br>◯ Difficulty concentrating on a conversation<br>◯ Afterwards, not knowing what a conversation was about<br>◯ Often changing the subject of the conversation<br>◯ Others saying that your thoughts are somewhere else<br>◯ Other:<br>Symptom present: ❑ Yes / ❑ No | ◯ Not knowing what parents/teachers have said<br>◯ Dreamy or preoccupied<br>◯ Only listening during eye contact or when a voice is raised<br>◯ Often having to be addressed again<br>◯ Questions having to be repeated<br>◯ Other:<br>Symptom present: ❑ Yes / ❑ No |

A4 Do you often fail to follow through on instructions and do you often fail to finish jobs or fail to meet obligations at work? And how was that during childhood (when doing schoolwork as opposed to when at work)?

| Examples during adulthood: | Examples during childhood: |
|---|---|
| ◯ Does things that are muddled up together without completing them<br>◯ Difficulty completing tasks once the novelty has worn off<br>◯ Needing a time limit to complete tasks<br>◯ Difficulty completing administrative tasks<br>◯ Difficulty following instructions from a manual<br>◯ Other:<br>Symptom present: ❑ Yes / ❑ No | ◯ Difficulty following instructions<br>◯ Difficulty with instructions involving more than one step<br>◯ Not completing things<br>◯ Not completing homework or handing it in<br>◯ Needing a lot of structure in order to complete tasks<br>◯ Other:<br>Symptom present: ❑ Yes / ❑ No |

A5 Do you often find it difficult to organise tasks and activities? And how was that during childhood?

| Examples during adulthood: | Examples during childhood: |
|---|---|
| ◯ Difficulty with planning activities of daily life<br>◯ House and/or workplace are disorganised<br>◯ Planning too many tasks or non-efficient planning<br>◯ Regularly booking things to take place at the same time (double-booking)<br>◯ Arriving late<br>◯ Not able to use an agenda or diary consistently<br>◯ Inflexible because of the need to keep to schedules<br>◯ Poor sense of time<br>◯ Creating schedules, but not using them<br>◯ Needing other people to structure things<br>◯ Other:<br>Symptom present: ❑ Yes / ❑ No | ◯ Difficulty being ready on time<br>◯ Messy room or desk<br>◯ Difficulty playing alone<br>◯ Difficulty planning tasks or homework<br>◯ Doing things in a muddled way<br>◯ Arriving late<br>◯ Poor sense of time<br>◯ Difficulty keeping himself/herself entertained<br>◯ Other:<br>Symptom present: ❑ Yes / ❑ No |

A6 Do you often avoid (or do you have an aversion to, or are you unwilling to do) tasks which require sustained mental effort? And how was that during childhood?

| Examples during adulthood: | Examples during childhood: |
|---|---|
| ◯ Do the easiest or nicest things first of all<br>◯ Often postpone boring or difficult tasks<br>◯ Postpone tasks so that deadlines are missed<br>◯ Avoid monotonous work, such as administration<br>◯ Do not like reading due to mental effort<br>◯ Avoidance of tasks that require a lot of concentration<br>◯ Other:<br>Symptom present: ❑ Yes / ❑ No | ◯ Avoidance of homework or has an aversion to this<br>◯ Reads few books or does not feel like reading due to mental effort<br>◯ Avoidance of tasks that require a lot of concentration<br>◯ Aversion to school subjects that require a lot of concentration<br>◯ Often postpones boring or difficult tasks.<br>◯ Other:<br>Symptom present: ❑ Yes / ❑ No |

A7 Do you often lose things that are needed for tasks or activities? And how was that during childhood?

| Examples during adulthood: | Examples during childhood: |
|---|---|
| ◯ Mislays wallet, keys, or agenda<br>◯ Often leaves things behind<br>◯ Loses papers for work<br>◯ Loses a lot of time searching for things<br>◯ Gets in a panic if other people move things around<br>◯ Stores things away in the wrong place<br>◯ Loses notes, lists or telephone numbers<br>◯ Other:<br>Symptom present: ❑ Yes / ❑ No | ◯ Loses diaries, pens, gym kit or other items<br>◯ Mislays toys, clothing, or homework<br>◯ Spends a lot of time searching for things<br>◯ Gets in a panic if other people move things around<br>◯ Comments from parents and/or teacher about things being lost<br>◯ Other:<br>Symptom present: ❑ Yes / ❑ No |

A8 Are you often easily distracted by external stimuli? And how was that during childhood?

| Examples during adulthood: | Examples during childhood: |
|---|---|
| ◯ Difficulty shutting off from external stimuli<br>◯ After being distracted, difficult to pick up the thread again<br>◯ Easily distracted by noises or events<br>◯ Easily distracted by the conversations of others<br>◯ Difficulty in filtering and/or selecting information<br>◯ Other:<br>Symptom present: ❑ Yes / ❑ No | ◯ In the classroom, often looking outside<br>◯ Easily distracted by noises or events<br>◯ After being distracted, has difficulty picking up the thread again<br>◯ Other:<br>Symptom present: ❑ Yes / ❑ No |

A9 Are you often forgetful during daily activities? And how was that during childhood?

| Examples during adulthood: | Examples during childhood: |
|---|---|
| ◯ Forgets appointments or other obligations<br>◯ Forgets keys, agenda etc.<br>◯ Needs frequent reminders for appointments<br>◯ Returning home to fetch forgotten things<br>◯ Rigid use of lists to make sure things aren't forgotten<br>◯ Forgets to keep or look at daily agenda<br>◯ Other:<br>Symptom present: ❑ Yes / ❑ No | ◯ Forgets appointments or instructions<br>◯ Has to be frequently reminded of things<br>◯ Half-way through a task, forgetting what has to be done<br>◯ Forgets to take things to school<br>◯ Leaving things behind at school or at friends' houses<br>◯ Other:<br>Symptom present: ❑ Yes / ❑ No |

**Supplement criterion A**

Adulthood:
Do you have more of these symptoms of attention deficit than other people, or do you experience these more frequently than other people of your age?
❑ Yes / ❑ No

Childhood:
Did you have more of these symptoms of attention deficit than other children of your age, or did you experience these more frequently than other children of your age?
❑ Yes / ❑ No

**Part 2: Symptoms of hyperactivity-impulsivity (DSM-IV criterion A2)**

**Instructions:** the symptoms in adulthood have to have been present for at least 6 months. The symptoms in childhood relate to the age of 5-12 years. For a symptom to be ascribed to ADHD it should have a chronic trait-like course and should not be episodic.

H/I 1 Do you often move your hands or feet in a restless manner, or do you often fidget in your chair? And how was that during childhood?

| Examples during adulthood: | Examples during childhood: |
|---|---|
| ◯ Difficulty sitting still<br>◯ Fidgets with the legs<br>◯ Tapping with a pen or playing with something<br>◯ Fiddling with hair or biting nails<br>◯ Able to control restlessness, but feels stressed as a result<br>◯ Other:<br>Symptom present: ❑ Yes / ❑ No | ◯ Parents often said "sit still" or similar<br>◯ Fidgets with the legs<br>◯ Tapping with a pen or playing with something<br>◯ Fiddling with hair or biting nails<br>◯ Unable to remain seated in a chair in a relaxed manner<br>◯ Able to control restlessness, but feels stressed as a result<br>◯ Other:<br>Symptom present: ❑ Yes / ❑ No |

H/I 2 Do you often stand up in situations where the expectation is that you should remain in your seat? And how was that during childhood?

| Examples during adulthood: | Examples during childhood: |
|---|---|
| ◯ Avoids symposiums, lectures, church etc.<br>◯ Prefers to walk around rather than sit<br>◯ Never sits still for long, always moving around<br>◯ Stressed owing to the difficulty of sitting still<br>◯ Makes excuses in order to be able to walk around<br>◯ Other:<br>Symptom present: ❑ Yes / ❑ No | ◯ Often stands up while eating or in the classroom<br>◯ Finds it very difficult to stay seated at school or during meals<br>◯ Being told to remain seated<br>◯ Making excuses in order to walk around<br>◯ Other:<br>Symptom present: ❑ Yes / ❑ No |

H/I 3 Do you often feel restless? And how was that during childhood?

| Examples during adulthood: | Examples during childhood: |
|---|---|
| ◯ Feeling restless or agitated inside<br>◯ Constantly having the feeling that you have to be doing something<br>◯ Finding it hard to relax<br>◯ Other:<br>Symptom present: ❑ Yes / ❑ No | ◯ Always running around<br>◯ Climbing on furniture, or jumping on the sofa<br>◯ Climbing in trees<br>◯ Feeling restless inside<br>◯ Other:<br>Symptom present: ❑ Yes / ❑ No |

H/I 4 Do you often find it difficult to engage in leisure activities quietly? And how was that during childhood?

| Examples during adulthood: | Examples during childhood: |
|---|---|
| ◯ Talks during activities when this is not appropriate<br>◯ Becoming quickly too cocky in public<br>◯ Being loud in all kinds of situations<br>◯ Difficulty doing activities quietly<br>◯ Difficulty in speaking softly<br>◯ Other:<br>Symptom present: ❑ Yes / ❑ No | ◯ Being loud-spoken during play or in the classroom<br>◯ Unable to watch TV or films quietly<br>◯ Asked to be quieter or calm down<br>◯ Becoming quickly too cocky in public<br>◯ Other:<br>Symptom present: ❑ Yes / ❑ No |

H/I 5 Are you often on the go or do you often act as if “driven by a motor”? And how was that during childhood?

| Examples during adulthood: | Examples during childhood: |
|---|---|
| ◯ Always busy doing something<br>◯ Has too much energy, always on the move<br>◯ Stepping over own boundaries<br>◯ Finds it difficult to let things go, excessively driven<br>◯ Other:<br>Symptom present: ❑ Yes / ❑ No | ◯ Constantly busy<br>◯ Excessively active at school and at home<br>◯ Has lots of energy<br>◯ Always on the go, excessively driven<br>◯ Other:<br>Symptom present: ❑ Yes / ❑ No |

H/I 6 Do you often talk excessively? And how was that during childhood?

| Examples during adulthood: | Examples during childhood: |
|---|---|
| ◯ So busy talking that other people find it tiring<br>◯ Known to be an incessant talker<br>◯ Finds it difficult to stop talking<br>◯ Tendency to talk too much<br>◯ Not giving others room to interject during a conversation<br>◯ Needing a lot of words to say something<br>◯ Other:<br><br>Symptom present: ❑ Yes / ❑ No | ◯ Known as a chatterbox<br>◯ Teachers and parents often ask you to be quiet<br>◯ Comments in school reports about talking too much<br>◯ Being punished for talking too much<br>◯ Keeping others from doing schoolwork by talking too much<br>◯ Not giving others room during a conversation<br>◯ Other:<br>Symptom present: ❑ Yes / ❑ No |

H/I 7 Do you often give the answer before questions have been completed? And how was that during

| Examples during adulthood: | Examples during childhood: |
|---|---|
| ◯ Being a blabbermouth, saying what you think<br>◯ Saying things without thinking first<br>◯ Giving people answers before they have finished speaking<br>◯ Completing other people's words<br>◯ Being tactless<br>◯ Other:<br>Symptom present: ❑ Yes / ❑ No | ◯ Being a blabbermouth, saying things without thinking first<br>◯ Wants to be the first to answer questions at school<br>◯ Blurts out an answer even if it is wrong<br>◯ Interrupts others before sentences are finished<br>◯ Coming across as being tactless<br>◯ Other:<br>Symptom present: ❑ Yes / ❑ No |

H/I 8 Do you often find it difficult to await your turn? And how was that during childhood?

| Examples during adulthood: | Examples during childhood: |
|---|---|
| ◯ Difficulty waiting in a queue, jumping the queue<br>◯ Difficulty in patiently waiting in the traffic/traffic jams<br>◯ Difficulty waiting your turn during conversations<br>◯ Being impatient<br>◯ Quickly starting relationships/jobs, or ending/leaving these because of impatience<br>◯ Other:<br>Symptom present: ❑ Yes / ❑ No | ◯ Difficulty waiting turn in group activities<br>◯ Difficulty waiting turn in the classroom<br>◯ Always being the first to talk or act<br>◯ Becomes quickly impatient<br>◯ Crosses the road without looking<br>◯ Other:<br><br>Symptom present: ❑ Yes / ❑ No |

H/I 9 Do you often interrupt the activities of others, or intrude on others? And how was that during childhood?

| Examples during adulthood: | Examples during childhood: |
|---|---|
| ◯ Being quick to interfere with others<br>◯ Interrupts others<br>◯ Disturbs other people's activities without being asked<br>◯ Comments from others about interference<br>◯ Difficulty respecting the boundaries of others<br>◯ Having an opinion about everything and immediately expressing this<br>◯ Other:<br>Symptom present: ❑ Yes / ❑ No | ◯ Impinges on the games of others<br>◯ Interrupts the conversations of others<br>◯ Reacts to everything<br>◯ Unable to wait<br>◯ Other:<br><br>Symptom present: ❑ Yes / ❑ No |

## Supplement criterion A

**Adulthood:**

Do you have more of these symptoms of hyperactivity/impulsivity than other people, or do you experience these more frequently than other people?

❑ Yes / ❑ No

**Childhood:**

Did you have more of these symptoms of hyperactivity/impulsivity than other children of your age, or did you experience these more frequently than other children of your age?

❑ Yes / ❑ No

## Part 3: Impairment on account of the symptoms (DSM-IV criteria B, C and D)

### Criterion B

Have you always had these symptoms of attention deficit and/or hyperactivity/impulsivity?

❑ Yes (a number of symptoms were present prior to the 7th year of age).

❑ No

If no is answered above, starting as from _____ year of age.

### Criterion C

In which areas do you have / have you had problems with these symptoms?

**Adulthood**

**Work/education**

◯ Did not complete education/training needed for work
◯ Work below level of education
◯ Tire quickly of a workplace
◯ Pattern of many short-lasting jobs
◯ Difficulty with administrative work/planning
◯ Not achieving promotions
◯ Under-performing at work
◯ Left work following arguments or dismissal
◯ Sickness benefits/disability benefit as a result of symptoms
◯ Limited impairment through compensation of high IQ
◯ Limited impairment through compensation of external structure
◯ Other:

**Relationship and/or family**

◯ Tire quickly of relationships
◯ Impulsively commencing/ending relationships
◯ Unequal partner relationship owing to symptoms
◯ Relationship problems, lots of arguments, lack of intimacy
◯ Divorced owing to symptoms
◯ Problems with sexuality as a result of symptoms
◯ Problems with upbringing as a result of symptoms
◯ Difficulty with housekeeping and/or administration
◯ Financial problems or gambling
◯ Not daring to start a relationship
◯ Other:

**Childhood and adolescence**

**Education**

◯ Lower educational level than expected based on IQ
◯ Staying back (repeating classes) as a result of concentration problems
◯ Education not completed / rejected from school
◯ Took much longer to complete education than usual
◯ Achieved education suited to IQ with a lot of effort
◯ Difficulty doing homework
◯ Followed special education on account of symptoms
◯ Comments from teachers about behaviour or concentration
◯ Limited impairment through compensation of high IQ
◯ Limited impairment through compensation of external structure
◯ Other:

**Family**

◯ Frequent arguments with brothers or sisters
◯ Frequent punishment or hiding
◯ Little contact with family on account of conflicts
◯ Required structure from parents for a longer period than would normally be the case
◯ Other:

| Adulthood | Childhood and adolescence |
|---|---|
| **Social contacts**<br>◯ Tire quickly of social contacts<br>◯ Difficulty maintaining social contacts<br>◯ Conflicts as a result of communication problems<br>◯ Difficulty initiating social contacts<br>◯ Low self-assertiveness as a result of negative experiences<br>◯ Not being attentive (i.e. forget to send a card/<br>◯ empathising/phoning, etc)<br>◯ Other: | **Social contacts**<br>◯ Difficulty maintaining social contacts<br>◯ Conflicts as a result of communication problems<br>◯ Difficulty entering into social contacts<br>◯ Low self-assertiveness as a result of negative experiences<br>◯ Few friends<br>◯ Being teased<br>◯ Shut out by, or not being allowed, to do things with a group<br>◯ Being a bully<br>◯ Other: |
| **Free time / hobby**<br>◯ Unable to relax properly during free time<br>◯ Having to play lots of sports in order to relax<br>◯ Injuries as a result of excessive sport<br>◯ Unable to finish a book or watch a film all the way through<br>◯ Being continually busy and therefore becoming overtired<br>◯ Tire quickly of hobbies<br>◯ Accidents/loss of driving licence as a result of reckless driving behaviour<br>◯ Sensation seeking and/or taking too many risks<br>◯ Contact with the police/the courts<br>◯ Binge eating<br>◯ Other: | **Free time/hobby**<br>◯ Unable to relax properly during free time<br>◯ Having to play lots of sport to be able to relax<br>◯ Injuries as a result of excessive sport<br>◯ Unable to finish a book or watch a film all the way through<br>◯ Being continually busy and therefore becoming overtired<br>◯ Tired quickly of hobbies<br>◯ Sensation seeking and/or taking too many risks<br>◯ Contact with the police/courts<br>◯ Increased number of accidents<br>◯ Other: |
| **Self-confidence / self-image**<br>◯ Uncertainty through negative comments of others<br>◯ Negative self-image due to experiences of failure<br>◯ Fear of failure in terms of starting new things<br>◯ Excessive intense reaction to criticism<br>◯ Perfectionism<br>◯ Distressed by the symptoms of ADHD<br>◯ Other: | **Self-confidence / self-image**<br>◯ Uncertainty through negative comments of others<br>◯ Negative self-image due to experiences of failure<br>◯ Fear of failure in terms of starting new things<br>◯ Excessive intense reaction to criticism<br>◯ Perfectionism<br>◯ Other: |

| Summary of symptoms A and H/I | | | |
|---|---|---|---|
| | Indicate which criteria were scored in parts 1 and 2 and add up | | |
| Criterion DSM-IV TR | Symptom | Present during adulthood | Present during childhood |
| A1a | **A1.** Often fails to pay close attention to details, or makes careless mistakes in schoolwork, work or during other activities | | |
| A1b | **A2.** Often has difficulty sustaining attention in tasks or play | | |
| A1c | **A3.** Often does not seem to listen when spoken to directly | | |
| A1d | **A4.** Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace | | |
| A1e | **A5.** Often has difficulty organizing tasks and activities | | |
| A1f | **A6.** Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as school of homework) | | |
| A1g | **A7.** Often loses things necessary for tasks or activities | | |
| A1h | **A8.** Often easily distracted by extraneous stimuli | | |
| A1i | **A9.** Often forgetful in daily activities | | |
| | Total number of criteria Attention Deficit | / 9 | / 9 |
| A2a | **H/I 1.** Often fidgets with hands or feet or squirms in seat | | |
| A2b | **H/I 2.** Often leaves seat in classroom or in other situations in which remaining seated is expected | | |
| A2c | **H/I 3.** Often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults this may be limited to subjective feelings of restlessness) | | |
| A2d | **H/I 4.** Often has difficulty playing or engaging in leisure activities quietly | | |
| A2e | **H/I 5.** Is often on the go or often acts as if 'driven by a motor' | | |
| A2f | **H/I 6.** Often talks excessively | | |
| A2g | **H/I 7.** Often blurts out answers before questions have been completed | | |
| A2h | **H/I 8.** Often has difficulty awaiting turn | | |
| A2i | **H/I 9.** Often interrupts or intrudes on others | | |
| | Total number of criteria Hyperactivity/Impulsivity | / 9 | / 9 |

| Score form | | |
|---|---|---|
| DSM-IV criterion A | Childhood<br>Is the number of A characteristics ≥ 6? | ❑ Yes / ❑ No |
| | Is the number of H/I characteristics ≥ 6? | ❑ Yes / ❑ No |
| | Adulthood*<br>Is the number of A characteristics ≥ 6? | ❑ Yes / ❑ No |
| | Is the number of H/I characteristics ≥ 6? | ❑ Yes / ❑ No |
| DSM-IV criterion B | Are there signs of a lifelong pattern of symptoms and limitations? | ❑ Yes / ❑ No |
| DSM-IV criterion C and D | The symptoms and the impairment are expressed in at least two domains of functioning | |
| | Adulthood | ❑ Yes / ❑ No |
| | Childhood | ❑ Yes / ❑ No |
| DSM-IV criterion E | The symptoms cannot be (better) explained by the presence of another psychiatric disorder | ❑ No<br>Yes, by _____ |
| | Diagnosis ADHD** | ❑ No<br>Yes, subtype<br>❑ 314.01 Combined type<br>❑ 314.00 Predominantly inattentive type<br>❑ 314.01 Predominantly hyperactive-impulsive type |

* Research has indicated that at adult age, four or more characteristics of attention problems and/or hyperactivity-impulsivity are sufficient for the diagnosis of ADHD to be made. Kooij e.a., Internal and external validity of Attention-Deficit Hyperactivity Disorder in a population-based sample of adults. Psychological Medicine 2005; 35(6):817-827. Barkley RA: Age dependent decline in ADHD: True recovery or statistical illusion? The ADHD Report 1997; 5:1-5.

** If the established sub-types differ in childhood and adulthood, the current adult sub-type prevails for the diagnosis.

# Appendix 4

## Physical characteristics observed during semi-structured interview

Appendix 4 Physical characteristics observed during interview

Participant Number: _____

Date: _____

- ○ Questions repeated multiple times
- ○ Explaining meaning of questions multiple times
- ○ Fidgeting
- ○ Wavering focus (e.g. looking elsewhere)
- ○ Wandering thoughts (i.e. mentioning unrelated topics)
- ○ Indecisiveness (i.e. can't choose one of the options)
- ○ Apparent boredom
- ○ Inappropriate comments
- ○ Rambling
- ○ Interjects often
- ○ Other:

_____

_____

_____

# Appendix 5

DNA extraction from human saliva

## Modified extraction method

Important to wear gloves at all times and work in the Bio-Safety Cabinet Class II up to step 9 where you add the isopropanol. Before you begin make sure that you booked the necessary laboratory for your extraction. Have all the chemicals ready for use in the Bio-Safety Cabinet Class II. If you are busy with step 1 to 4 make sure to heat up the water bath to 53° C before you begin with the extraction steps.

1. Add 1 ml saliva to 1 ml lysis buffer (1 ml of saliva does not include bubbles).
2. Add 20 µl Proteinase K (20mg/ml).
3. Add 150 µl of 10% SDS.
4. Incubate overnight at 53° C in a water bath.
5. Add 400 µl of 5M NaCl.
6. Incubate on ice for 10 min.
7. Centrifuge for 20min at 4500 rpm.
8. Distribute 1 ml into 1.7 ml Eppendorf tubes.
9. Add 700 µl of isopropanol.
10. Place on the orbital shaker for 10 min.
11. Centrifuge for 15 min at 13000 rpm.
12. Discard the supernatant.
13. Wash pellet with 500 µl of 70% ethanol on the orbital shaker for 30 min.
14. Discard the supernatant.
15. Wash pellet with 500 µl of 70% ethanol on the orbital shaker for 30 min.
16. Leave the pellet to dry at room temperature for 3 hours or overnight.
17. Dissolve the pellet by adding 100 µl of nuclease free water (place in heating block for one hour at 50° C) and quantify your DNA by using the Nanodrop spectrophotometer.

# Appendix 6

PCR information for gene regions

## *5-HTT* SNP (Rs25531)
### PCR Mix

| | Proposed | Modified |
|---|---|---|
| DreamTaq Master Mix | 10 µl | 6 µl |
| Forward Primer | 1.5 µl (10µM) | 1.5 µl |
| Reverse Primer | 1.5 µl (10µM) | 1.5 µl |
| Template DNA | 4 µl (50ng/µl) | 4 µl |
| Water | 3 µl | 7 µl |
| Total Volume | 20 µl | 20 µl |

### PCR Regime

| | Proposed | | | Modified | | |
|---|---|---|---|---|---|---|
| PCR step | Temp | Time | Cycles | Temp | Time | Cycles |
| Initial denaturation | 94˚C | 5 mins | 1 | 95˚C | 2 mins | 1 |
| Denaturation | 94˚C | 30 sec | 35 | 98˚C | 20 sec | 35 |
| Annealing | 60˚C | 40 sec | | 65˚C | 15 sec | |
| Extension | 72˚C | 50 sec | | 72˚C | 15 sec | |
| Final Extension | 72˚C | 10 min | 1 | 72˚C | 5 min | 1 |

(Peyrot *et al.*, 2012; Wendland, Martin, Kruse, Lesch, & Murphy, 2006)

### Restriction Enzyme Digestion: MspI

| | Proposed |
|---|---|
| Water | 18 µl |
| Tango buffer | 4 µl |
| Restriction Enzyme: MSP I | 4 µl |
| PCR product | 10 µl |
| Total Volume | 36 µl |
| Incubation temperature | 37˚C |

| | |
|---|---|
| A allele | 512 bp |
| G allele | 403 bp + 109 bp |

## *HTR2A* (Rs6311)
### PCR Mix

| | Proposed |
|---|---|
| DreamTaq Master Mix | 10 µl |
| Forward Primer | 1.5 µl (10µM) |
| Reverse Primer | 1.5 µl (10µM) |
| Template DNA | 4 µl (50ng/µl) |
| Water | 3 µl |
| Total Volume | 20 µl |

PCR Regime

| PCR step | Temp | Time | Cycles |
|---|---|---|---|
| Initial denaturation | 94˚C | 5 mins | 1 |
| Denaturation | 94˚C | 20 sec | 30 |
| Annealing | 60˚C | 60 sec | |
| Extension | 72˚C | 30 sec | |
| Final Extension | 72˚C | 10 min | 1 |

(Nakamura, Ueno, & Tanabe, 2000; Noskova *et al.*, 2009)

Restriction Enzyme Digestion: MspI

| | Proposed |
|---|---|
| Water | 18 µl |
| Tango buffer | 4 µl |
| Restriction Enzyme: MSP I | 4 µl |
| PCR product | 10 µl |
| Total Volume | 36 µl |
| Incubation temperature | 37˚C |

| | |
|---|---|
| A allele | 468 bp |
| G allele | 224 bp + 244 bp |

*HTR1B* (Rs6297)
PCR Mix

| PCR Mix | 1 |
|---|---|
| DreamTaq Master Mix | 10 µl |
| Forward Primer | 1.5 µl (10µM) |
| Reverse Primer | 1.5 µl (10µM) |
| Template DNA | 4 µl (50ng/µl) |
| Water | 3 µl |
| Total Volume | 20 µl |

PCR Regime

| PCR Step | Temp | Time | Cycles |
|---|---|---|---|
| Initial denaturation | 94˚C | 5 mins | 1 |
| Denaturation | 94˚C | 20 sec | 31 |
| Annealing | 61˚C | 45 sec | |
| Extension | 72˚C | 30 sec | |
| Final Extension | 72˚C | 10 min | 1 |

(Cao, LaRocque, & Li, 2013; Hasegawa, Higuchi, Matsushita, & Miyaoka, 2002; Noskova *et al.*, 2009)

## Restriction Enzyme Digestion: HincII

| | Proposed |
|---|---|
| Water | 18 µl |
| Tango buffer | 2 µl |
| Restriction Enzyme: HincII | 2 µl |
| PCR product | 10 µl |
| Total Volume | 32 µl |
| Incubation temperature | 37˚C |

| | |
|---|---|
| G allele | 452 bp + 96 bp |
| C allele | 142 bp + 310 bp + 96 bp |

## *5-HTT*LPR
## PCR Mix

| PCR Mix | 1 |
|---|---|
| Kapa Taq Master Mix | 10 µl |
| Forward Primer | 0.5 µl (10µM) |
| Reverse Primer | 0.5 µl (10µM) |
| Template DNA | 4 µl (50ng/µl) |
| Water | 4.2 µl |
| DMSO | 0.8 µl |
| Total Volume | 20 µl |

## PCR Regime

| PCR Step | Temp | Time | Cycles |
|---|---|---|---|
| Initial denaturation | 95˚C | 7 mins | 1 |
| Denaturation | 98˚C | 30 sec | 3 |
| Annealing | 63˚C | 30 sec | |
| Extension | 72˚C | 1 min | |
| Denaturation | 98˚C | 30 sec | 25 |
| Annealing | 61˚C | 30 sec | |
| Extension | 72˚C | 1 min | |
| Final Extension | 72˚C | 10 min | 1 |

(Heils *et al.*, 1996; Malan, 2013; Nakamura *et al.*, 2000)

| | |
|---|---|
| S allele | 484 bp |
| L allele | 528 bp |

# Appendix 7

## Chapter 3 outputs

## Correlations

| | | Medical probs corr | Medical_problems | Psychological_problems | Psychological_problems_corr | Developmental_problems | Developmental_probs_corr | Learning_Disorder | Learning_disorder_corr | Smoker | Smoker_corr | Hypoxia_corr | Poor_diet_corr | Poor_sleep | Poor_sleep_corr | WFIRS_RiskyAct_Imp | RiskyAct_Impairment | WFIRS_SocialAct_Imp | SocialAct_Impairment | WFIRS_SelfConcept_Imp | SelfConcept_Impairment | WFIRS_LifeSkills_Imp | Life_Skills_Impairment | WFIRS_SchoolWork_Imp | Work_Impairment | WFIRS_Family_Imp |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Medical_problems | r | .551 | | | | | | | | | | | | | | | | | | | | | | | | |
| | Sig | .000 | | | | | | | | | | | | | | | | | | | | | | | | |
| | n | 53 | | | | | | | | | | | | | | | | | | | | | | | | |
| Psychological_problems | r | .440 | .373 | | | | | | | | | | | | | | | | | | | | | | | |
| | Sig | .001 | .003 | | | | | | | | | | | | | | | | | | | | | | | |
| | n | 53 | 63 | | | | | | | | | | | | | | | | | | | | | | | |
| Psychological_problems_corr | r | .608 | .332 | .551 | | | | | | | | | | | | | | | | | | | | | | |
| | Sig | .000 | .015 | .000 | | | | | | | | | | | | | | | | | | | | | | |
| | n | 53 | 53 | 53 | | | | | | | | | | | | | | | | | | | | | | |
| Developmental_problems | r | .532 | .279 | .295 | .354 | | | | | | | | | | | | | | | | | | | | | |
| | Sig | .000 | .043 | .032 | .009 | | | | | | | | | | | | | | | | | | | | | |
| | n | 53 | 53 | 53 | 53 | | | | | | | | | | | | | | | | | | | | | |
| Developmental_probs_corr | r | .561 | .390 | .390 | .410 | .840 | | | | | | | | | | | | | | | | | | | | |
| | Sig | .000 | .004 | .004 | .002 | .000 | | | | | | | | | | | | | | | | | | | | |
| | n | 53 | 53 | 53 | 53 | 53 | | | | | | | | | | | | | | | | | | | | |
| Learning_Disorder | r | .551 | .319 | .121 | .413 | .230 | .370 | | | | | | | | | | | | | | | | | | | |
| | Sig | .000 | .020 | .388 | .002 | .098 | .006 | | | | | | | | | | | | | | | | | | | |
| | n | 53 | 53 | 53 | 53 | 53 | 53 | | | | | | | | | | | | | | | | | | | |
| Learning_disorder_corr | r | .623 | .332 | .199 | .505 | .304 | .505 | .887 | | | | | | | | | | | | | | | | | | |
| | Sig | .000 | .015 | .154 | .000 | .027 | .000 | .000 | | | | | | | | | | | | | | | | | | |
| | n | 53 | 53 | 53 | 53 | 53 | 53 | 53 | | | | | | | | | | | | | | | | | | |
| Smoker | r | .502 | .176 | .522 | .362 | .404 | .442 | .172 | .249 | | | | | | | | | | | | | | | | | |
| | Sig | .000 | .207 | .000 | .008 | .003 | .001 | .218 | .073 | | | | | | | | | | | | | | | | | |
| | n | 53 | 53 | 53 | 53 | 53 | 53 | 53 | 53 | | | | | | | | | | | | | | | | | |
| Smoker_corr | r | .601 | .216 | .484 | .432 | .392 | .421 | .201 | .246 | .919 | | | | | | | | | | | | | | | | |
| | Sig | .000 | .121 | .000 | .001 | .004 | .002 | .148 | .075 | .000 | | | | | | | | | | | | | | | | |
| | n | 53 | 53 | 53 | 53 | 53 | 53 | 53 | 53 | 53 | | | | | | | | | | | | | | | | |
| Hypoxia_corr | r | .637 | .425 | .296 | .314 | .363 | .402 | .430 | .364 | .420 | .496 | | | | | | | | | | | | | | | |

| | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Sig | .000 | .001 | .032 | .022 | .008 | .003 | .001 | .007 | .002 | .000 | | | | | | | | | | | | | | |
| | n | 53 | 53 | 53 | 53 | 53 | 53 | 53 | 53 | 53 | 53 | | | | | | | | | | | | | | |
| Poor_diet_corr | r | .187 | .186 | .383 | .253 | .073 | .231 | .000 | .050 | .097 | .200 | .172 | | | | | | | | | | | | | |
| | Sig | .179 | .182 | .005 | .068 | .603 | .095 | .998 | .723 | .487 | .152 | .218 | | | | | | | | | | | | | |
| | n | 53 | 53 | 53 | 53 | 53 | 53 | 53 | 53 | 53 | 53 | 53 | | | | | | | | | | | | | |
| Poor_sleep | r | .113 | .168 | .130 | .139 | .267 | .224 | .128 | .113 | .092 | .134 | .153 | .190 | | | | | | | | | | | | |
| | Sig | .421 | .230 | .352 | .320 | .053 | .106 | .362 | .419 | .511 | .338 | .274 | .173 | | | | | | | | | | | | |
| | n | 53 | 53 | 53 | 53 | 53 | 53 | 53 | 53 | 53 | 53 | 53 | 53 | | | | | | | | | | | | |
| Poor_sleep_corr | r | .432 | .435 | .385 | .353 | .445 | .407 | .192 | .196 | .477 | .556 | .465 | .281 | .602 | | | | | | | | | | | |
| | Sig | .001 | .001 | .004 | .009 | .001 | .002 | .169 | .160 | .000 | .000 | .000 | .042 | .000 | | | | | | | | | | | |
| | n | 53 | 53 | 53 | 53 | 53 | 53 | 53 | 53 | 53 | 53 | 53 | 53 | 53 | | | | | | | | | | | |
| WFIRS_RiskyAct_Imp | r | .327 | .229 | .628 | .425 | .373 | .558 | .011 | .274 | .553 | .549 | .279 | .369 | .100 | .215 | | | | | | | | | | |
| | Sig | .110 | .270 | .001 | .034 | .066 | .004 | .960 | .185 | .004 | .004 | .177 | .069 | .636 | .302 | | | | | | | | | | |
| | n | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | | | | | | | | | | |
| RiskyAct_Impairment | r | .182 | .199 | .487 | .265 | .315 | .386 | -.217 | -.046 | .371 | .418 | .101 | .152 | .114 | .315 | .721 | | | | | | | | | |
| | Sig | .384 | .340 | .013 | .201 | .125 | .056 | .298 | .828 | .068 | .038 | .629 | .467 | .588 | .125 | .000 | | | | | | | | | |
| | n | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | | | | | | | | | |
| WFIRS_SocialAct_Imp | r | .422 | .334 | .394 | .234 | .519 | .653 | .049 | .348 | .265 | .248 | .278 | .299 | .155 | .298 | .645 | .456 | | | | | | | | |
| | Sig | .036 | .102 | .052 | .261 | .008 | .000 | .818 | .088 | .200 | .231 | .178 | .147 | .461 | .148 | .000 | .022 | | | | | | | | |
| | n | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | | | | | | | | |
| SocialAct_Impairment | r | .289 | .196 | .294 | .053 | .333 | .362 | -.115 | .127 | .196 | .180 | .136 | .072 | .060 | .322 | .315 | .315 | .745 | | | | | | | |
| | Sig | .162 | .347 | .153 | .803 | .103 | .076 | .585 | .544 | .347 | .388 | .516 | .732 | .775 | .117 | .126 | .125 | .000 | | | | | | | |
| | n | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | | | | | | | |
| WFIRS_SelfConcept_Imp | r | .496 | .379 | .218 | .271 | .537 | .598 | .353 | .520 | .204 | .155 | .277 | -.027 | .310 | .115 | .537 | .346 | .669 | .394 | | | | | | |
| | Sig | .012 | .062 | .296 | .191 | .006 | .002 | .083 | .008 | .329 | .459 | .180 | .900 | .131 | .584 | .006 | .090 | .000 | .051 | | | | | | |
| | n | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | | | | | | |
| SelfConcept_Impairment | r | .035 | .012 | -.012 | -.044 | .361 | .273 | .166 | .144 | .012 | .014 | -.040 | -.318 | .457 | .136 | .135 | .114 | .218 | .361 | .504 | | | | | |
| | Sig | .869 | .955 | .955 | .834 | .076 | .187 | .429 | .491 | .955 | .946 | .848 | .122 | .022 | .518 | .521 | .588 | .295 | .076 | .010 | | | | | |
| | n | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | | | | | |
| WFIRS_LifeSkills_Imp | r | .223 | .319 | .178 | .189 | .443 | .452 | .113 | .261 | .167 | .079 | .095 | .030 | .400 | .226 | .517 | .485 | .508 | .104 | .675 | .272 | | | | |
| | Sig | .283 | .120 | .394 | .365 | .026 | .023 | .590 | .208 | .425 | .706 | .653 | .886 | .047 | .277 | .008 | .014 | .010 | .621 | .000 | .188 | | | | |
| | n | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | | | | |
| Life_Skills_Impairment | r | .180 | .236 | -.017 | .168 | .312 | .088 | .245 | .214 | -.201 | -.167 | .189 | -.127 | .676 | .344 | .070 | .168 | .182 | .089 | .364 | .273 | .592 | | | |
| | Sig | .389 | .256 | .934 | .421 | .129 | .675 | .237 | .305 | .336 | .424 | .366 | .547 | .000 | .092 | .741 | .421 | .384 | .672 | .074 | .186 | .002 | | | |
| | n | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | | | |
| WFIRS_SchoolWork_Imp | r | .066 | .006 | .525 | .157 | .443 | .412 | -.079 | .079 | .377 | .230 | -.022 | .022 | .249 | .148 | .548 | .579 | .407 | .263 | .353 | .219 | .464 | .259 | | |
| | Sig | .753 | .976 | .007 | .454 | .026 | .041 | .707 | .708 | .063 | .269 | .917 | .918 | .230 | .480 | .005 | .002 | .044 | .204 | .084 | .292 | .019 | .211 | | |
| | n | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | | |

| | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Work_Impairment | r | 0.00 | -.080 | .480 | .193 | .204 | .173 | -.187 | -.089 | .320 | .283 | .197 | -.050 | .221 | .263 | .466 | .514 | .262 | .204 | .000 | .221 | .332 | .327 | .644 | | |
| | Sig | 1.00 | .704 | .015 | .355 | .328 | .407 | .370 | .672 | .119 | .170 | .345 | .811 | .288 | .205 | .019 | .009 | .205 | .328 | 1.00 | .288 | .105 | .110 | .001 | | |
| | n | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | | |
| WFIRS_Family_Imp | r | .161 | .285 | .577 | .271 | .226 | .473 | .201 | .338 | .418 | .212 | .134 | .086 | .165 | .083 | .662 | .517 | .407 | .049 | .531 | .165 | .710 | .246 | .736 | .489 | |
| | Sig | .442 | .168 | .003 | .191 | .277 | .017 | .336 | .098 | .037 | .308 | .522 | .684 | .430 | .693 | .000 | .008 | .043 | .816 | .006 | .430 | .000 | .235 | .000 | .013 | |
| | n | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | |
| Family_Impairment | r | .126 | .292 | .599 | .241 | -.145 | .062 | .142 | .107 | .292 | .230 | .354 | .184 | .144 | .199 | .412 | .336 | .289 | .218 | .148 | .144 | .260 | .214 | .491 | .579 | .639 |
| | Sig | .548 | .156 | .002 | .247 | .488 | .769 | .499 | .610 | .156 | .269 | .082 | .378 | .491 | .341 | .041 | .100 | .162 | .295 | .479 | .491 | .209 | .305 | .013 | .002 | .001 |
| | n | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 |

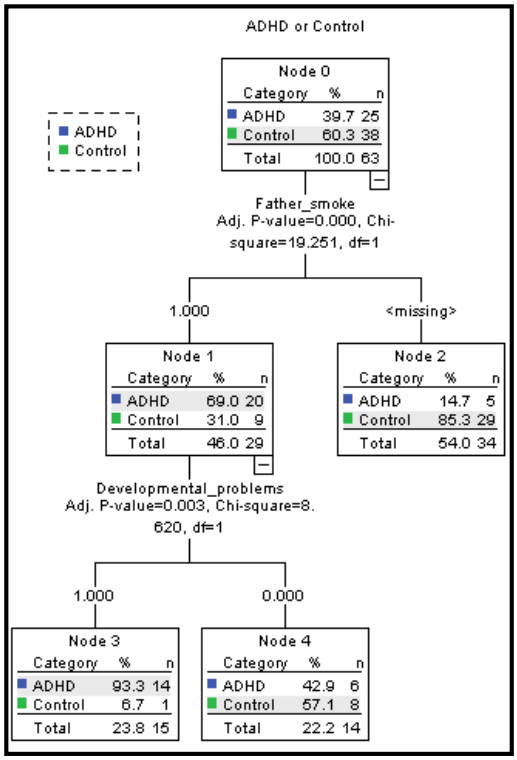
## Figure 3.6 (a)

**Decision Tree**
**Target Category: ADHD**

**Gains for Nodes**

| Node | Node | | Gain | | Response | Index |
|---|---|---|---|---|---|---|
| | N | Percent | N | Percent | | |
| 3 | 15 | 23.8% | 14 | 56.0% | 93.3% | 235.2% |
| 4 | 14 | 22.2% | 6 | 24.0% | 42.9% | 108.0% |
| 2 | 34 | 54.0% | 5 | 20.0% | 14.7% | 37.1% |

Growing Method: CHAID
Dependent Variable: ADHD or Control




**Risk**

| Estimate | Std. Error |
|---|---|
| .190 | .049 |

Growing Method: CHAID
Dependent Variable: ADHD or Control

**Classification**

| Observed | Predicted | | |
|---|---|---|---|
| | ADHD | Control | Percent Correct |
| ADHD | 14 | 11 | 56.0% |
| Control | 1 | 37 | 97.4% |
| Overall Percentage | 23.8% | 76.2% | 81.0% |

Growing Method: CHAID
Dependent Variable: ADHD or Control

## Figure 3.6 (b)

**Decision Tree**
**Target Category: ADHD combined type**

**Gains for Nodes**

| Node | Node | | Gain | | Response | Index |
|---|---|---|---|---|---|---|
| | N | Percent | N | Percent | | |
| 3 | 15 | 23.8% | 4 | 50.0% | 26.7% | 210.0% |
| 4 | 14 | 22.2% | 2 | 25.0% | 14.3% | 112.5% |
| 2 | 34 | 54.0% | 2 | 25.0% | 5.9% | 46.3% |

Growing Method: CHAID
Dependent Variable: ADHD_Type

**Target Category: ADHD inattentive**

**Gains for Nodes**

| Node | Node | | Gain | | Response | Index |
|---|---|---|---|---|---|---|
| | N | Percent | N | Percent | | |
| 3 | 15 | 23.8% | 9 | 69.2% | 60.0% | 290.8% |
| 4 | 14 | 22.2% | 3 | 23.1% | 21.4% | 103.8% |
| 2 | 34 | 54.0% | 1 | 7.7% | 2.9% | 14.3% |

Growing Method: CHAID
Dependent Variable: ADHD_Type

**Target Category: ADHD Hyperactive**

**Gains for Nodes**

| Node | Node | | Gain | | Response | Index |
|---|---|---|---|---|---|---|
| | N | Percent | N | Percent | | |
| 3 | 15 | 23.8% | 1 | 50.0% | 6.7% | 210.0% |
| 2 | 34 | 54.0% | 1 | 50.0% | 2.9% | 92.6% |
| 4 | 14 | 22.2% | 0 | 0.0% | 0.0% | 0.0% |

Growing Method: CHAID
Dependent Variable: ADHD_Type

**Risk**

| Estimate | Std. Error |
|---|---|
| .238 | .054 |

Growing Method: CHAID
Dependent Variable: ADHD_Type

**Classification**

| Observed | Predicted | | | | |
|---|---|---|---|---|---|
| | Control | ADHD combined type | ADHD inattentive | ADHD Hyperactive | Percent Correct |
| Control | 39 | 0 | 1 | 0 | 97.5% |
| ADHD combined type | 4 | 0 | 4 | 0 | 0.0% |
| ADHD inattentive | 4 | 0 | 9 | 0 | 69.2% |
| ADHD Hyperactive | 1 | 0 | 1 | 0 | 0.0% |
| Overall Percentage | 76.2% | 0.0% | 23.8% | 0.0% | 76.2% |

Growing Method: CHAID
Dependent Variable: ADHD_Type

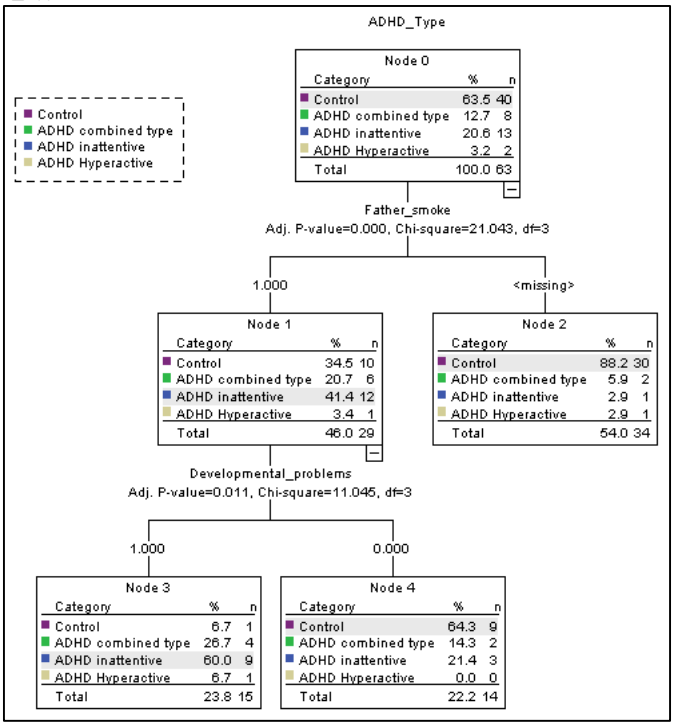


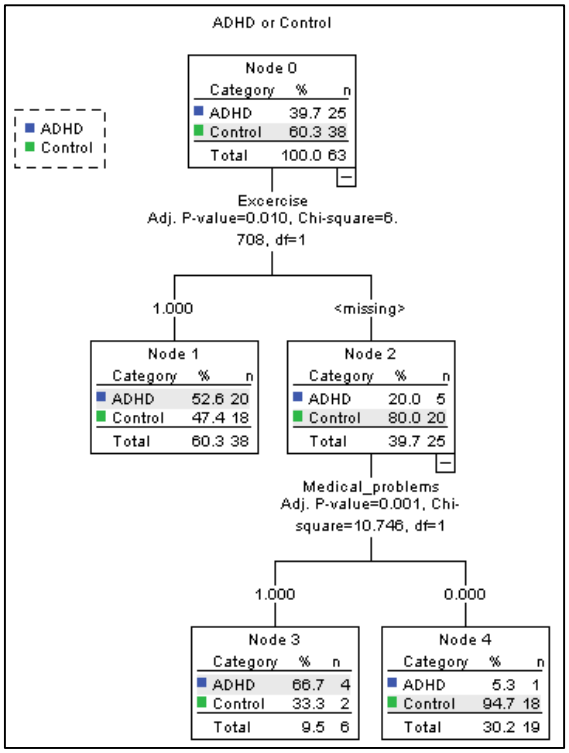
Figure 3.7

**Decision Tree**
**Target Category: ADHD**

**Gains for Nodes**

| Node | Node | | Gain | | Response | Index |
|---|---|---|---|---|---|---|
| | N | Percent | N | Percent | | |
| 3 | 6 | 9.5% | 4 | 16.0% | 66.7% | 168.0% |
| 1 | 38 | 60.3% | 20 | 80.0% | 52.6% | 132.6% |
| 4 | 19 | 30.2% | 1 | 4.0% | 5.3% | 13.3% |

Growing Method: CHAID
Dependent Variable: ADHD or Control




**Risk**

| Estimate | Std. Error |
|---|---|
| .333 | .059 |

Growing Method: CHAID
Dependent Variable:
ADHD or Control

**Classification**

| Observed | Predicted | | |
|---|---|---|---|
| | ADHD | Control | Percent Correct |
| ADHD | 24 | 1 | 96.0% |
| Control | 20 | 18 | 47.4% |
| Overall Percentage | 69.8% | 30.2% | 66.7% |

Growing Method: CHAID
Dependent Variable: ADHD or Control

Figure 3.8

**Logistic Regression**

**Notes**

**Syntax**

```
LOGISTIC REGRESSION VARIABLES Control_ADHD
  /METHOD=ENTER Developmental_probs_corr Smoker_corr
  /CRITERIA=PIN(.05) POUT(.10) ITERATE(20) CUT(.5).
```

**Case Processing Summary**

| Unweighted Cases[a] | | N | Percent |
|---|---|---|---|
| Selected Cases | Included in Analysis | 53 | 71.6 |
| | Missing Cases | 21 | 28.4 |
| | Total | 74 | 100.0 |
| Unselected Cases | | 0 | 0.0 |
| Total | | 74 | 100.0 |

a. If weight is in effect, see classification table for the total number of cases.

**Dependent Variable Encoding**

| Original Value | Internal Value |
|---|---|
| Control | 0 |
| ADHD | 1 |

## Block 0: Beginning Block

**Classification Table[a,b]**

| Observed | | | Predicted | | |
|---|---|---|---|---|---|
| | | | Control_ADHD | | Percentage Correct |
| | | | Control | ADHD | |
| Step 0 | Control_ADHD | Control | 28 | 0 | 100.0 |
| | | ADHD | 25 | 0 | 0.0 |
| | Overall Percentage | | | | 52.8 |

a. Constant is included in the model.

b. The cut value is .500

**Variables in the Equation**

| | | B | S.E. | Wald | df | Sig. | Exp(B) |
|---|---|---|---|---|---|---|---|
| Step 0 | Constant | -.113 | .275 | .170 | 1 | .680 | .893 |

**Variables not in the Equation**

| | | | Score | df | Sig. |
|---|---|---|---|---|---|
| Step 0 | Variables | Developmental_probs_corr | 9.049 | 1 | .003 |
| | | Smoker_corr | 11.155 | 1 | .001 |
| | Overall Statistics | | 14.271 | 2 | .001 |

## Block 1: Method = Enter

**Omnibus Tests of Model Coefficients**

| | | Chi-square | df | Sig. |
|---|---|---|---|---|
| Step 1 | Step | 17.338 | 2 | .000 |
| | Block | 17.338 | 2 | .000 |
| | Model | 17.338 | 2 | .000 |

**Model Summary**

| Step | -2 Log likelihood | Cox & Snell R Square | Nagelkerke R Square |
|---|---|---|---|
| 1 | 55.966[a] | .279 | .372 |

a. Estimation terminated at iteration number 5 because parameter estimates changed by less than .001.

**Classification Table[a]**

| Observed | | | Predicted | | |
|---|---|---|---|---|---|
| | | | Control_ADHD | | Percentage Correct |
| | | | Control | ADHD | |
| Step 1 | Control_ADHD | Control | 24 | 4 | 85.7 |
| | | ADHD | 11 | 14 | 56.0 |
| | Overall Percentage | | | | 71.7 |

a. The cut value is .500

**Variables in the Equation**

| | | B | S.E. | Wald | df | Sig. | Exp(B) |
|---|---|---|---|---|---|---|---|
| Step 1[a] | Developmental_probs_corr | .981 | .505 | 3.774 | 1 | .052 | 2.667 |
| | Smoker_corr | .417 | .183 | 5.202 | 1 | .023 | 1.517 |
| | Constant | -1.068 | .404 | 7.007 | 1 | .008 | .344 |

a. Variable(s) entered on step 1: Developmental_probs_corr, Smoker_corr.

Figure 3.9

**Regression**

**Notes**

```
Syntax
REGRESSION
  /MISSING LISTWISE
  /STATISTICS COEFF OUTS R ANOVA
  /CRITERIA=PIN(.05) POUT(.10)
  /NOORIGIN
  /DEPENDENT ASRS_Full_Diag
  /METHOD=ENTER Medical_probs_corr Psychological_problems_corr Developmental_probs_corr Learning_disorder_corr
  /METHOD=ENTER Smoker_corr Hypoxia_corr Poor_sleep_corr
  /METHOD=ENTER WFIRS_Family_Imp WFIRS_SchoolWork_Imp WFIRS_RiskyAct_Imp.
```

**Variables Entered/Removed[a]**

| Model | Variables Entered | Variables Removed | Method |
|---|---|---|---|
| 1 | Learning_disorder_corr, Developmental_probs_corr, Psychological_problems_corr, Medical_probs_corr[b] | | Enter |
| 2 | Poor_sleep_corr, Smoker_corr, Hypoxia_corr[b] | | Enter |
| 3 | WFIRS_SchoolWork_Imp, WFIRS_RiskyAct_Imp, WFIRS_Family_Imp[b] | | Enter |

a. Dependent Variable: ASRS_Full_Diag
b. All requested variables entered.

**Model Summary**

| Model | R | R Square | Adjusted R Square | Std. Error of the Estimate |
|---|---|---|---|---|
| 1 | .728[a] | .530 | .436 | 2.51417 |
| 2 | .760[b] | .577 | .403 | 2.58653 |
| 3 | .804[c] | .647 | .395 | 2.60436 |

a. Predictors: (Constant), Learning_disorder_corr, Developmental_probs_corr, Psychological_problems_corr, Medical_probs_corr
b. Predictors: (Constant), Learning_disorder_corr, Developmental_probs_corr, Psychological_problems_corr, Medical_probs_corr, Poor_sleep_corr, Smoker_corr, Hypoxia_corr
c. Predictors: (Constant), Learning_disorder_corr, Developmental_probs_corr, Psychological_problems_corr, Medical_probs_corr, Poor_sleep_corr, Smoker_corr, Hypoxia_corr, WFIRS_SchoolWork_Imp, WFIRS_RiskyAct_Imp, WFIRS_Family_Imp

**ANOVA[a]**

| Model | | Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|---|
| 1 | Regression | 142.619 | 4 | 35.655 | 5.641 | .003[b] |
| | Residual | 126.421 | 20 | 6.321 | | |
| | Total | 269.040 | 24 | | | |
| 2 | Regression | 155.308 | 7 | 22.187 | 3.316 | .021[c] |
| | Residual | 113.732 | 17 | 6.690 | | |
| | Total | 269.040 | 24 | | | |
| 3 | Regression | 174.082 | 10 | 17.408 | 2.567 | .052[d] |
| | Residual | 94.958 | 14 | 6.783 | | |
| | Total | 269.040 | 24 | | | |

a. Dependent Variable: ASRS_Full_Diag
b. Predictors: (Constant), Learning_disorder_corr, Developmental_probs_corr, Psychological_problems_corr, Medical_probs_corr
c. Predictors: (Constant), Learning_disorder_corr, Developmental_probs_corr, Psychological_problems_corr, Medical_probs_corr, Poor_sleep_corr, Smoker_corr, Hypoxia_corr
d. Predictors: (Constant), Learning_disorder_corr, Developmental_probs_corr, Psychological_problems_corr, Medical_probs_corr, Poor_sleep_corr, Smoker_corr, Hypoxia_corr, WFIRS_SchoolWork_Imp, WFIRS_RiskyAct_Imp, WFIRS_Family_Imp

**Coefficients[a]**

| Model | | Unstandardised Coefficients | | Standardised Coefficients | t | Sig. |
|---|---|---|---|---|---|---|
| | | B | Std. Error | Beta | | |
| 1 | (Constant) | 8.055 | 1.153 | | 6.985 | .000 |
| | Medical_probs_corr | .793 | 1.052 | .205 | .754 | .459 |
| | Psychological_problems_corr | 1.599 | .930 | .455 | 1.720 | .101 |
| | Developmental_probs_corr | 1.406 | .596 | .445 | 2.359 | .029 |
| | Learning_disorder_corr | -1.293 | .767 | -.354 | -1.686 | .107 |
| 2 | (Constant) | 8.296 | 1.529 | | 5.425 | .000 |
| | Medical_probs_corr | -.607 | 1.510 | -.157 | -.402 | .693 |
| | Psychological_problems_corr | 1.738 | 1.116 | .494 | 1.557 | .138 |
| | Developmental_probs_corr | 1.503 | .662 | .476 | 2.272 | .036 |
| | Learning_disorder_corr | -1.061 | .902 | -.291 | -1.176 | .256 |
| | Smoker_corr | .038 | .285 | .033 | .133 | .896 |
| | Hypoxia_corr | .724 | .675 | .291 | 1.073 | .298 |
| | Poor_sleep_corr | .175 | .438 | .081 | .400 | .694 |
| 3 | (Constant) | 6.874 | 1.822 | | 3.773 | .002 |
| | Medical_probs_corr | .010 | 1.662 | .003 | .006 | .995 |
| | Psychological_problems_corr | 1.386 | 1.164 | .394 | 1.191 | .254 |
| | Developmental_probs_corr | .989 | .801 | .313 | 1.235 | .237 |
| | Learning_disorder_corr | -.986 | .957 | -.270 | -1.031 | .320 |
| | Smoker_corr | .010 | .315 | .009 | .031 | .976 |
| | Hypoxia_corr | .739 | .714 | .297 | 1.035 | .318 |
| | Poor_sleep_corr | .111 | .449 | .052 | .248 | .808 |
| | WFIRS_Family_Imp | .256 | 1.633 | .047 | .157 | .877 |
| | WFIRS_SchoolWork_Imp | 1.900 | 1.724 | .288 | 1.102 | .289 |

| | | | | | |
|---|---|---|---|---|---|
| WFIRS_RiskyAct_Imp | -.258 | 2.147 | -.033 | -.120 | .906 |

a. Dependent Variable: ASRS_Full_Diag

**Excluded Variables[a]**

| Model | | Beta In | t | Sig. | Partial Correlation | Collinearity Statistics |
|---|---|---|---|---|---|---|
| | | | | | | Tolerance |
| 1 | Smoker_corr | .155[b] | .704 | .490 | .159 | .498 |
| | Hypoxia_corr | .328[b] | 1.352 | .192 | .296 | .384 |
| | Poor_sleep_corr | .138[b] | .751 | .462 | .170 | .710 |
| | WFIRS_Family_Imp | .291[b] | 1.640 | .118 | .352 | .686 |
| | WFIRS_SchoolWork_Imp | .319[b] | 1.909 | .071 | .401 | .741 |
| | WFIRS_RiskyAct_Imp | .192[b] | .952 | .353 | .213 | .583 |
| 2 | WFIRS_Family_Imp | .246[c] | 1.276 | .220 | .304 | .646 |
| | WFIRS_SchoolWork_Imp | .309[c] | 1.767 | .096 | .404 | .724 |
| | WFIRS_RiskyAct_Imp | .136[c] | .571 | .576 | .141 | .456 |

a. Dependent Variable: ASRS_Full_Diag

b. Predictors in the Model: (Constant), Learning_disorder_corr, Developmental_probs_corr, Psychological_problems_corr, Medical_probs_corr

c. Predictors in the Model: (Constant), Learning_disorder_corr, Developmental_probs_corr, Psychological_problems_corr, Medical_probs_corr, Poor_sleep_corr, Smoker_corr, Hypoxia_corr

## Figure 3.10

**Regression**

**Notes**

```
Syntax
REGRESSION
 /MISSING LISTWISE
 /STATISTICS COEFF OUTS R ANOVA
 /CRITERIA=PIN(.05) POUT(.10)
 /NOORIGIN
 /DEPENDENT ASRS_Full_Diag
 /METHOD=ENTER Medical_probs_corr Psychological_problems_corr Developmental_probs_corr Learning_disorder_corr
 /METHOD=ENTER WFIRS_Family_Imp WFIRS_SchoolWork_Imp WFIRS_RiskyAct_Imp
 /METHOD=ENTER Poor_sleep_corr Hypoxia_corr.
```

**Variables Entered/Removed[a]**

| Model | Variables Entered | Variables Removed | Method |
|---|---|---|---|
| 1 | Learning_disorder_corr, Developmental_probs_corr, Psychological_problems_corr, Medical_probs_corr[b] | | Enter |
| 2 | WFIRS_SchoolWork_Imp, WFIRS_RiskyAct_Imp, WFIRS_Family_Imp[b] | | Enter |
| 3 | Poor_sleep_corr, Hypoxia_corr[b] | | Enter |

a. Dependent Variable: ASRS_Full_Diag

b. All requested variables entered.

**Model Summary**

| Model | R | R Square | Adjusted R Square | Std. Error of the Estimate |
|---|---|---|---|---|
| 1 | .728[a] | .530 | .436 | 2.51417 |
| 2 | .782[b] | .611 | .451 | 2.48018 |
| 3 | .804[c] | .647 | .435 | 2.51614 |

a. Predictors: (Constant), Learning_disorder_corr, Developmental_probs_corr, Psychological_problems_corr, Medical_probs_corr
b. Predictors: (Constant), Learning_disorder_corr, Developmental_probs_corr, Psychological_problems_corr, Medical_probs_corr, WFIRS_SchoolWork_Imp, WFIRS_RiskyAct_Imp, WFIRS_Family_Imp
c. Predictors: (Constant), Learning_disorder_corr, Developmental_probs_corr, Psychological_problems_corr, Medical_probs_corr, WFIRS_SchoolWork_Imp, WFIRS_RiskyAct_Imp, WFIRS_Family_Imp, Poor_sleep_corr, Hypoxia_corr

ANOVA[a]

| Model | | Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|---|
| 1 | Regression | 142.619 | 4 | 35.655 | 5.641 | .003[b] |
| | Residual | 126.421 | 20 | 6.321 | | |
| | Total | 269.040 | 24 | | | |
| 2 | Regression | 164.468 | 7 | 23.495 | 3.820 | .011[c] |
| | Residual | 104.572 | 17 | 6.151 | | |
| | Total | 269.040 | 24 | | | |
| 3 | Regression | 174.076 | 9 | 19.342 | 3.055 | .027[d] |
| | Residual | 94.964 | 15 | 6.331 | | |
| | Total | 269.040 | 24 | | | |

a. Dependent Variable: ASRS_Full_Diag
b. Predictors: (Constant), Learning_disorder_corr, Developmental_probs_corr, Psychological_problems_corr, Medical_probs_corr
c. Predictors: (Constant), Learning_disorder_corr, Developmental_probs_corr, Psychological_problems_corr, Medical_probs_corr, WFIRS_SchoolWork_Imp, WFIRS_RiskyAct_Imp, WFIRS_Family_Imp
d. Predictors: (Constant), Learning_disorder_corr, Developmental_probs_corr, Psychological_problems_corr, Medical_probs_corr, WFIRS_SchoolWork_Imp, WFIRS_RiskyAct_Imp, WFIRS_Family_Imp, Poor_sleep_corr, Hypoxia_corr

Coefficients[a]

| Model | | Unstandardised Coefficients | | Standardised Coefficients | t | Sig. |
|---|---|---|---|---|---|---|
| | | B | Std. Error | Beta | | |
| 1 | (Constant) | 8.055 | 1.153 | | 6.985 | .000 |
| | Medical_probs_corr | .793 | 1.052 | .205 | .754 | .459 |
| | Psychological_problems_corr | 1.599 | .930 | .455 | 1.720 | .101 |
| | Developmental_probs_corr | 1.406 | .596 | .445 | 2.359 | .029 |
| | Learning_disorder_corr | -1.293 | .767 | -.354 | -1.686 | .107 |
| 2 | (Constant) | 6.463 | 1.423 | | 4.543 | .000 |
| | Medical_probs_corr | 1.434 | 1.098 | .371 | 1.306 | .209 |
| | Psychological_problems_corr | 1.078 | 1.003 | .307 | 1.075 | .297 |
| | Developmental_probs_corr | .738 | .724 | .234 | 1.020 | .322 |
| | Learning_disorder_corr | -1.168 | .834 | -.320 | -1.401 | .179 |
| | WFIRS_Family_Imp | .591 | 1.502 | .108 | .394 | .699 |
| | WFIRS_SchoolWork_Imp | 1.580 | 1.590 | .239 | .993 | .334 |
| | WFIRS_RiskyAct_Imp | .205 | 1.831 | .026 | .112 | .912 |
| 3 | (Constant) | 6.855 | 1.653 | | 4.146 | .001 |
| | Medical_probs_corr | .010 | 1.606 | .003 | .006 | .995 |
| | Psychological_problems_corr | 1.399 | 1.050 | .398 | 1.332 | .203 |
| | Developmental_probs_corr | .990 | .774 | .313 | 1.280 | .220 |
| | Learning_disorder_corr | -.997 | .868 | -.273 | -1.148 | .269 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | WFIRS_Family_Imp | .249 | 1.562 | .046 | .160 | .875 |
| | WFIRS_SchoolWork_Imp | 1.902 | 1.665 | .288 | 1.142 | .271 |
| | WFIRS_RiskyAct_Imp | -.231 | 1.893 | -.030 | -.122 | .904 |
| | Poor_sleep_corr | .116 | .406 | .054 | .286 | .779 |
| | Hypoxia_corr | .743 | .675 | .299 | 1.101 | .288 |

a. Dependent Variable: ASRS_Full_Diag

**Excluded Variables[a]**

| Model | | Beta In | t | Sig. | Partial Correlation | Collinearity Statistics |
|---|---|---|---|---|---|---|
| | | | | | | Tolerance |
| 1 | WFIRS_Family_Imp | .291[b] | 1.640 | .118 | .352 | .686 |
| | WFIRS_SchoolWork_Imp | .319[b] | 1.909 | .071 | .401 | .741 |
| | WFIRS_RiskyAct_Imp | .192[b] | .952 | .353 | .213 | .583 |
| | Poor_sleep_corr | .138[b] | .751 | .462 | .170 | .710 |
| | Hypoxia_corr | .328[b] | 1.352 | .192 | .296 | .384 |
| 2 | Poor_sleep_corr | .101[c] | .548 | .591 | .136 | .698 |
| | Hypoxia_corr | .316[c] | 1.234 | .235 | .295 | .337 |

a. Dependent Variable: ASRS_Full_Diag
b. Predictors in the Model: (Constant), Learning_disorder_corr, Developmental_probs_corr, Psychological_problems_corr, Medical_probs_corr
c. Predictors in the Model: (Constant), Learning_disorder_corr, Developmental_probs_corr, Psychological_problems_corr, Medical_probs_corr, WFIRS_SchoolWork_Imp, WFIRS_RiskyAct_Imp, WFIRS_Family_Imp

## Figure 3.11

**Regression**

**Notes**

**Syntax**

```
REGRESSION
 /MISSING LISTWISE
 /STATISTICS COEFF OUTS R ANOVA
 /CRITERIA=PIN(.05) POUT(.10)
 /NOORIGIN
 /DEPENDENT ASRS_Inattention_Diag
 /METHOD=ENTER Medical_probs_corr Psychological_problems Developmental_probs_corr
 /METHOD=ENTER Smoker_corr Poor_sleep_corr
 /METHOD=ENTER WFIRS_SchoolWork_Imp WFIRS_LifeSkills_Imp
```

**Variables Entered/Removed[a]**

| Model | Variables Entered | Variables Removed | Method |
|---|---|---|---|
| 1 | Developmental_probs_corr, Psychological_problems, Medical_probs_corr[b] | | Enter |
| 2 | Poor_sleep_corr, Smoker_corr[b] | | Enter |
| 3 | WFIRS_LifeSkills_Imp, WFIRS_SchoolWork_Imp[b] | | Enter |

a. Dependent Variable: ASRS_Inattention_Diag
b. All requested variables entered.

**Model Summary**

| Model | R | R Square | Adjusted R Square | Std. Error of the Estimate |
|---|---|---|---|---|
| 1 | .597[a] | .356 | .264 | 1.54504 |
| 2 | .663[b] | .439 | .292 | 1.51568 |
| 3 | .736[c] | .542 | .354 | 1.44770 |

a. Predictors: (Constant), Developmental_probs_corr, Psychological_problems, Medical_probs_corr
b. Predictors: (Constant), Developmental_probs_corr, Psychological_problems, Medical_probs_corr, Poor_sleep_corr, Smoker_corr

c. Predictors: (Constant), Developmental_probs_corr, Psychological_problems, Medical_probs_corr, Poor_sleep_corr, Smoker_corr, WFIRS_LifeSkills_Imp, WFIRS_SchoolWork_Imp

**ANOVA[a]**

| Model | | Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|---|
| 1 | Regression | 27.710 | 3 | 9.237 | 3.869 | .024[b] |
| | Residual | 50.130 | 21 | 2.387 | | |
| | Total | 77.840 | 24 | | | |
| 2 | Regression | 34.192 | 5 | 6.838 | 2.977 | .038[c] |
| | Residual | 43.648 | 19 | 2.297 | | |
| | Total | 77.840 | 24 | | | |
| 3 | Regression | 42.211 | 7 | 6.030 | 2.877 | .036[d] |
| | Residual | 35.629 | 17 | 2.096 | | |
| | Total | 77.840 | 24 | | | |

a. Dependent Variable: ASRS_Inattention_Diag
b. Predictors: (Constant), Developmental_probs_corr, Psychological_problems, Medical_probs_corr
c. Predictors: (Constant), Developmental_probs_corr, Psychological_problems, Medical_probs_corr, Poor_sleep_corr, Smoker_corr
d. Predictors: (Constant), Developmental_probs_corr, Psychological_problems, Medical_probs_corr, Poor_sleep_corr, Smoker_corr, WFIRS_LifeSkills_Imp, WFIRS_SchoolWork_Imp

**Coefficients[a]**

| Model | | Unstandardised Coefficients | | Standardised Coefficients | t | Sig. |
|---|---|---|---|---|---|---|
| | | B | Std. Error | Beta | | |
| 1 | (Constant) | 5.748 | .661 | | 8.689 | .000 |
| | Medical_probs_corr | .012 | .449 | .006 | .027 | .978 |
| | Psychological_problems | .949 | .715 | .269 | 1.327 | .199 |
| | Developmental_probs_corr | .726 | .361 | .427 | 2.012 | .057 |
| 2 | (Constant) | 5.135 | .812 | | 6.321 | .000 |
| | Medical_probs_corr | -.303 | .491 | -.146 | -.617 | .544 |
| | Psychological_problems | .760 | .746 | .215 | 1.018 | .321 |
| | Developmental_probs_corr | .714 | .354 | .420 | 2.016 | .058 |
| | Smoker_corr | .046 | .146 | .075 | .314 | .757 |
| | Poor_sleep_corr | .343 | .245 | .296 | 1.400 | .178 |
| 3 | (Constant) | 4.055 | .966 | | 4.197 | .001 |
| | Medical_probs_corr | -.096 | .511 | -.046 | -.189 | .853 |
| | Psychological_problems | .319 | .827 | .090 | .386 | .704 |
| | Developmental_probs_corr | .381 | .379 | .224 | 1.005 | .329 |
| | Smoker_corr | .069 | .142 | .112 | .483 | .635 |
| | Poor_sleep_corr | .272 | .238 | .234 | 1.140 | .270 |
| | WFIRS_SchoolWork_Imp | .808 | .839 | .228 | .962 | .349 |
| | WFIRS_LifeSkills_Imp | .727 | .631 | .238 | 1.152 | .265 |

a. Dependent Variable: ASRS_Inattention_Diag

**Excluded Variables[a]**

| Model | | Beta In | t | Sig. | Partial Correlation | Collinearity Statistics |
|---|---|---|---|---|---|---|
| | | | | | | Tolerance |
| 1 | Smoker_corr | .205[b] | .906 | .376 | .199 | .606 |
| | Poor_sleep_corr | .322[b] | 1.689 | .107 | .353 | .775 |
| | WFIRS_SchoolWork_Imp | .371[b] | 1.695 | .106 | .354 | .586 |
| | WFIRS_LifeSkills_Imp | .340[b] | 1.823 | .083 | .378 | .796 |
| 2 | WFIRS_SchoolWork_Imp | .340[c] | 1.567 | .135 | .346 | .581 |
| | WFIRS_LifeSkills_Imp | .320[c] | 1.706 | .105 | .373 | .762 |

a. Dependent Variable: ASRS_Inattention_Diag
b. Predictors in the Model: (Constant), Developmental_probs_corr, Psychological_problems, Medical_probs_corr
c. Predictors in the Model: (Constant), Developmental_probs_corr, Psychological_problems, Medical_probs_corr, Poor_sleep_corr, Smoker_corr

Figure 3.12

**Regression**

**Notes**

**Syntax**

```
REGRESSION
 /MISSING LISTWISE
 /STATISTICS COEFF OUTS R ANOVA
 /CRITERIA=PIN(.05) POUT(.10)
 /NOORIGIN
 /DEPENDENT ASRS_Hyperactivity_Diag
 /METHOD=ENTER Medical_probs_corr Psychological_problems_corr Developmental_probs_corr Learning_disorder_corr
 /METHOD=ENTER Work_Impairment
 /METHOD=ENTER Smoker_corr Hypoxia_corr Poor_sleep_corr.
```

**Variables Entered/Removed[a]**

| Model | Variables Entered | Variables Removed | Method |
|---|---|---|---|
| 1 | Learning_disorder_corr, Developmental_probs_corr, Psychological_problems_corr, Medical_probs_corr[b] | | Enter |
| 2 | Work_Impairment[b] | | Enter |
| 3 | Poor_sleep_corr, Smoker_corr, Hypoxia_corr[b] | | Enter |

a. Dependent Variable: ASRS_Hyperactivity_Diag
b. All requested variables entered.

**Model Summary**

| Model | R | R Square | Adjusted R Square | Std. Error of the Estimate |
|---|---|---|---|---|
| 1 | .642[a] | .412 | .294 | 1.82920 |
| 2 | .736[b] | .542 | .422 | 1.65521 |
| 3 | .767[c] | .588 | .382 | 1.71201 |

a. Predictors: (Constant), Learning_disorder_corr, Developmental_probs_corr, Psychological_problems_corr, Medical_probs_corr
b. Predictors: (Constant), Learning_disorder_corr, Developmental_probs_corr, Psychological_problems_corr, Medical_probs_corr, Work_Impairment
c. Predictors: (Constant), Learning_disorder_corr, Developmental_probs_corr, Psychological_problems_corr, Medical_probs_corr, Work_Impairment, Poor_sleep_corr, Smoker_corr, Hypoxia_corr

**ANOVA[a]**

| Model | | Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|---|
| 1 | Regression | 46.841 | 4 | 11.710 | 3.500 | .025[b] |
| | Residual | 66.919 | 20 | 3.346 | | |
| | Total | 113.760 | 24 | | | |
| 2 | Regression | 61.705 | 5 | 12.341 | 4.505 | .007[c] |
| | Residual | 52.055 | 19 | 2.740 | | |
| | Total | 113.760 | 24 | | | |
| 3 | Regression | 66.864 | 8 | 8.358 | 2.852 | .035[d] |
| | Residual | 46.896 | 16 | 2.931 | | |
| | Total | 113.760 | 24 | | | |

a. Dependent Variable: ASRS_Hyperactivity_Diag
b. Predictors: (Constant), Learning_disorder_corr, Developmental_probs_corr, Psychological_problems_corr, Medical_probs_corr
c. Predictors: (Constant), Learning_disorder_corr, Developmental_probs_corr, Psychological_problems_corr, Medical_probs_corr, Work_Impairment
d. Predictors: (Constant), Learning_disorder_corr, Developmental_probs_corr, Psychological_problems_corr, Medical_probs_corr, Work_Impairment, Poor_sleep_corr, Smoker_corr, Hypoxia_corr

**Coefficients[a]**

| Model | | Unstandardised Coefficients | | Standardised Coefficients | t | Sig. |
|---|---|---|---|---|---|---|
| | | B | Std. Error | Beta | | |
| 1 | (Constant) | 2.734 | .839 | | 3.258 | .004 |
| | Medical_probs_corr | 1.001 | .765 | .398 | 1.308 | .206 |
| | Psychological_problems_corr | .637 | .677 | .279 | .942 | .357 |
| | Developmental_probs_corr | .336 | .433 | .163 | .775 | .448 |
| | Learning_disorder_corr | -.373 | .558 | -.157 | -.669 | .511 |
| 2 | (Constant) | 1.159 | 1.017 | | 1.140 | .269 |
| | Medical_probs_corr | 1.521 | .728 | .605 | 2.091 | .050 |
| | Psychological_problems_corr | -.021 | .674 | -.009 | -.032 | .975 |
| | Developmental_probs_corr | .026 | .414 | .013 | .063 | .951 |
| | Learning_disorder_corr | .022 | .533 | .009 | .041 | .968 |
| | Work_Impairment | 2.202 | .945 | .413 | 2.329 | .031 |
| 3 | (Constant) | 1.847 | 1.302 | | 1.418 | .175 |
| | Medical_probs_corr | 1.680 | 1.213 | .668 | 1.385 | .185 |
| | Psychological_problems_corr | -.378 | .857 | -.165 | -.441 | .665 |
| | Developmental_probs_corr | -.014 | .483 | -.007 | -.028 | .978 |
| | Learning_disorder_corr | .140 | .621 | .059 | .226 | .824 |
| | Work_Impairment | 2.376 | 1.144 | .446 | 2.077 | .054 |
| | Smoker_corr | .165 | .189 | .224 | .871 | .396 |
| | Hypoxia_corr | .070 | .497 | .043 | .141 | .890 |
| | Poor_sleep_corr | -.355 | .299 | -.254 | -1.188 | .252 |

a. Dependent Variable: ASRS_Hyperactivity_Diag

**Excluded Variables[a]**

| Model | | Beta In | t | Sig. | Partial Correlation | Collinearity Statistics |
|---|---|---|---|---|---|---|
| | | | | | | Tolerance |
| 1 | Work_Impairment | .413[b] | 2.329 | .031 | .471 | .766 |
| | Smoker_corr | .206[b] | .839 | .412 | .189 | .498 |
| | Hypoxia_corr | .348[b] | 1.279 | .216 | .281 | .384 |
| | Poor_sleep_corr | -.035[b] | -.169 | .868 | -.039 | .710 |
| 2 | Smoker_corr | .131[c] | .577 | .571 | .135 | .486 |
| | Hypoxia_corr | .096[c] | .330 | .745 | .077 | .300 |
| | Poor_sleep_corr | -.183[c] | -.942 | .359 | -.217 | .645 |

a. Dependent Variable: ASRS_Hyperactivity_Diag
b. Predictors in the Model: (Constant), Learning_disorder_corr, Developmental_probs_corr, Psychological_problems_corr, Medical_probs_corr
c. Predictors in the Model: (Constant), Learning_disorder_corr, Developmental_probs_corr, Psychological_problems_corr, Medical_probs_corr, Work_Impairment

Figure 3.13

Nominal Regression

Notes

| Syntax |
| --- |
| NOMREG VAR00001 (BASE=FIRST ORDER=ASCENDING) WITH Developmental_probs_corr Smoker_corr<br>/CRITERIA CIN(95) DELTA(0) MXITER(100) MXSTEP(5) CHKSEP(20) LCONVERGE(0) PCONVERGE(0.000001)<br>SINGULAR(0.00000001)<br>/MODEL<br>/STEPWISE=PIN(.05) POUT(0.1) MINEFFECT(0) RULE(SINGLE) ENTRYMETHOD(LR) REMOVALMETHOD(LR)<br>/INTERCEPT=INCLUDE<br>/PRINT=CELLPROB CLASSTABLE FIT PARAMETER SUMMARY LRT CPS STEP MFI. |

Case Processing Summary

| | | N | Marginal Percentage |
| --- | --- | --- | --- |
| ADHD type | Control | 30 | 56.6% |
| | ADHD Hyperactive | 2 | 3.8% |
| | ADHD combined type | 8 | 15.1% |
| | ADHD inattentive | 13 | 24.5% |
| Valid | | 53 | 100.0% |
| Missing | | 21 | |
| Total | | 74 | |
| Subpopulation | | 16a | |

a. The dependent variable has only one value observed in 12 (75.0%) subpopulations.

Model Fitting Information

| | Model Fitting Criteria | Likelihood Ratio Tests | | |
| --- | --- | --- | --- | --- |
| Model | -2 Log Likelihood | Chi-Square | df | Sig. |
| Intercept Only | 69.330 | | | |
| Final | 43.874 | 25.456 | 6 | .000 |

Goodness-of-Fit

| | Chi-Square | df | Sig. |
| --- | --- | --- | --- |
| Pearson | 26.172 | 39 | .942 |
| Deviance | 27.106 | 39 | .925 |

**Pseudo R-Square**

| | |
|---|---|
| Cox and Snell | .381 |
| Nagelkerke | .432 |
| McFadden | .223 |

**Likelihood Ratio Tests**

| Effect | Model Fitting Criteria | Likelihood Ratio Tests | | |
|---|---|---|---|---|
| | -2 Log Likelihood of Reduced Model | Chi-Square | df | Sig. |
| Intercept | 87.932 | 44.058 | 3 | .000 |
| Developmental_probs_corr | 51.667 | 7.793 | 3 | .050 |
| Smoker_corr | 55.419 | 11.545 | 3 | .009 |

The chi-square statistic is the difference in -2 log-likelihoods between the final model and a reduced model. The reduced model is formed by omitting an effect from the final model. The null hypothesis is that all parameters of that effect are 0.

**Parameter Estimates**

| ADHD type[a] | | B | Std. Error | Wald | df | Sig. | Exp(B) | 95% Confidence Interval for Exp(B) | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Lower Bound | Upper Bound |
| ADHD Hyperactive | Intercept | -2.880 | .885 | 10.586 | 1 | .001 | | | |
| | Developmental_probs_corr | .962 | 1.066 | .814 | 1 | .367 | 2.618 | .324 | 21.170 |
| | Smoker_corr | -8.785 | 0.000 | | 1 | | .000 | .000 | .000 |
| ADHD combined type | Intercept | -3.090 | .804 | 14.779 | 1 | .000 | | | |
| | Developmental_probs_corr | 1.032 | .654 | 2.488 | 1 | .115 | 2.807 | .778 | 10.124 |
| | Smoker_corr | .586 | .207 | 7.987 | 1 | .005 | 1.797 | 1.197 | 2.698 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| ADHD inattentive | Intercept | -1.728 | .492 | 12.321 | 1 | .000 | | | |
| | Developmental_probs_corr | 1.320 | .552 | 5.718 | 1 | .017 | 3.743 | 1.269 | 11.041 |
| | Smoker_corr | .216 | .188 | 1.327 | 1 | .249 | 1.242 | .859 | 1.794 |

a. The reference category is: Control.

**Classification**

| | Predicted | | | | |
|---|---|---|---|---|---|
| Observed | Control | ADHD Hyperactive | ADHD combined type | ADHD inattentive | Percent Correct |
| Control | 26 | 0 | 1 | 3 | 86.7% |
| ADHD Hyperactive | 2 | 0 | 0 | 0 | 0.0% |
| ADHD combined type | 4 | 0 | 4 | 0 | 50.0% |
| ADHD inattentive | 7 | 0 | 2 | 4 | 30.8% |
| Overall Percentage | 73.6% | 0.0% | 13.2% | 13.2% | 64.2% |

**Observed and Predicted Frequencies**

| | | | | Frequency | | Percentage | |
|---|---|---|---|---|---|---|---|
| Smoker_corr | | | Observed | Predicted | Pearson Residual | Observed | Predicted |
| .00 | .00 | Control | 24 | 22.668 | .599 | 82.8% | 78.2% |
| | | ADHD Hyperactive | 1 | 1.273 | -.247 | 3.4% | 4.4% |
| | | ADHD combined type | 1 | 1.032 | -.032 | 3.4% | 3.6% |
| | | ADHD inattentive | 3 | 4.028 | -.552 | 10.3% | 13.9% |
| | 1.00 | Control | 1 | 3.093 | -1.710 | 16.7% | 51.6% |
| | | ADHD Hyperactive | 1 | .455 | .841 | 16.7% | 7.6% |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | ADHD combined type | 1 | .395 | .996 | 16.7% | 6.6% |
| | | ADHD inattentive | 3 | 2.057 | .811 | 50.0% | 34.3% |
| | 2.00 | Control | 2 | .709 | 1.755 | 66.7% | 23.6% |
| | | ADHD Hyperactive | 0 | .273 | -.548 | 0.0% | 9.1% |
| | | ADHD combined type | 0 | .254 | -.527 | 0.0% | 8.5% |
| | | ADHD inattentive | 1 | 1.764 | -.897 | 33.3% | 58.8% |
| 2.00 | 1.00 | Control | 0 | .410 | -.834 | 0.0% | 41.0% |
| | | ADHD Hyperactive | 0 | .000 | .000 | 0.0% | .0% |
| | | ADHD combined type | 0 | .169 | -.451 | 0.0% | 16.9% |
| | | ADHD inattentive | 1 | .421 | 1.174 | 100.0% | 42.1% |
| | 4.00 | Control | 0 | .016 | -.126 | 0.0% | 1.6% |
| | | ADHD Hyperactive | 0 | .000 | .000 | 0.0% | .0% |
| | | ADHD combined type | 0 | .143 | -.408 | 0.0% | 14.3% |
| | | ADHD inattentive | 1 | .842 | .434 | 100.0% | 84.2% |
| 3.00 | .00 | Control | 0 | .623 | -1.287 | 0.0% | 62.3% |
| | | ADHD Hyperactive | 0 | .000 | .000 | 0.0% | .0% |
| | | ADHD combined type | 1 | .165 | 2.253 | 100.0% | 16.5% |
| | | ADHD inattentive | 0 | .212 | -.519 | 0.0% | 21.2% |
| | 1.00 | Control | 0 | .332 | -.705 | 0.0% | 33.2% |
| | | ADHD Hyperactive | 0 | .000 | .000 | 0.0% | .0% |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | ADHD combined type | 0 | .246 | -.571 | 0.0% | 24.6% |
| | | ADHD inattentive | 1 | .422 | 1.169 | 100.0% | 42.2% |
| 4.00 | 1.00 | Control | 1 | .256 | 1.706 | 100.0% | 25.6% |
| | | ADHD Hyperactive | 0 | .000 | .000 | 0.0% | .0% |
| | | ADHD combined type | 0 | .340 | -.718 | 0.0% | 34.0% |
| | | ADHD inattentive | 0 | .404 | -.823 | 0.0% | 40.4% |
| 5.00 | .00 | Control | 1 | 1.262 | -.307 | 33.3% | 42.1% |
| | | ADHD Hyperactive | 0 | .000 | .000 | 0.0% | .0% |
| | | ADHD combined type | 1 | 1.076 | -.091 | 33.3% | 35.9% |
| | | ADHD inattentive | 1 | .662 | .471 | 33.3% | 22.1% |
| 6.00 | .00 | Control | 1 | .314 | 1.477 | 100.0% | 31.4% |
| | | ADHD Hyperactive | 0 | .000 | .000 | 0.0% | .0% |
| | | ADHD combined type | 0 | .481 | -.963 | 0.0% | 48.1% |
| | | ADHD inattentive | 0 | .205 | -.507 | 0.0% | 20.5% |
| | 1.00 | Control | 0 | .129 | -.385 | 0.0% | 12.9% |
| | | ADHD Hyperactive | 0 | .000 | .000 | 0.0% | .0% |
| | | ADHD combined type | 0 | .556 | -1.118 | 0.0% | 55.6% |
| | | ADHD inattentive | 1 | .315 | 1.475 | 100.0% | 31.5% |
| | 2.00 | Control | 0 | .045 | -.217 | 0.0% | 4.5% |
| | | ADHD Hyperactive | 0 | .000 | .000 | 0.0% | .0% |
| | | ADHD combined type | 0 | .544 | -1.092 | 0.0% | 54.4% |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | ADHD inattentive | 1 | .411 | 1.197 | 100.0% | 41.1% |
| 7.00 | 1.00 | Control | 0 | .085 | -.305 | 0.0% | 8.5% |
| | | ADHD Hyperactive | 0 | .000 | .000 | 0.0% | .0% |
| | | ADHD combined type | 1 | .657 | .722 | 100.0% | 65.7% |
| | | ADHD inattentive | 0 | .258 | -.589 | 0.0% | 25.8% |
| | 2.00 | Control | 0 | .029 | -.174 | 0.0% | 2.9% |
| | | ADHD Hyperactive | 0 | .000 | .000 | 0.0% | .0% |
| | | ADHD combined type | 1 | .638 | .754 | 100.0% | 63.8% |
| | | ADHD inattentive | 0 | .333 | -.707 | 0.0% | 33.3% |
| | 3.00 | Control | 0 | .010 | -.098 | 0.0% | 1.0% |
| | | ADHD Hyperactive | 0 | .000 | .000 | 0.0% | .0% |
| | | ADHD combined type | 1 | .584 | .844 | 100.0% | 58.4% |
| | | ADHD inattentive | 0 | .407 | -.828 | 0.0% | 40.7% |
| 8.00 | 2.00 | Control | 0 | .019 | -.137 | 0.0% | 1.9% |
| | | ADHD Hyperactive | 0 | .000 | .000 | 0.0% | .0% |
| | | ADHD combined type | 1 | .721 | .622 | 100.0% | 72.1% |
| | | ADHD inattentive | 0 | .260 | -.593 | 0.0% | 26.0% |

The percentages are based on total observed frequencies in each subpopulation.

Wilcoxon signed-rank test

**Hypothesis Test Summary**

| | Null Hypothesis | Test | Sig. | Decision |
|---|---|---|---|---|
| 1 | The distributions of Zscore (ASRS_Full_Diag), Zscore (DIVA_Full_Adult) and Difference are the same. | Related-Samples Friedman's Two-Way Analysis of Variance by Ranks | .882 | Retain the null hypothesis. |

Asymptotic significances are displayed. The significance level is .05.

**Hypothesis Test Summary**

| | Null Hypothesis | Test | Sig. | Decision |
|---|---|---|---|---|
| 1 | The distributions of Zscore (Inattention_Adult), Zscore (ASRS_Inattention_Diag) and Difference_Innatention are the same. | Related-Samples Friedman's Two-Way Analysis of Variance by Ranks | .417 | Retain the null hypothesis. |

Asymptotic significances are displayed. The significance level is .05.

**Hypothesis Test Summary**

| | Null Hypothesis | Test | Sig. | Decision |
|---|---|---|---|---|
| 1 | The distributions of Zscore (Hyperactivity_Adult), Zscore (ASRS_Hyperactivity_Diag) and Difference_Hyperactivity are the same. | Related-Samples Friedman's Two-Way Analysis of Variance by Ranks | .882 | Retain the null hypothesis. |

Asymptotic significances are displayed. The significance level is .05.

## Analysis of environmental influence on the presence of ADHD

### Logistic Regression

**Case Processing Summary**

| Unweighted Cases[a] | | N | Percent |
|---|---|---|---|
| Selected Cases | Included in Analysis | 53 | 71.6 |
| | Missing Cases | 21 | 28.4 |
| | Total | 74 | 100.0 |
| Unselected Cases | | 0 | 0.0 |
| Total | | 74 | 100.0 |

a. If weight is in effect, see classification table for the total number of cases.

**Dependent Variable Encoding**

| Original Value | Internal Value |
|---|---|
| ADHD | 0 |
| Control | 1 |

### Block 0: Beginning Block

**Classification Table[a,b]**

| Observed | | Predicted | | |
|---|---|---|---|---|
| | | ADHD or Control | | Percentage Correct |
| | | ADHD | Control | |
| Step 0 | ADHD or Control | ADHD | 0 | 25 | 0.0 |

| | | | | |
|---|---|---|---|---|
| | Control | 0 | 28 | 100.0 |
| Overall Percentage | | | 52.8 | |

a. Constant is included in the model.
b. The cut value is .500

**Variables in the Equation**

| | | B | S.E. | Wald | df | Sig. | Exp (B) |
|---|---|---|---|---|---|---|---|
| Step 0 | Constant | .113 | .275 | .170 | 1 | .680 | 1.120 |

**Variables not in the Equation**

| | | | Score | df | Sig |
|---|---|---|---|---|---|
| Step 0 | Variables | Medical_probs_corr | 12.830 | 1 | .000 |
| | | Psychological_problems_corr | 2.298 | 1 | .130 |
| | | Developmental_probs_corr | 9.049 | 1 | .003 |
| | | Hypoxia_corr | 4.300 | 1 | .038 |
| | | Poor_sleep_corr | 9.492 | 1 | .002 |
| | | Learning_disorder_corr | 5.966 | 1 | .015 |
| | | Smoker_corr | 11.155 | 1 | .001 |
| | Overall Statistics | | 20.118 | 7 | .005 |

**Block 1: Method = Enter**

**Omnibus Tests of Model Coefficients**

| | | Chi-square | df | Sig. |
|---|---|---|---|---|
| Step 1 | Step | 36.133 | 7 | .000 |
| | Block | 36.133 | 7 | .000 |
| | Model | 36.133 | 7 | .000 |

**Model Summary**

| Step | -2 Log likelihood | Cox & Snell R Square | Nagelkerke R Square |
|---|---|---|---|
| 1 | 37.171[a] | .494 | .660 |

a. Estimation terminated at iteration number 20 because maximum iterations has been reached. Final solution cannot be found.

**Hosmer and Lemeshow Test**

| Step | Chi-square | df | Sig. |
|---|---|---|---|
| 1 | 2.692 | 8 | .952 |

**Contingency Table for Hosmer and Lemeshow Test**

| | | ADHD or Control = ADHD | | ADHD or Control = Control | | |
|---|---|---|---|---|---|---|
| | | Observed | Expected | Observed | Expected | Total |
| Step 1 | 1 | 5 | 5.000 | 0 | .000 | 5 |
| | 2 | 5 | 5.000 | 0 | .000 | 5 |
| | 3 | 4 | 4.630 | 1 | .370 | 5 |
| | 4 | 4 | 3.399 | 1 | 1.601 | 5 |
| | 5 | 3 | 2.727 | 3 | 3.273 | 6 |
| | 6 | 1 | 1.640 | 4 | 3.360 | 5 |
| | 7 | 1 | 1.095 | 4 | 3.905 | 5 |
| | 8 | 1 | .722 | 4 | 4.278 | 5 |
| | 9 | 1 | .554 | 4 | 4.446 | 5 |
| | 10 | 0 | | | | 7 |

**Classification Table[a]**

| Observed | | Predicted | | |
|---|---|---|---|---|
| | | ADHD or Control | | Percentage Correct |
| | | ADHD | Control | |
| Step 1 | ADHD or Control | ADHD | 19 | 6 | 76.0 |
| | | Control | 2 | 26 | 92.9 |
| | Overall Percentage | | | 84.9 | |

a. The cut value is .500

**Variables in the Equation**

| | | B | S.E. | Wald | df | Sig. | | 95% C.I.for EXP(B) |
|---|---|---|---|---|---|---|---|---|

| | | | | | | | Exp(B) | Lower | Upper |
|---|---|---|---|---|---|---|---|---|---|
| Step 1[a] | Medical_probs_corr | -20.606 | 6489.580 | .000 | 1 | .997 | .000 | 0.000 | |
| | Psychological_problems_corr | 1.205 | .825 | 2.133 | 1 | .144 | 3.338 | .662 | 16.825 |
| | Developmental_probs_corr | -1.245 | .813 | 2.344 | 1 | .126 | .288 | .059 | 1.417 |
| | Hypoxia_corr | 1.246 | .651 | 3.660 | 1 | .056 | 3.477 | .970 | 12.466 |
| | Poor_sleep_corr | -.535 | .377 | 2.016 | 1 | .156 | .586 | .280 | 1.226 |
| | Learning_disorder_corr | -22.076 | 8692.970 | .000 | 1 | .998 | .000 | 0.000 | |
| | Smoker_corr | -.322 | .243 | 1.758 | 1 | .185 | .725 | .451 | 1.166 |
| | Constant | 21.285 | 6489.580 | .000 | 1 | .997 | ######## | | |

a. Variable(s) entered on step 1: Medical_probs_corr, Psychological_problems_corr, Developmental_probs_corr, Hypoxia_corr, Poor_sleep_corr, Learning_disorder_corr, Smoker_corr.

# Appendix 8

## Chapter 4 outputs

## Additive and interactive effects

Regression

| Notes |
|---|
| REGRESSION<br>/MISSING LISTWISE<br>/STATISTICS COEFF OUTS R ANOVA<br>/CRITERIA=PIN(.05) POUT(.10)<br>/NOORIGIN<br>/DEPENDENT Q_3.9<br>/METHOD=ENTER *HTR2A*_TDominant. |

**Variables Entered/Removed[a]**

| Model | Variables Entered | Variables Removed | Method |
|---|---|---|---|
| 1 | *HTR2A*_TDominant[b] | . | Enter |

a. Dependent Variable: I have been diagnosed with:
b. All requested variables entered.

**Model Summary**

| Model | R | R Square | Adjusted R Square | Std. Error of the Estimate |
|---|---|---|---|---|
| 1 | .136[a] | .019 | -.010 | .949 |

a. Predictors: (Constant), *HTR2A*_TDominant

**ANOVA[a]**

| Model | | Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|---|
| 1 | Regression | .578 | 1 | .578 | .642 | .429[b] |
| | Residual | 30.644 | 34 | .901 | | |
| | Total | 31.222 | 35 | | | |

a. Dependent Variable: I have been diagnosed with:
b. Predictors: (Constant), *HTR2A*_TDominant

**Coefficients[a]**

| Model | | Unstandardised Coefficients | | Standardised Coefficients | t | Sig. |
|---|---|---|---|---|---|---|
| | | B | Std. Error | Beta | | |
| 1 | (Constant) | 1.096 | .493 | | 2.224 | .033 |
| | *HTR2A*_TDominant | -.254 | .317 | -.136 | -.801 | .429 |

a. Dependent Variable: I have been diagnosed with:

Regression

| Notes |
|---|
| REGRESSION<br>/MISSING LISTWISE<br>/STATISTICS COEFF OUTS R ANOVA<br>/CRITERIA=PIN(.05) POUT(.10)<br>/NOORIGIN<br>/DEPENDENT Q_3.9<br>/METHOD=ENTER *HTR2A*_CDominant. |

**Variables Entered/Removed[a]**

| Model | Variables Entered | Variables Removed | Method |
|---|---|---|---|
| 1 | *HTR2A*_CDominant[b] | . | Enter |

a. Dependent Variable: I have been diagnosed with:

b. All requested variables entered.

**Model Summary**

| Model | R | R Square | Adjusted R Square | Std. Error of the Estimate |
|---|---|---|---|---|
| 1 | .084[a] | .007 | -.022 | .955 |

a. Predictors: (Constant), *HTR2A*_CDominant

**ANOVA[a]**

| Model | | Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|---|
| 1 | Regression | .222 | 1 | .222 | .244 | .625[b] |
| | Residual | 31.000 | 34 | .912 | | |
| | Total | 31.222 | 35 | | | |

a. Dependent Variable: I have been diagnosed with:
b. Predictors: (Constant), *HTR2A*_CDominant

**Coefficients[a]**

| Model | | Unstandardised Coefficients | | Standardised Coefficients | t | Sig. |
|---|---|---|---|---|---|---|
| | | B | Std. Error | Beta | | |
| 1 | (Constant) | 1.000 | .585 | | 1.710 | .096 |
| | *HTR2A*_CDominant | -.250 | .506 | -.084 | -.494 | .625 |

a. Dependent Variable: I have been diagnosed with:

Regression

| Notes |
|---|
| REGRESSION<br>/MISSING LISTWISE<br>/STATISTICS COEFF OUTS R ANOVA<br>/CRITERIA=PIN(.05) POUT(.10)<br>/NOORIGIN<br>/DEPENDENT ADHD<br>/METHOD=ENTER *HTR1B*_G_C. |

**Variables Entered/Removed[a]**

| Model | Variables Entered | Variables Removed | Method |
|---|---|---|---|
| 1 | *HTR1B*_G_C[b] | . | Enter |

a. Dependent Variable: ADHD or Control
b. All requested variables entered.

**Model Summary**

| Model | R | R Square | Adjusted R Square | Std. Error of the Estimate |
|---|---|---|---|---|
| 1 | .083[a] | .007 | -.015 | .49507 |

a. Predictors: (Constant), *HTR1B*_G_C

**ANOVA[a]**

| Model | | Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|---|
| 1 | Regression | .077 | 1 | .077 | .315 | .577[b] |
| | Residual | 11.029 | 45 | .245 | | |
| | Total | 11.106 | 46 | | | |

a. Dependent Variable: ADHD or Control
b. Predictors: (Constant), *HTR1B*_G_C

**Coefficients[a]**

| Model | | Unstandardised Coefficients | | Standardised Coefficients | t | Sig. |
|---|---|---|---|---|---|---|
| | | B | Std. Error | Beta | | |
| 1 | (Constant) | 1.459 | .290 | | 5.033 | .000 |
| | *HTR1B*_G_C | .145 | .259 | .083 | .562 | .577 |

a. Dependent Variable: ADHD or Control

Regression

| Notes |
|---|
| REGRESSION<br>/MISSING LISTWISE<br>/STATISTICS COEFF OUTS R ANOVA<br>/CRITERIA=PIN(.05) POUT(.10)<br>/NOORIGIN<br>/DEPENDENT ADHD<br>/METHOD=ENTER *HTR1B*_C_G. |

**Variables Entered/Removed[a]**

| Model | Variables Entered | Variables Removed | Method |
|---|---|---|---|
| 1 | *HTR1B*_C_G[b] | . | Enter |

a. Dependent Variable: ADHD or Control
b. All requested variables entered.

**Model Summary**

| Model | R | R Square | Adjusted R Square | Std. Error of the Estimate |
|---|---|---|---|---|
| 1 | .012[a] | .000 | -.022 | .49676 |

a. Predictors: (Constant), *HTR1B*_C_G

**ANOVA[a]**

| Model | | Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|---|
| 1 | Regression | .002 | 1 | .002 | .006 | .937[b] |
| | Residual | 11.105 | 45 | .247 | | |
| | Total | 11.106 | 46 | | | |

a. Dependent Variable: ADHD or Control
b. Predictors: (Constant), *HTR1B*_C_G

**Coefficients[a]**

| Model | | Unstandardised Coefficients | | Standardised Coefficients | t | Sig. |
|---|---|---|---|---|---|---|
| | | B | Std. Error | Beta | | |
| 1 | (Constant) | 1.601 | .217 | | 7.363 | .000 |
| | *HTR1B*_C_G | .012 | .153 | .012 | .079 | .937 |

a. Dependent Variable: ADHD or Control

Regression

| Notes |
|---|
| REGRESSION<br>/MISSING LISTWISE<br>/STATISTICS COEFF OUTS R ANOVA<br>/CRITERIA=PIN(.05) POUT(.10)<br>/NOORIGIN<br>/DEPENDENT ADHD<br>/METHOD=ENTER HTTsnp_GDominant. |

**Variables Entered/Removed[a]**

| Model | Variables Entered | Variables Removed | Method |
|---|---|---|---|
| 1 | HTTsnp_GDominant[b] | . | Enter |

a. Dependent Variable: ADHD or Control
b. All requested variables entered.

**Model Summary**

| Model | R | R Square | Adjusted R Square | Std. Error of the Estimate |
|---|---|---|---|---|
| 1 | .417[a] | .174 | .139 | .46033 |

a. Predictors: (Constant), HTTsnp_GDominant

**ANOVA[a]**

| Model | | Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|---|
| 1 | Regression | 1.068 | 1 | 1.068 | 5.041 | .034[b] |
| | Residual | 5.086 | 24 | .212 | | |
| | Total | 6.154 | 25 | | | |

a. Dependent Variable: ADHD or Control
b. Predictors: (Constant), HTTsnp_GDominant

**Coefficients[a]**

| Model | | Unstandardised Coefficients | | Standardised Coefficients | t | Sig. |
|---|---|---|---|---|---|---|
| | | B | Std. Error | Beta | | |
| 1 | (Constant) | .686 | .424 | | 1.618 | .119 |
| | HTTsnp_GDominant | .514 | .229 | .417 | 2.245 | .034 |

a. Dependent Variable: ADHD or Control

Regression

| Notes |
|---|
| REGRESSION<br>/MISSING LISTWISE<br>/STATISTICS COEFF OUTS R ANOVA<br>/CRITERIA=PIN(.05) POUT(.10)<br>/NOORIGIN<br>/DEPENDENT ADHD<br>/METHOD=ENTER HTTLPR_SDominant. |

**Variables Entered/Removed[a]**

| Model | Variables Entered | Variables Removed | Method |
|---|---|---|---|
| 1 | HTTLPR_SDominant[b] | . | Enter |

a. Dependent Variable: ADHD or Control
b. All requested variables entered.

**Model Summary**

| Model | R | R Square | Adjusted R Square | Std. Error of the Estimate |
|---|---|---|---|---|
| 1 | .584[a] | .341 | .316 | .42044 |

a. Predictors: (Constant), HTTLPR_SDominant

**ANOVA[a]**

| Model | | Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|---|
| 1 | Regression | 2.469 | 1 | 2.469 | 13.966 | .001[b] |
| | Residual | 4.773 | 27 | .177 | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | Total | 7.241 | 28 | | | |

a. Dependent Variable: ADHD or Control
b. Predictors: (Constant), HTTLPR_SDominant

**Coefficients[a]**

| Model | | Unstandardised Coefficients | | Standardised Coefficients | t | Sig. |
|---|---|---|---|---|---|---|
| | | B | Std. Error | Beta | | |
| 1 | (Constant) | .636 | .240 | | 2.656 | .013 |
| | HTTLPR_SDominant | .682 | .182 | .584 | 3.737 | .001 |

a. Dependent Variable: ADHD or Control

Regression

| Notes |
|---|
| REGRESSION<br>/MISSING LISTWISE<br>/STATISTICS COEFF OUTS R ANOVA<br>/CRITERIA=PIN(.05) POUT(.10)<br>/NOORIGIN<br>/DEPENDENT ADHD<br>/METHOD=ENTER HTTLPR_LDominant. |

**Variables Entered/Removed[a]**

| Model | Variables Entered | Variables Removed | Method |
|---|---|---|---|
| 1 | HTTLPR_LDominant[b] | . | Enter |

a. Dependent Variable: ADHD or Control
b. All requested variables entered.

**Model Summary**

| Model | R | R Square | Adjusted R Square | Std. Error of the Estimate |
|---|---|---|---|---|
| 1 | .251[a] | .063 | .028 | .50127 |

a. Predictors: (Constant), HTTLPR_LDominant

**ANOVA[a]**

| Model | | Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|---|
| 1 | Regression | .457 | 1 | .457 | 1.819 | .189[b] |
| | Residual | 6.784 | 27 | .251 | | |
| | Total | 7.241 | 28 | | | |

a. Dependent Variable: ADHD or Control
b. Predictors: (Constant), HTTLPR_LDominant

**Coefficients[a]**

| Model | | Unstandardised Coefficients | | Standardised Coefficients | t | Sig. |
|---|---|---|---|---|---|---|
| | | B | Std. Error | Beta | | |
| 1 | (Constant) | 1.843 | .283 | | 6.514 | .000 |
| | HTTLPR_LDominant | -.255 | .189 | -.251 | -1.349 | .189 |

a. Dependent Variable: ADHD or Control

## Figure 4.13

**Regression**

| Notes |
|---|
| REGRESSION<br>/MISSING LISTWISE<br>/STATISTICS COEFF OUTS R ANOVA<br>/CRITERIA=PIN(.05) POUT(.10)<br>/NOORIGIN<br>/DEPENDENT ADHD_diagnosis_type<br>/METHOD=ENTER *HTR2A*_Corr_Reshuffled. |

**Variables Entered/Removed[a]**

| Model | Variables Entered | Variables Removed | Method |
|---|---|---|---|
| 1 | *HTR2A*_Corr_Reshuffled[b] | | Enter |

a. Dependent Variable: I have been diagnosed with:
b. All requested variables entered.

**Model Summary**

| Model | R | R Square | Adjusted R Square | Std. Error of the Estimate |
|---|---|---|---|---|
| 1 | .528[a] | .279 | .231 | .629 |

a. Predictors: (Constant), *HTR2A*_Corr_Reshuffled

**ANOVA[a]**

| Model | | Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|---|
| 1 | Regression | 2.298 | 1 | 2.298 | 5.805 | .029[b] |
| | Residual | 5.938 | 15 | .396 | | |
| | Total | 8.235 | 16 | | | |

b. Predictors: (Constant), *HTR2A*_Corr_Reshuffled

**Coefficients[a]**

| Model | | Unstandardised Coefficients | Standardised Coefficients | | t | Sig. |
|---|---|---|---|---|---|---|
| | | B | Std. Error | Beta | | |
| 1 | (Constant) | .917 | .297 | | 3.091 | .007 |
| | *HTR2A*_Corr_Reshuffled | .260 | .108 | .528 | 2.409 | .029 |

## Figure 4.15

**Decision Tree**
**Target Category: ADHD**

| | Node | | Gain | | | |
|---|---|---|---|---|---|---|
| Node | N | Percent | N | Percent | Response | Index |
| 2 | 22 | 42.3% | 15 | 83.3% | 68.2% | 197.0% |
| 1 | 30 | 57.7% | 3 | 16.7% | 10.0% | 28.9% |

Growing Method: CHAID
Dependent Variable: ADHD or Control

**Risk**

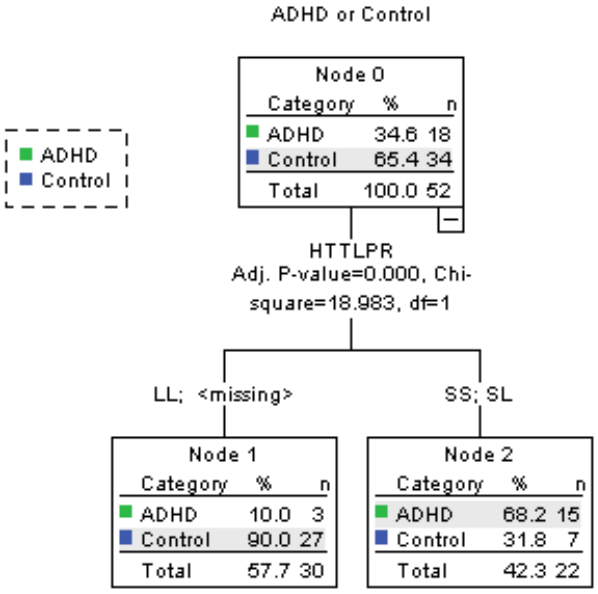
| Estimate | Std. Error |
|---|---|
| .192 | .055 |

Growing Method: CHAID
Dependent Variable: ADHD or Control

**Classification**

| Observed | Predicted | | |
|---|---|---|---|
| | ADHD | Control | Percent Correct |
| ADHD | 15 | 3 | 83.3% |
| Control | 7 | 27 | 79.4% |
| Overall Percentage | 42.3% | 57.7% | 80.8% |

Growing Method: CHAID
Dependent Variable: ADHD or Control




## ANOVA – 5-HTTLPR and ADHD presence

**Oneway**

**Descriptives**

Control_ADHD

| | N | Mean | Std. Deviation | Std. Error | 95% Confidence Interval for Mean | | Minimum | Maximum |
|---|---|---|---|---|---|---|---|---|
| | | | | | Lower Bound | Upper Bound | | |
| SS | 12 | 1.6667 | .49237 | .14213 | 1.3538 | 1.9795 | 1.00 | 2.00 |
| SL | 10 | 1.7000 | .48305 | .15275 | 1.3544 | 2.0456 | 1.00 | 2.00 |
| LL | 7 | 1.0000 | .00000 | .00000 | 1.0000 | 1.0000 | 1.00 | 1.00 |
| Total | 29 | 1.5172 | .50855 | .09443 | 1.3238 | 1.7107 | 1.00 | 2.00 |

**ANOVA**

Control_ADHD

| | Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|
| Between Groups | 2.475 | 2 | 1.237 | 6.749 | .004 |
| Within Groups | 4.767 | 26 | .183 | | |
| Total | 7.241 | 28 | | | |

## Figure 4.16

**Regression**

| Notes |
|---|

```
REGRESSION
  /MISSING LISTWISE
  /STATISTICS COEFF OUTS R ANOVA
  /CRITERIA=PIN(.05) POUT(.10)
  /NOORIGIN
  /DEPENDENT Inattentive
                /METHOD=ENTER HTTLPR_SDominant.
```

**Variables Entered/Removed[a]**

| Model | Variables Entered | Variables Removed | Method |
|---|---|---|---|
| 1 | HTTLPR_SDominant[b] | . | Enter |

a. Dependent Variable: Inattentive
b. All requested variables entered.

**Model Summary**

| Model | R | R Square | Adjusted R Square | Std. Error of the Estimate |
|---|---|---|---|---|
| 1 | .553[a] | .306 | .275 | .43127 |

a. Predictors: (Constant), HTTLPR_SDominant

**ANOVA[a]**

| Model | | Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|---|
| 1 | Regression | 1.882 | 1 | 1.882 | 10.120 | .004[b] |
| | Residual | 4.278 | 23 | .186 | | |
| | Total | 6.160 | 24 | | | |

a. Dependent Variable: Inattentive
b. Predictors: (Constant), HTTLPR_SDominant

**Coefficients[a]**

| Model | | Unstandardised Coefficients | | Standardised Coefficients | t | Sig. |
|---|---|---|---|---|---|---|
| | | B | Std. Error | Beta | | |
| 1 | (Constant) | 1.222 | .261 | | 4.690 | .000 |
| | HTTLPR_SDominant | -.611 | .192 | -.553 | -3.181 | .004 |

a. Dependent Variable: Inattentive

**Regression**

**Notes**

```
REGRESSION
  /MISSING LISTWISE
  /STATISTICS COEFF OUTS R ANOVA
  /CRITERIA=PIN(.05) POUT(.10)
  /NOORIGIN
  /DEPENDENT Hyperactive
                /METHOD=ENTER HTTLPR_SDominant.
```

**Variables Entered/Removed[a]**

| Model | Variables Entered | Variables Removed | Method |
|---|---|---|---|
| 1 | HTTLPR_SDominant[b] | . | Enter |

a. Dependent Variable: Hyperactive
b. All requested variables entered.

**Model Summary**

| Model | R | R Square | Adjusted R Square | Std. Error of the Estimate |
|---|---|---|---|---|
| 1 | .468[a] | .219 | .185 | .44233 |

a. Predictors: (Constant), HTTLPR_SDominant

**ANOVA[a]**

| Model | | Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|---|
| 1 | Regression | 1.260 | 1 | 1.260 | 6.440 | .018[b] |
| | Residual | 4.500 | 23 | .196 | | |
| | Total | 5.760 | 24 | | | |

a. Dependent Variable: Hyperactive
b. Predictors: (Constant), HTTLPR_SDominant

**Coefficients[a]**

| Model | | Unstandardised Coefficients | | Standardised Coefficients | t | Sig. |
|---|---|---|---|---|---|---|
| | | B | Std. Error | Beta | | |
| 1 | (Constant) | 1.000 | .267 | | 3.742 | .001 |
| | HTTLPR_SDominant | -.500 | .197 | -.468 | -2.538 | .018 |

a. Dependent Variable: Hyperactive

**Logistic Regression**

| Notes |
|---|
| LOGISTIC REGRESSION VARIABLES ADHD<br>/METHOD=ENTER HTTLPR<br>/CLASSPLOT<br>/CASEWISE OUTLIER(2)<br>/PRINT=GOODFIT CI(95)<br>/CRITERIA=PIN(0.05) POUT(0.10) ITERATE(20) CUT(0.5). |

**Block 0: Beginning Block**

**Classification Table[a,b]**

| Observed | | | Predicted | | |
|---|---|---|---|---|---|
| | | | ADHD or Control | | Percentage Correct |
| | | | ADHD | Control | |
| Step 0 | ADHD or Control | ADHD | 15 | 0 | 100.0 |
| | | Control | 14 | 0 | 0.0 |
| | Overall Percentage | | | | 51.7 |

a. Constant is included in the model.
b. The cut value is .500

**Variables in the Equation**

| | | B | S.E. | Wald | df | Sig. | Exp(B) |
|---|---|---|---|---|---|---|---|
| Step 0 | Constant | -.069 | .372 | .034 | 1 | .853 | .933 |

Variables not in the Equation

| | | | Score | df | Sig. |
|---|---|---|---|---|---|
| Step 0 | Variables | HTTLPR | 6.471 | 1 | .011 |
| | Overall Statistics | | 6.471 | 1 | .011 |

Block 1: Method = Enter

Omnibus Tests of Model Coefficients

| | | Chi-square | df | Sig. |
|---|---|---|---|---|
| Step 1 | Step | 6.915 | 1 | .009 |
| | Block | 6.915 | 1 | .009 |
| | Model | 6.915 | 1 | .009 |

Model Summary

| Step | -2 Log likelihood | Cox & Snell R Square | Nagelkerke R Square |
|---|---|---|---|
| 1 | 33.253[a] | .212 | .283 |

a. Estimation terminated at iteration number 4 because parameter estimates changed by less than .001.

Hosmer and Lemeshow Test

| Step | Chi-square | df | Sig. |
|---|---|---|---|
| 1 | 4.583 | 1 | .032 |

Contingency Table for Hosmer and Lemeshow Test

| | | ADHD or Control = ADHD | | ADHD or Control = Control | | |
|---|---|---|---|---|---|---|
| | | Observed | Expected | Observed | Expected | Total |
| Step 1 | 1 | 8 | 9.221 | 4 | 2.779 | 12 |
| | 2 | 7 | 4.558 | 3 | 5.442 | 10 |
| | 3 | 0 | 1.221 | 7 | 5.779 | 7 |

Classification Table[a]

| | | Predicted | | |
|---|---|---|---|---|
| | | ADHD or Control | | Percentage Correct |
| Observed | | ADHD | Control | |
| Step 1 | ADHD | 8 | 7 | 53.3 |

| | | | | |
|---|---|---|---|---|
| | ADHD or Control | Control | 4 | 10 | 71.4 |
| | Overall Percentage | | | | 62.1 |

a. The cut value is .500

**Variables in the Equation**

| | | B | S.E. | Wald | df | Sig. | Exp(B) | 95% C.I.for EXP(B) Lower | Upper |
|---|---|---|---|---|---|---|---|---|---|
| Step 1[a] | HTTLPR | 1.377 | .585 | 5.531 | 1 | .019 | 3.963 | 1.258 | 12.483 |
| | Constant | -2.576 | 1.135 | 5.154 | 1 | .023 | .076 | | |

a. Variable(s) entered on step 1: HTTLPR.

Figure 4.17

**Target Category: ADHD combined type**

**Gains for Nodes**

| Node | Node | | Gain | | Response | Index |
|---|---|---|---|---|---|---|
| | N | Percent | N | Percent | | |
| 1 | 18 | 43.9% | 3 | 100.0% | 16.7% | 227.8% |
| 2 | 23 | 56.1% | 0 | 0.0% | 0.0% | 0.0% |

Growing Method: CHAID
Dependent Variable: ADHD_Type

**Risk**

| Estimate | Std. Error |
|---|---|
| .317 | .073 |

Growing Method: CHAID
Dependent Variable: ADHD_Type

**Classification**

| Observed | Predicted | | | | |
|---|---|---|---|---|---|
| | Control | ADHD combined | ADHD inattentive | ADHD Hyperactive | Percent Correct |
| Control | 20 | 0 | 7 | 0 | 74.1% |
| ADHD combined type | 0 | 0 | 3 | 0 | 0.0% |
| ADHD inattentive | 1 | 0 | 8 | 0 | 88.9% |
| ADHD Hyperactive | 2 | 0 | 0 | 0 | 0.0% |
| Overall Percentage | 56.1% | 0.0% | 43.9% | 0.0% | 68.3% |

Growing Method: CHAID
Dependent Variable: ADHD_Type

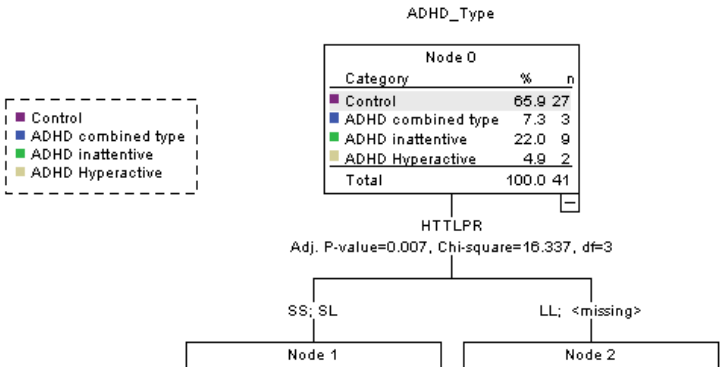


Figure 4.20

**Regression**

**Notes**

```
REGRESSION
  /MISSING LISTWISE
  /STATISTICS COEFF OUTS R ANOVA
  /CRITERIA=PIN(.05) POUT(.10)
  /NOORIGIN
  /DEPENDENT ASRS_Full_Diag
  /METHOD=ENTER HTTsnp.
```

**Variables Entered/Removed[a]**

| Model | Variables Entered | Variables Removed | Method |
|---|---|---|---|
| 1 | HTTsnp[b] | | Enter |

a. Dependent Variable: ASRS_Full_Diag

b. All requested variables entered.

**Model Summary**

| Model | R | R Square | Adjusted R Square | Std. Error of the Estimate |
|---|---|---|---|---|
| 1 | .618[a] | .381 | .320 | 5.09510 |

a. Predictors: (Constant), HTTsnp

**ANOVA[a]**

| Model | | Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|---|
| 1 | Regression | 160.067 | 1 | 160.067 | 6.166 | .032[b] |
| | Residual | 259.600 | 10 | 25.960 | | |
| | Total | 419.667 | 11 | | | |

a. Dependent Variable: ASRS_Full_Diag

b. Predictors: (Constant), HTTsnp

**Coefficients[a]**

| Model | Unstandardised Coefficients | Standardised Coefficients | t | Sig. |
|---|---|---|---|---|

| | | B | Std. Error | Beta | | |
|---|---|---|---|---|---|---|
| 1 | (Constant) | -3.600 | 4.834 | | -.745 | .474 |
| | HTTsnp | 9.800 | 3.947 | .618 | 2.483 | .032 |

a. Dependent Variable: ASRS_Full_Diag

Regression

Notes

```
REGRESSION
 /MISSING LISTWISE
 /STATISTICS COEFF OUTS R ANOVA
 /CRITERIA=PIN(.05) POUT(.10)
 /NOORIGIN
 /DEPENDENT ASRS_Hyperactivity_Diag
 /METHOD=ENTER HTTsnp.
```

Variables Entered/Removed[a]

| Model | Variables Entered | Variables Removed | Method |
|---|---|---|---|
| 1 | HTTsnp[b] | | Enter |

a. Dependent Variable: ASRS_Hyperactivity_Diag

b. All requested variables entered.

Model Summary

| Model | R | R Square | Adjusted R Square | Std. Error of the Estimate |
|---|---|---|---|---|
| 1 | .623[a] | .388 | .327 | 2.46171 |

a. Predictors: (Constant), HTTsnp

ANOVA[a]

| Model | | Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|---|
| 1 | Regression | 38.400 | 1 | 38.400 | 6.337 | .031[b] |
| | Residual | 60.600 | 10 | 6.060 | | |
| | Total | 99.000 | 11 | | | |

a. Dependent Variable: ASRS_Hyperactivity_Diag

b. Predictors: (Constant), HTTsnp

Coefficients[a]

| | | Unstandardised Coefficients | | Standardised Coefficients | | |
|---|---|---|---|---|---|---|
| Model | | B | Std. Error | Beta | t | Sig. |
| 1 | (Constant) | -2.100 | 2.335 | | -.899 | .390 |
| | HTTsnp | 4.800 | 1.907 | .623 | 2.517 | .031 |

a. Dependent Variable: ASRS_Hyperactivity_Diag

Figure 4.21

Regression

Notes

```
REGRESSION
  /MISSING LISTWISE
  /STATISTICS COEFF OUTS R ANOVA
  /CRITERIA=PIN(.05) POUT(.10)
  /NOORIGIN
  /DEPENDENT Inattentive
 /METHOD=ENTER HTTLPR_SDominant HTR1B_Corrected.
```

Variables Entered/Removed[a]

| Model | Variables Entered | Variables Removed | Method |
|---|---|---|---|
| 1 | *HTR1B*_Corrected, HTTLPR_SDominant[b] | . | Enter |

a. Dependent Variable: Inattentive
b. All requested variables entered.

Model Summary

| Model | R | R Square | Adjusted R Square | Std. Error of the Estimate |
|---|---|---|---|---|
| 1 | .660[a] | .436 | .382 | .40008 |

a. Predictors: (Constant), *HTR1B*_Corrected, HTTLPR_SDominant

ANOVA[a]

| Model | | Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|---|
| 1 | Regression | 2.597 | 2 | 1.298 | 8.112 | .002[b] |
| | Residual | 3.361 | 21 | .160 | | |
| | Total | 5.958 | 23 | | | |

a. Dependent Variable: Inattentive
b. Predictors: (Constant), *HTR1B*_Corrected, HTTLPR_SDominant

Coefficients[a]

| Model | | Unstandardised Coefficients | | Standardised Coefficients | t | Sig. |
|---|---|---|---|---|---|---|
| | | B | Std. Error | Beta | | |
| 1 | (Constant) | 1.725 | .343 | | 5.032 | .000 |
| | HTTLPR_SDominant | -.726 | .185 | -.662 | -3.925 | .001 |
| | *HTR1B*_Corrected | -.239 | .133 | -.304 | -1.804 | .086 |

a. Dependent Variable: Inattentive

# Appendix 9

## Chapter 5 outputs

Correlations

| | | ADHD_Type | *HTR2A*_Corr_Reshuffled | *HTR2A*_Corrected | HTTLPR_SDominant | *HTR1B*_Corrected | *HTR1B*_Reshuffled | HTTsnp | Medical_problems | Medical_probs_corr | Psychological_problems | Psychological_problems_corr | Developmental_problems | Developmental_probs_corr | Learning_Disorder | Learning_disorder_corr | Smoker | Smoker_corr | Hypoxia_corr | Poor_sleep | Poor_sleep_corr | ASRS_Pre_Diag | ASRS_Pre_Diag_Innattentive | ASRS_Pre_Diag_Hyper | ASRS_Full_Diag | ASRS_Inattention_Diag |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *HTR2A*_Corr_Reshuffled | r | -.062 | | | | | | | | | | | | | | | | | | | | | | | | |
| | Sig | .690 | | | | | | | | | | | | | | | | | | | | | | | | |
| | n | 44 | | | | | | | | | | | | | | | | | | | | | | | | |
| *HTR2A*_Corrected | r | .062 | .675 | | | | | | | | | | | | | | | | | | | | | | | |
| | Sig | .689 | .000 | | | | | | | | | | | | | | | | | | | | | | | |
| | n | 44 | 44 | | | | | | | | | | | | | | | | | | | | | | | |
| HTTLPR_SDominant | r | -.419 | .155 | -.005 | | | | | | | | | | | | | | | | | | | | | | |
| | Sig | .024 | .449 | .980 | | | | | | | | | | | | | | | | | | | | | | |
| | n | 29 | 26 | 26 | | | | | | | | | | | | | | | | | | | | | | |
| *HTR1B*_Corrected | r | -.228 | .097 | .108 | -.273 | | | | | | | | | | | | | | | | | | | | | |
| | Sig | .123 | .552 | .507 | .160 | | | | | | | | | | | | | | | | | | | | | |
| | n | 47 | 40 | 40 | 28 | | | | | | | | | | | | | | | | | | | | | |
| *HTR1B*_Reshuffled | r | .016 | .080 | -.140 | .000 | .035 | | | | | | | | | | | | | | | | | | | | |
| | Sig | .913 | .626 | .389 | 1.000 | .814 | | | | | | | | | | | | | | | | | | | | |
| | n | 47 | 40 | 40 | 28 | 47 | | | | | | | | | | | | | | | | | | | | |
| HTTsnp | r | .055 | -.069 | -.158 | -.054 | .174 | -.110 | | | | | | | | | | | | | | | | | | | |
| | Sig | .790 | .742 | .450 | .838 | .417 | .610 | | | | | | | | | | | | | | | | | | | |
| | n | 26 | 25 | 25 | 17 | 24 | 24 | | | | | | | | | | | | | | | | | | | |
| Medical_problems | r | .246 | -.084 | -.072 | -.194 | .029 | .035 | .268 | | | | | | | | | | | | | | | | | | |
| | Sig | .052 | .643 | .691 | .353 | .860 | .832 | .268 | | | | | | | | | | | | | | | | | | |
| | n | 63 | 33 | 33 | 25 | 39 | 39 | 19 | | | | | | | | | | | | | | | | | | |
| Medical_probs_corr | r | .386 | -.175 | .076 | -.430 | -.135 | -.042 | .207 | .551 | | | | | | | | | | | | | | | | | |
| | Sig | .004 | .392 | .711 | .032 | .460 | .819 | .442 | .000 | | | | | | | | | | | | | | | | | |
| | n | 53 | 26 | 26 | 25 | 32 | 32 | 16 | 53 | | | | | | | | | | | | | | | | | |
| Psychological_problems | r | .214 | -.001 | -.035 | .036 | -.056 | .196 | .215 | .373 | .440 | | | | | | | | | | | | | | | | |
| | Sig | .092 | .994 | .847 | .863 | .735 | .232 | .376 | .003 | .001 | | | | | | | | | | | | | | | | |
| | n | 63 | 33 | 33 | 25 | 39 | 39 | 19 | 63 | 53 | | | | | | | | | | | | | | | | |
| | r | .074 | -.205 | .023 | -.120 | -.194 | -.124 | -.112 | .332 | .608 | .551 | | | | | | | | | | | | | | | |

| | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Psychological_problems_corr | Sig | .599 | .314 | .911 | .569 | .287 | .501 | .681 | .015 | .000 | .000 | | | | | | | | | | | | | | |
| | n | 53 | 26 | 26 | 25 | 32 | 32 | 16 | 53 | 53 | 53 | | | | | | | | | | | | | | |
| Developmental_problems | r | .483 | -.164 | .026 | -.509 | .050 | -.263 | .022 | .279 | .532 | .295 | .354 | | | | | | | | | | | | | |
| | Sig | .000 | .422 | .899 | .009 | .787 | .146 | .937 | .043 | .000 | .032 | .009 | | | | | | | | | | | | | |
| | n | 53 | 26 | 26 | 25 | 32 | 32 | 16 | 53 | 53 | 53 | 53 | | | | | | | | | | | | | |
| Developmental_pro bs_corr | r | .383 | -.273 | -.057 | -.441 | -.044 | -.122 | .225 | .390 | .561 | .390 | .410 | .840 | | | | | | | | | | | | |
| | Sig | .005 | .178 | .782 | .027 | .813 | .505 | .402 | .004 | .000 | .004 | .002 | .000 | | | | | | | | | | | | |
| | n | 53 | 26 | 26 | 25 | 32 | 32 | 16 | 53 | 53 | 53 | 53 | 53 | | | | | | | | | | | | |
| Learning_Disorder | r | .280 | -.241 | .027 | -.184 | -.186 | -.058 | .[c] | .319 | .551 | .121 | .413 | .230 | .370 | | | | | | | | | | | |
| | Sig | .042 | .235 | .895 | .379 | .309 | .753 | 0.000 | .020 | .000 | .388 | .002 | .098 | .006 | | | | | | | | | | | |
| | n | 53 | 26 | 26 | 25 | 32 | 32 | 16 | 53 | 53 | 53 | 53 | 53 | 53 | | | | | | | | | | | |
| Learning_disorder_corr | r | .294 | -.246 | -.057 | -.184 | -.174 | -.054 | .[c] | .332 | .623 | .199 | .505 | .304 | .505 | .887 | | | | | | | | | | |
| | Sig | .032 | .226 | .782 | .379 | .341 | .768 | 0.000 | .015 | .000 | .154 | .000 | .027 | .000 | .000 | | | | | | | | | | |
| | n | 53 | 26 | 26 | 25 | 32 | 32 | 16 | 53 | 53 | 53 | 53 | 53 | 53 | 53 | | | | | | | | | | |
| Smoker | r | .295 | .091 | .055 | -.468 | .067 | .021 | -.041 | .176 | .502 | .522 | .362 | .404 | .442 | .172 | .249 | | | | | | | | | |
| | Sig | .032 | .659 | .791 | .018 | .716 | .910 | .879 | .207 | .000 | .000 | .008 | .003 | .001 | .218 | .073 | | | | | | | | | |
| | n | 53 | 26 | 26 | 25 | 32 | 32 | 16 | 53 | 53 | 53 | 53 | 53 | 53 | 53 | 53 | | | | | | | | | |
| Smoker_corr | r | .221 | -.035 | .036 | -.433 | -.005 | .017 | .097 | .216 | .601 | .484 | .432 | .392 | .421 | .201 | .246 | .919 | | | | | | | | |
| | Sig | .112 | .864 | .860 | .031 | .979 | .928 | .721 | .121 | .000 | .000 | .001 | .004 | .002 | .148 | .075 | .000 | | | | | | | | |
| | n | 53 | 26 | 26 | 25 | 32 | 32 | 16 | 53 | 53 | 53 | 53 | 53 | 53 | 53 | 53 | 53 | | | | | | | | |
| Hypoxia_corr | r | .155 | -.320 | -.126 | -.431 | .005 | .118 | -.037 | .425 | .637 | .296 | .314 | .363 | .402 | .430 | .364 | .420 | .496 | | | | | | | |
| | Sig | .269 | .110 | .540 | .032 | .977 | .519 | .893 | .001 | .000 | .032 | .022 | .008 | .003 | .001 | .007 | .002 | .000 | | | | | | | |
| | n | 53 | 26 | 26 | 25 | 32 | 32 | 16 | 53 | 53 | 53 | 53 | 53 | 53 | 53 | 53 | 53 | 53 | | | | | | | |
| Poor_sleep | r | .033 | -.017 | -.203 | .127 | -.218 | .068 | .231 | .168 | .113 | .130 | .139 | .267 | .224 | .128 | .113 | .092 | .134 | .153 | | | | | | |
| | Sig | .814 | .936 | .320 | .544 | .230 | .712 | .390 | .230 | .421 | .352 | .320 | .053 | .106 | .362 | .419 | .511 | .338 | .274 | | | | | | |
| | n | 53 | 26 | 26 | 25 | 32 | 32 | 16 | 53 | 53 | 53 | 53 | 53 | 53 | 53 | 53 | 53 | 53 | 53 | | | | | | |
| Poor_sleep_corr | r | .290 | -.007 | -.084 | -.161 | -.293 | -.062 | .272 | .435 | .432 | .385 | .353 | .445 | .407 | .192 | .196 | .477 | .556 | .465 | .602 | | | | | |
| | Sig | .035 | .974 | .685 | .443 | .104 | .736 | .307 | .001 | .001 | .004 | .009 | .001 | .002 | .169 | .160 | .000 | .000 | .000 | .000 | | | | | |
| | n | 53 | 26 | 26 | 25 | 32 | 32 | 16 | 53 | 53 | 53 | 53 | 53 | 53 | 53 | 53 | 53 | 53 | 53 | 53 | | | | | |
| ASRS_Pre_Diag | r | .569 | -.164 | -.085 | -.595 | -.126 | .142 | .269 | .303 | .500 | .378 | .325 | .660 | .594 | .229 | .259 | .405 | .419 | .410 | .183 | .474 | | | | |
| | Sig | .000 | .414 | .673 | .004 | .486 | .430 | .352 | .028 | .001 | .005 | .033 | .000 | .000 | .139 | .094 | .007 | .005 | .006 | .241 | .001 | | | | |
| | n | 53 | 27 | 27 | 21 | 33 | 33 | 14 | 53 | 43 | 53 | 43 | 43 | 43 | 43 | 43 | 43 | 43 | 43 | 43 | 43 | | | | |
| ASRS_Pre_Diag_Innattentive | r | .518 | -.044 | -.081 | -.548 | -.196 | .094 | .285 | .286 | .452 | .288 | .284 | .613 | .518 | .208 | .209 | .328 | .317 | .354 | .255 | .441 | .944 | | | | |
| | Sig | .000 | .829 | .686 | .010 | .274 | .603 | .322 | .038 | .002 | .036 | .065 | .000 | .000 | .182 | .179 | .032 | .039 | .020 | .098 | .003 | .000 | | | | |
| | n | 53 | 27 | 27 | 21 | 33 | 33 | 14 | 53 | 43 | 53 | 43 | 43 | 43 | 43 | 43 | 43 | 43 | 43 | 43 | 43 | 53 | | | |
| ASRS_Pre_Diag_Hyper | r | .473 | -.351 | -.061 | -.486 | .069 | .191 | .101 | .232 | .432 | .423 | .299 | .539 | .550 | .197 | .272 | .421 | .481 | .385 | -.016 | .385 | .765 | .511 | | | |
| | Sig | .000 | .073 | .764 | .026 | .703 | .287 | .732 | .095 | .004 | .002 | .051 | .000 | .000 | .205 | .078 | .005 | .001 | .011 | .917 | .011 | .000 | .000 | | | |
| | n | 53 | 27 | 27 | 21 | 33 | 33 | 14 | 53 | 43 | 53 | 43 | 43 | 43 | 43 | 43 | 43 | 43 | 43 | 43 | 43 | 53 | 53 | | |
| ASRS_Full_Diag | r | .719 | .092 | .109 | -.445 | -.061 | .177 | .618 | .476 | .590 | .490 | .438 | .598 | .564 | .338 | .362 | .479 | .495 | .406 | -.070 | .539 | .850 | .713 | .698 | | |
| | Sig | .000 | .683 | .629 | .073 | .767 | .386 | .032 | .001 | .000 | .001 | .006 | .000 | .000 | .038 | .025 | .002 | .002 | .011 | .677 | .000 | .000 | .000 | .000 | | |
| | n | 45 | 22 | 22 | 17 | 26 | 26 | 12 | 45 | 38 | 45 | 38 | 38 | 38 | 38 | 38 | 38 | 38 | 38 | 38 | 38 | 45 | 45 | 45 | | |

| | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ASRS_Inattention_Diag | r | .729 | .220 | .095 | -.433 | -.104 | .159 | .556 | .445 | .477 | .431 | .349 | .620 | .562 | .248 | .276 | .400 | .399 | .316 | .050 | .543 | .885 | .834 | .571 | .951 | |
| | Sig | .000 | .326 | .674 | .082 | .614 | .438 | .060 | .002 | .002 | .003 | .032 | .000 | .000 | .133 | .094 | .013 | .013 | .054 | .765 | .000 | .000 | .000 | .000 | .000 | |
| | n | 45 | 22 | 22 | 17 | 26 | 26 | 12 | 45 | 38 | 45 | 38 | 38 | 38 | 38 | 38 | 38 | 38 | 38 | 38 | 38 | 45 | 45 | 45 | 45 | |
| ASRS_Hyperactivity_Diag | r | .635 | -.058 | .112 | -.413 | -.009 | .178 | .623 | .458 | .641 | .501 | .480 | .508 | .503 | .393 | .411 | .507 | .538 | .454 | -.186 | .474 | .726 | .516 | .757 | .948 | .803 |
| | Sig | .000 | .797 | .620 | .099 | .967 | .385 | .031 | .002 | .000 | .000 | .002 | .001 | .001 | .015 | .010 | .001 | .000 | .004 | .263 | .003 | .000 | .000 | .000 | .000 | .000 |
| | n | 45 | 22 | 22 | 17 | 26 | 26 | 12 | 45 | 38 | 45 | 38 | 38 | 38 | 38 | 38 | 38 | 38 | 38 | 38 | 38 | 45 | 45 | 45 | 45 | 45 |

| | | ADHD_Type | *HTR2A*_Corr_Reshuffled | *HTR2A*_Corrected | HTTLPR_SDominant | *HTR1B*_Corrected | *HTR1B*_Reshuffled | HTTsnp | ASRS_Pre_Diag | ASRS_Pre_Diag_Innattentive | ASRS_Pre_Diag_Hyper | ASRS_Full_Diag | ASRS_Inattention_Diag | ASRS_Hyperactivity_Diag | WFIRS_Family | Family_Impairment | WFIRS_SchoolWork | Work_Impairment | WFIRS_LifeSkills | Life_Skills_Impairment | WFIRS_SelfConcept | SelfConcept_Impairment | WFIRS_SocialAct | SocialAct_Impairment | WFIRS_RiskyAct |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *HTR2A*_Corr_Reshuffled | r | -.062 | | | | | | | | | | | | | | | | | | | | | | | |
| | Sig | .690 | | | | | | | | | | | | | | | | | | | | | | | |
| | n | 44 | | | | | | | | | | | | | | | | | | | | | | | |
| *HTR2A*_Corrected | r | .062 | .675 | | | | | | | | | | | | | | | | | | | | | | |
| | Sig | .689 | .000 | | | | | | | | | | | | | | | | | | | | | | |
| | n | 44 | 44 | | | | | | | | | | | | | | | | | | | | | | |
| HTTLPR_SDominant | r | -.419 | .155 | -.005 | | | | | | | | | | | | | | | | | | | | | |
| | Sig | .024 | .449 | .980 | | | | | | | | | | | | | | | | | | | | | |
| | n | 29 | 26 | 26 | | | | | | | | | | | | | | | | | | | | | |
| *HTR1B*_Corrected | r | -.228 | .097 | .108 | -.273 | | | | | | | | | | | | | | | | | | | | |
| | Sig | .123 | .552 | .507 | .160 | | | | | | | | | | | | | | | | | | | | |
| | n | 47 | 40 | 40 | 28 | | | | | | | | | | | | | | | | | | | | |
| *HTR1B*_Reshuffled | r | .016 | .080 | -.140 | .000 | .035 | | | | | | | | | | | | | | | | | | | |
| | Sig | .913 | .626 | .389 | 1.000 | .814 | | | | | | | | | | | | | | | | | | | |
| | n | 47 | 40 | 40 | 28 | 47 | | | | | | | | | | | | | | | | | | | |
| HTTsnp | r | .055 | -.069 | -.158 | -.054 | .174 | -.110 | | | | | | | | | | | | | | | | | | |
| | Sig | .790 | .742 | .450 | .838 | .417 | .610 | | | | | | | | | | | | | | | | | | |
| | n | 26 | 25 | 25 | 17 | 24 | 24 | | | | | | | | | | | | | | | | | | |
| ASRS_Pre_Diag | r | .569 | -.164 | -.085 | -.595 | -.126 | .142 | .269 | | | | | | | | | | | | | | | | | |
| | Sig | .000 | .414 | .673 | .004 | .486 | .430 | .352 | | | | | | | | | | | | | | | | | |
| | n | 53 | 27 | 27 | 21 | 33 | 33 | 14 | | | | | | | | | | | | | | | | | |
| | r | .518 | -.044 | -.081 | -.548 | -.196 | .094 | .285 | .944 | | | | | | | | | | | | | | | | |
| | Sig | .000 | .829 | .686 | .010 | .274 | .603 | .322 | .000 | | | | | | | | | | | | | | | | |

| | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ASRS_Pre_Diag_Inattentive | n | 53 | 27 | 27 | 21 | 33 | 33 | 14 | 53 | | | | | | | | | | | | | | | |
| ASRS_Pre_Diag_Hyper | r | .473 | -.351 | -.061 | -.486 | .069 | .191 | .101 | .765 | .511 | | | | | | | | | | | | | | |
| | Sig | .000 | .073 | .764 | .026 | .703 | .287 | .732 | .000 | .000 | | | | | | | | | | | | | | |
| | n | 53 | 27 | 27 | 21 | 33 | 33 | 14 | 53 | 53 | | | | | | | | | | | | | | |
| ASRS_Full_Diag | r | .719 | .092 | .109 | -.445 | -.061 | .177 | .618 | .850 | .713 | .698 | | | | | | | | | | | | | |
| | Sig | .000 | .683 | .629 | .073 | .767 | .386 | .032 | .000 | .000 | .000 | | | | | | | | | | | | | |
| | n | 45 | 22 | 22 | 17 | 26 | 26 | 12 | 45 | 45 | 45 | | | | | | | | | | | | | |
| ASRS_Inattention_Diag | r | .729 | .220 | .095 | -.433 | -.104 | .159 | .556 | .885 | .834 | .571 | .951 | | | | | | | | | | | | |
| | Sig | .000 | .326 | .674 | .082 | .614 | .438 | .060 | .000 | .000 | .000 | .000 | | | | | | | | | | | | |
| | n | 45 | 22 | 22 | 17 | 26 | 26 | 12 | 45 | 45 | 45 | 45 | | | | | | | | | | | | |
| ASRS_Hyperactivity_Diag | r | .635 | -.058 | .112 | -.413 | -.009 | .178 | .623 | .726 | .516 | .757 | .948 | .803 | | | | | | | | | | | |
| | Sig | .000 | .797 | .620 | .099 | .967 | .385 | .031 | .000 | .000 | .000 | .000 | .000 | | | | | | | | | | | |
| | n | 45 | 22 | 22 | 17 | 26 | 26 | 12 | 45 | 45 | 45 | 45 | 45 | | | | | | | | | | | |
| WFIRS_Family | r | -.111 | -.217 | -.163 | .[c] | .632 | .632 | .533 | .379 | .334 | .226 | .431 | .444 | .295 | | | | | | | | | | |
| | Sig | .599 | .477 | .595 | 0.000 | .015 | .015 | .218 | .062 | .102 | .277 | .032 | .026 | .153 | | | | | | | | | | |
| | n | 25 | 13 | 13 | 11 | 14 | 14 | 7 | 25 | 25 | 25 | 25 | 25 | 25 | | | | | | | | | | |
| Family_Impairment | r | -.452 | -.053 | -.118 | .[c] | .452 | .452 | .400 | .216 | .263 | .032 | .270 | .325 | .147 | .629 | | | | | | | | | |
| | Sig | .023 | .864 | .701 | 0.000 | .104 | .104 | .374 | .299 | .204 | .881 | .191 | .113 | .483 | .001 | | | | | | | | | |
| | n | 25 | 13 | 13 | 11 | 14 | 14 | 7 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | | | | | | | | | |
| WFIRS_SchoolWork | r | -.156 | .096 | -.183 | .[c] | -.060 | -.060 | .504 | .558 | .501 | .321 | .482 | .530 | .303 | .731 | .490 | | | | | | | | |
| | Sig | .456 | .756 | .550 | 0.000 | .839 | .839 | .249 | .004 | .011 | .118 | .015 | .006 | .141 | .000 | .013 | | | | | | | | |
| | n | 25 | 13 | 13 | 11 | 14 | 14 | 7 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | | | | | | | | |
| Work_Impairment | r | -.267 | -.010 | -.234 | .[c] | .330 | .330 | .400 | .649 | .463 | .532 | .622 | .657 | .413 | .480 | .579 | .645 | | | | | | | |
| | Sig | .197 | .974 | .443 | 0.000 | .249 | .249 | .374 | .000 | .020 | .006 | .001 | .000 | .040 | .015 | .002 | .000 | | | | | | | |
| | n | 25 | 13 | 13 | 11 | 14 | 14 | 7 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | | | | | | | |
| WFIRS_LifeSkills | r | .166 | -.233 | -.363 | .[c] | .355 | .355 | .349 | .471 | .469 | .207 | .386 | .513 | .169 | .717 | .256 | .479 | .331 | | | | | | |
| | Sig | .429 | .444 | .223 | 0.000 | .213 | .213 | .444 | .018 | .018 | .320 | .057 | .009 | .420 | .000 | .217 | .016 | .106 | | | | | | |
| | n | 25 | 13 | 13 | 11 | 14 | 14 | 7 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | | | | | | |
| Life_Skills_Impairment | r | -.087 | -.214 | -.284 | .[c] | -.055 | -.055 | .091 | .294 | .356 | .045 | .104 | .228 | -.029 | .256 | .214 | .258 | .327 | .596 | | | | | |
| | Sig | .678 | .483 | .347 | 0.000 | .852 | .852 | .846 | .154 | .081 | .830 | .622 | .274 | .892 | .218 | .305 | .214 | .110 | .002 | | | | | |
| | n | 25 | 13 | 13 | 11 | 14 | 14 | 7 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | | | | | |
| WFIRS_SelfConcept | r | .076 | -.226 | -.384 | .[c] | .257 | .257 | -.021 | .405 | .392 | .195 | .209 | .247 | .117 | .538 | .128 | .326 | -.018 | .639 | .352 | | | | |
| | Sig | .719 | .458 | .195 | 0.000 | .375 | .375 | .965 | .044 | .052 | .351 | .315 | .233 | .577 | .006 | .543 | .112 | .933 | .001 | .085 | | | | |
| | n | 25 | 13 | 13 | 11 | 14 | 14 | 7 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | | | | |
| | r | -.158 | .064 | -.523 | .[c] | .145 | .145 | .258 | .505 | .566 | .139 | .115 | .321 | -.088 | .160 | .144 | .219 | .221 | .273 | .273 | .499 | | | |

| | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SelfConcept_Impairment | Sig | .452 | .835 | .067 | 0.000 | .621 | .621 | .576 | .010 | .003 | .506 | .584 | .118 | .674 | .444 | .491 | .293 | .288 | .187 | .186 | .011 | | | | |
| | n | 25 | 13 | 13 | 11 | 14 | 14 | 7 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | | | | |
| WFIRS_SocialAct | r | .127 | .047 | -.268 | .[c] | .210 | .210 | -.065 | .426 | .272 | .393 | .332 | .444 | .143 | .402 | .284 | .400 | .259 | .491 | .179 | .645 | .216 | | | |
| | Sig | .546 | .880 | .376 | 0.000 | .472 | .472 | .890 | .034 | .189 | .052 | .105 | .026 | .495 | .046 | .169 | .048 | .212 | .013 | .393 | .001 | .299 | | | |
| | n | 25 | 13 | 13 | 11 | 14 | 14 | 7 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | | | |
| SocialAct_Impairment | r | 0.000 | .318 | -.181 | .[c] | .101 | .101 | -.091 | .312 | .216 | .266 | .119 | .194 | .023 | .035 | .218 | .258 | .204 | .095 | .089 | .369 | .361 | .739 | | |
| | Sig | 1.000 | .289 | .554 | 0.000 | .732 | .732 | .846 | .129 | .300 | .200 | .569 | .352 | .913 | .867 | .295 | .212 | .328 | .652 | .672 | .070 | .076 | .000 | | |
| | n | 25 | 13 | 13 | 11 | 14 | 14 | 7 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | | |
| WFIRS_RiskyAct | r | -.152 | -.182 | -.253 | .[c] | .618 | .618 | .109 | .527 | .295 | .542 | .525 | .493 | .400 | .657 | .393 | .521 | .451 | .471 | .057 | .528 | .126 | .597 | .291 | |
| | Sig | .468 | .553 | .404 | 0.000 | .019 | .019 | .816 | .007 | .152 | .005 | .007 | .012 | .048 | .000 | .052 | .008 | .024 | .018 | .787 | .007 | .549 | .002 | .159 | |
| | n | 25 | 13 | 13 | 11 | 14 | 14 | 7 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | |
| RiskyAct_Impairment | r | -.252 | -.053 | -.118 | .[c] | .389 | .389 | .548 | .676 | .465 | .578 | .503 | .503 | .357 | .516 | .336 | .579 | .514 | .484 | .168 | .325 | .114 | .466 | .315 | .700 |
| | Sig | .224 | .864 | .701 | 0.000 | .169 | .169 | .203 | .000 | .019 | .002 | .010 | .010 | .080 | .008 | .100 | .002 | .009 | .014 | .421 | .113 | .588 | .019 | .125 | .000 |
| | n | 25 | 13 | 13 | 11 | 14 | 14 | 7 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 |

Figure 5.1

**Regression**

| Notes |
|---|
| REGRESSION<br>/MISSING LISTWISE<br>/STATISTICS COEFF OUTS R ANOVA<br>/CRITERIA=PIN(.05) POUT(.10)<br>/NOORIGIN<br>/DEPENDENT WFIRS_RiskyAct<br>/METHOD=ENTER ASRS_Inattention_Diag *HTR1B*_Corrected. |

**Variables Entered/Removed[a]**

| Model | Variables Entered | Variables Removed | Method |
|---|---|---|---|
| 1 | *HTR1B*_Corrected, ASRS_Inattention_Diag[b] | | Enter |

a. Dependent Variable: WFIRS_RiskyAct
b. All requested variables entered.

**Model Summary**

| Model | R | R Square | Adjusted R Square | Std. Error of the Estimate |
|---|---|---|---|---|
| 1 | .733[a] | .537 | .453 | 3.02999 |

a. Predictors: (Constant), *HTR1B*_Corrected, ASRS_Inattention_Diag

**ANOVA[a]**

| Model | | Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|---|
| 1 | Regression | 117.011 | 2 | 58.505 | 6.373 | .015[b] |
| | Residual | 100.989 | 11 | 9.181 | | |
| | Total | 218.000 | 13 | | | |

a. Dependent Variable: WFIRS_RiskyAct
b. Predictors: (Constant), *HTR1B*_Corrected, ASRS_Inattention_Diag

**Coefficients[a]**

| Model | | Unstandardised Coefficients | | Standardised Coefficients | | |
|---|---|---|---|---|---|---|
| | | B | Std. Error | Beta | t | Sig. |
| 1 | (Constant) | -9.547 | 4.157 | | -2.297 | .042 |
| | ASRS_Inattention_Diag | .925 | .482 | .395 | 1.920 | .081 |
| | *HTR1B*_Corrected | 5.715 | 1.977 | .594 | 2.891 | .015 |

a. Dependent Variable: WFIRS_RiskyAct

Regression

| Notes |
|---|
| REGRESSION<br>/MISSING LISTWISE<br>/STATISTICS COEFF OUTS R ANOVA<br>/CRITERIA=PIN(.05) POUT(.10)<br>/NOORIGIN<br>/DEPENDENT WFIRS_RiskyAct<br>/METHOD=ENTER *HTR1B*_Reshuffled ASRS_Inattention_Diag. |

**Variables Entered/Removed[a]**

| Model | Variables Entered | Variables Removed | Method |
|---|---|---|---|
| 1 | ASRS_Inattention_Diag, *HTR1B*_Reshuffled[b] | . | Enter |

a. Dependent Variable: WFIRS_RiskyAct
b. All requested variables entered.

**Model Summary**

| Model | R | R Square | Adjusted R Square | Std. Error of the Estimate |
|---|---|---|---|---|
| 1 | .733[a] | .537 | .453 | 3.02999 |

a. Predictors: (Constant), ASRS_Inattention_Diag, *HTR1B*_Reshuffled

**ANOVA[a]**

| Model | | Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|---|
| 1 | Regression | 117.011 | 2 | 58.505 | 6.373 | .015[b] |
| | Residual | 100.989 | 11 | 9.181 | | |
| | Total | 218.000 | 13 | | | |

a. Dependent Variable: WFIRS_RiskyAct
b. Predictors: (Constant), ASRS_Inattention_Diag, *HTR1B*_Reshuffled

**Coefficients[a]**

| Model | | Unstandardised Coefficients | | Standardised Coefficients | t | Sig. |
|---|---|---|---|---|---|---|
| | | B | Std. Error | Beta | | |
| 1 | (Constant) | -15.262 | 5.466 | | -2.792 | .018 |
| | *HTR1B*_Reshuffled | 5.715 | 1.977 | .594 | 2.891 | .015 |
| | ASRS_Inattention_Diag | .925 | .482 | .395 | 1.920 | .081 |

a. Dependent Variable: WFIRS_RiskyAct

Figure 5.2

## Nominal Regression

| Notes |
|---|
| NOMREG HTR1B_Corrected (BASE=LAST ORDER=ASCENDING) WITH WFIRS_RiskyAct_Imp<br>/CRITERIA CIN(95) DELTA(0) MXITER(100) MXSTEP(5) CHKSEP(20) LCONVERGE(0) PCONVERGE(0.000001)<br>SINGULAR(0.00000001)<br>/MODEL<br>/STEPWISE=PIN(.05) POUT(0.1) MINEFFECT(0) RULE(SINGLE) ENTRYMETHOD(LR) REMOVALMETHOD(LR)<br>/INTERCEPT=INCLUDE<br>/PRINT=CELLPROB CLASSTABLE FIT PARAMETER SUMMARY LRT CPS STEP MFI. |

**Case Processing Summary**

| | | N | Marginal Percentage |
|---|---|---|---|
| HTR1B_Corrected | GG | 11 | 78.6% |
| | GC | 3 | 21.4% |
| Valid | | 14 | 100.0% |
| Missing | | 60 | |
| Total | | 74 | |
| Subpopulation | | 9[a] | |

a. The dependent variable has only one value observed in 8 (88.9%) subpopulations.

**Model Fitting Information**

| Model | Model Fitting Criteria | Likelihood Ratio Tests | | |
|---|---|---|---|---|
| | -2 Log Likelihood | Chi-Square | df | Sig. |
| Intercept Only | 13.162 | | | |
| Final | 8.326 | 4.836 | 1 | .028 |

**Goodness-of-Fit**

| | Chi-Square | df | Sig. |
|---|---|---|---|
| Pearson | 6.116 | 7 | .526 |
| Deviance | 6.940 | 7 | .435 |

**Pseudo R-Square**

| | |
|---|---|
| Cox and Snell | .292 |

| | |
|---|---|
| Nagelkerke | .452 |
| McFadden | .332 |

**Likelihood Ratio Tests**

| Effect | Model Fitting Criteria | Likelihood Ratio Tests | | |
|---|---|---|---|---|
| | -2 Log Likelihood of Reduced Model | Chi-Square | df | Sig. |
| Intercept | 17.917 | 9.591 | 1 | .002 |
| WFIRS_RiskyAct_Imp | 13.162 | 4.836 | 1 | .028 |

The chi-square statistic is the difference in -2 log-likelihoods between the final model and a reduced model. The reduced model is formed by omitting an effect from the final model. The null hypothesis is that all parameters of that effect are 0.

**Parameter Estimates**

| HTR1B_Corrected[a] | | B | Std. Error | Wald | df | Sig. | Exp(B) | 95% Confidence Interval for Exp(B) | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Lower Bound | Upper Bound |
| GG | Intercept | 3.709 | 1.911 | 3.769 | 1 | .052 | | | |
| | WFIRS_RiskyAct_Imp | -4.582 | 3.125 | 2.150 | 1 | .143 | .010 | 2.237E-5 | 4.678 |

a. The reference category is: GC.

**Classification**

| Observed | Predicted | | |
|---|---|---|---|
| | GG | GC | Percent Correct |
| GG | 11 | 0 | 100.0% |
| GC | 2 | 1 | 33.3% |
| Overall Percentage | 92.9% | 7.1% | 85.7% |

**Observed and Predicted Frequencies**

| WFIRS_RiskyAct_Imp | HTR1B_Corrected | Frequency | | | Percentage | |
|---|---|---|---|---|---|---|
| | | Observed | Predicted | Pearson Residual | Observed | Predicted |
| .00 | GG | 4 | 3.904 | .313 | 100.0% | 97.6% |
| | GC | 0 | .096 | -.313 | 0.0% | 2.4% |
| .20 | GG | 1 | .942 | .247 | 100.0% | 94.2% |
| | GC | 0 | .058 | -.247 | 0.0% | 5.8% |

| | | | | | | |
|---|---|---|---|---|---|---|
| .30 | GG | 1 | .912 | .311 | 100.0% | 91.2% |
| | GC | 0 | .088 | -.311 | 0.0% | 8.8% |
| .40 | GG | 1 | 1.734 | -1.530 | 50.0% | 86.7% |
| | GC | 1 | .266 | 1.530 | 50.0% | 13.3% |
| .50 | GG | 2 | 1.610 | .696 | 100.0% | 80.5% |
| | GC | 0 | .390 | -.696 | 0.0% | 19.5% |
| .60 | GG | 1 | .723 | .619 | 100.0% | 72.3% |
| | GC | 0 | .277 | -.619 | 0.0% | 27.7% |
| .70 | GG | 0 | .623 | -1.285 | 0.0% | 62.3% |
| | GC | 1 | .377 | 1.285 | 100.0% | 37.7% |
| .80 | GG | 1 | .511 | .979 | 100.0% | 51.1% |
| | GC | 0 | .489 | -.979 | 0.0% | 48.9% |
| 1.50 | GG | 0 | .041 | -.206 | 0.0% | 4.1% |
| | GC | 1 | .959 | .206 | 100.0% | 95.9% |

The percentages are based on total observed frequencies in each subpopulation.

Regression

**Notes**

```
REGRESSION
  /MISSING LISTWISE
  /STATISTICS COEFF OUTS R ANOVA
  /CRITERIA=PIN(.05) POUT(.10)
  /NOORIGIN
  /DEPENDENT HTR1B_Reshuffled
 /METHOD=ENTER WFIRS_RiskyAct.
```

**Variables Entered/Removed[a]**

| Model | Variables Entered | Variables Removed | Method |
|---|---|---|---|
| 1 | WFIRS_RiskyAct[b] | . | Enter |

a. Dependent Variable: *HTR1B*_Reshuffled
b. All requested variables entered.

**Model Summary**

| Model | R | R Square | Adjusted R Square | Std. Error of the Estimate |
|---|---|---|---|---|
| 1 | .618[a] | .381 | .330 | .34858 |

a. Predictors: (Constant), WFIRS_RiskyAct

**ANOVA[a]**

| Model | | Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|---|
| 1 | Regression | .899 | 1 | .899 | 7.400 | .019[b] |
| | Residual | 1.458 | 12 | .122 | | |
| | Total | 2.357 | 13 | | | |

a. Dependent Variable: *HTR1B*_Reshuffled
b. Predictors: (Constant), WFIRS_RiskyAct

**Coefficients[a]**

| Model | | Unstandardised Coefficients | | Standardised Coefficients | t | Sig. |
|---|---|---|---|---|---|---|
| | | B | Std. Error | Beta | | |
| 1 | (Constant) | 1.957 | .133 | | 14.756 | .000 |
| | WFIRS_RiskyAct | .064 | .024 | .618 | 2.720 | .019 |

a. Dependent Variable: *HTR1B*_Reshuffled

**Regression**

**Notes**

```
REGRESSION
/MISSING LISTWISE
/STATISTICS COEFF OUTS R ANOVA
/CRITERIA=PIN(.05) POUT(.10)
/NOORIGIN
/DEPENDENT ASRS_Full_Diag
/METHOD=ENTER WFIRS_RiskyAct.
```

**Variables Entered/Removed[a]**

| Model | Variables Entered | Variables Removed | Method |
|---|---|---|---|
| 1 | WFIRS_RiskyAct[b] | | Enter |

a. Dependent Variable: ASRS_Full_Diag
b. All requested variables entered.

**Model Summary**

| Model | R | R Square | Adjusted R Square | Std. Error of the Estimate |
|---|---|---|---|---|
| 1 | .525[a] | .275 | .244 | 2.91120 |

a. Predictors: (Constant), WFIRS_RiskyAct

**ANOVA[a]**

| Model | | Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|---|
| 1 | Regression | 74.113 | 1 | 74.113 | 8.745 | .007[b] |
| | Residual | 194.927 | 23 | 8.475 | | |
| | Total | 269.040 | 24 | | | |

a. Dependent Variable: ASRS_Full_Diag
b. Predictors: (Constant), WFIRS_RiskyAct

**Coefficients[a]**

| Model | | Unstandardised Coefficients | | Standardised Coefficients | t | Sig. |
|---|---|---|---|---|---|---|
| | | B | Std. Error | Beta | | |
| 1 | (Constant) | 10.319 | .882 | | 11.693 | .000 |

| | | | | | |
|---|---|---|---|---|---|
| WFIRS_RiskyAct | .409 | .138 | .525 | 2.957 | .007 |

a. Dependent Variable: ASRS_Full_Diag

Regression

| Notes |
|---|
| REGRESSION<br>/MISSING LISTWISE<br>/STATISTICS COEFF OUTS R ANOVA<br>/CRITERIA=PIN(.05) POUT(.10)<br>/NOORIGIN<br>/DEPENDENT WFIRS_RiskyAct<br>/METHOD=ENTER ASRS_Inattention_Diag ASRS_Hyperactivity_Diag. |

Variables Entered/Removed[a]

| Model | Variables Entered | Variables Removed | Method |
|---|---|---|---|
| 1 | ASRS_Hyperactivity_Diag, ASRS_Inattention_Diag[b] | | Enter |

a. Dependent Variable: WFIRS_RiskyAct
b. All requested variables entered.

Model Summary

| Model | R | R Square | Adjusted R Square | Std. Error of the Estimate |
|---|---|---|---|---|
| 1 | .538[a] | .289 | .225 | 3.78695 |

a. Predictors: (Constant), ASRS_Hyperactivity_Diag, ASRS_Inattention_Diag

ANOVA[a]

| Model | | Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|---|
| 1 | Regression | 128.499 | 2 | 64.250 | 4.480 | .023[b] |
| | Residual | 315.501 | 22 | 14.341 | | |
| | Total | 444.000 | 24 | | | |

a. Dependent Variable: WFIRS_RiskyAct
b. Predictors: (Constant), ASRS_Hyperactivity_Diag, ASRS_Inattention_Diag

Coefficients[a]

| Model | | Unstandardised Coefficients | | Standardised Coefficients | | |
|---|---|---|---|---|---|---|
| | | B | Std. Error | Beta | t | Sig. |
| 1 | (Constant) | -4.241 | 3.155 | | -1.344 | .193 |
| | ASRS_Inattention_Diag | .944 | .471 | .395 | 2.004 | .057 |
| | ASRS_Hyperactivity_Diag | .468 | .390 | .237 | 1.202 | .242 |

a. Dependent Variable: WFIRS_RiskyAct

Figure 5.3

Nominal Regression

| Notes |
|---|

```
NOMREG ADHD_Type (BASE=FIRST ORDER=ASCENDING) BY
HTR1B_Corrected WITH Medical_probs_corr
   Psychological_problems_corr Developmental_probs_corr
Learning_disorder_corr
  /CRITERIA CIN(95) DELTA(0) MXITER(100) MXSTEP(5)
CHKSEP(20) LCONVERGE(0) PCONVERGE(0.000001)
   SINGULAR(0.00000001)
  /MODEL
  /STEPWISE=PIN(.05) POUT(0.1) MINEFFECT(0) RULE(SINGLE)
ENTRYMETHOD(LR) REMOVALMETHOD(LR)
  /INTERCEPT=INCLUDE
  /PRINT=CELLPROB CLASSTABLE FIT PARAMETER SUMMARY LRT
                              CPS STEP MFI.
```

**Case Processing Summary**

| | | N | Marginal Percentage |
|---|---|---|---|
| ADHD_Type | Control | 18 | 56.3% |
| | ADHD combined type | 3 | 9.4% |
| | ADHD inattentive | 9 | 28.1% |
| | ADHD Hyperactive | 2 | 6.3% |
| HTR1B_Corrected | GG | 23 | 71.9% |
| | GC | 6 | 18.8% |
| | CC | 3 | 9.4% |
| Valid | | 32 | 100.0% |
| Missing | | 42 | |
| Total | | 74 | |
| Subpopulation | | 18[a] | |

a. The dependent variable has only one value observed in 16 (88.9%) subpopulations.

**Model Fitting Information**

| | Model Fitting Criteria | Likelihood Ratio Tests | | |
|---|---|---|---|---|
| Model | -2 Log Likelihood | Chi-Square | df | Sig. |
| Intercept Only | 56.256 | | | |
| Final | 20.146 | 36.111 | 18 | .007 |

**Goodness-of-Fit**

| | Chi-Square | df | Sig. |
|---|---|---|---|

| | | | |
|---|---|---|---|
| Pearson | 13.662 | 33 | .999 |
| Deviance | 13.357 | 33 | .999 |

**Pseudo R-Square**

| | |
|---|---|
| Cox and Snell | .676 |
| Nagelkerke | .766 |
| McFadden | .525 |

**Likelihood Ratio Tests**

| | Model Fitting Criteria | Likelihood Ratio Tests | | |
|---|---|---|---|---|
| Effect | -2 Log Likelihood of Reduced Model | Chi-Square | df | Sig. |
| Intercept | 20.146[a] | 0.000 | 0 | |
| Medical_probs_corr | 29.230 | 9.085 | 3 | .028 |
| Psychological_problems_corr | 24.300 | 4.154 | 3 | .245 |
| Developmental_probs_corr | 29.439 | 9.294 | 3 | .026 |
| Learning_disorder_corr | 24.218 | 4.073 | 3 | .254 |
| HTR1B_Corrected | 28.329 | 8.183 | 6 | .225 |

The chi-square statistic is the difference in -2 log-likelihoods between the final model and a reduced model. The reduced model is formed by omitting an effect from the final model. The null hypothesis is that all parameters of that effect are 0.

a. This reduced model is equivalent to the final model because omitting the effect does not increase the degrees of freedom.

**Parameter Estimates**

| ADHD_Type[a] | | B | Std. Error | Wald | df | Sig. | Exp(B) | 95% Confidence Interval for Exp(B) | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Lower Bound | Upper Bound |
| ADHD combined type | Intercept | -41.507 | 4927.977 | .000 | 1 | .993 | | | |
| | Medical_probs_corr | 18.493 | 4927.977 | .000 | 1 | .997 | ######## | 0.000 | .[b] |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Psychological_problems_corr | -1.661 | 1.370 | 1.469 | 1 | .225 | .190 | .013 | 2.786 |
| | Developmental_probs_corr | 4.270 | 2.141 | 3.977 | 1 | .046 | 71.552 | 1.076 | 4757.390 |
| | Learning_disorder_corr | 23.744 | 22838.885 | .000 | 1 | .999 | ######## | 0.000 | .[b] |
| | [HTR1B_Corrected=1.00] | 19.247 | 2.460 | 61.212 | 1 | .000 | ######## | ######## | ######## |
| | [HTR1B_Corrected=2.00] | 22.584 | 0.000 | | 1 | | ######## | ######## | ######## |
| | [HTR1B_Corrected=3.00] | 0[c] | | | 0 | | | | |
| ADHD inattentive | Intercept | -38.938 | 4927.977 | .000 | 1 | .994 | | | |
| | Medical_probs_corr | 18.332 | 4927.977 | .000 | 1 | .997 | ######## | 0.000 | .[b] |
| | Psychological_problems_corr | -2.094 | 1.235 | 2.876 | 1 | .090 | .123 | .011 | 1.386 |
| | Developmental_probs_corr | 3.298 | 1.666 | 3.920 | 1 | .048 | 27.072 | 1.034 | 708.995 |
| | Learning_disorder_corr | 21.735 | 22838.885 | .000 | 1 | .999 | ######## | 0.000 | .[b] |
| | [HTR1B_Corrected=1.00] | 20.848 | 1.456 | 204.949 | 1 | .000 | ######## | ######## | ######## |
| | [HTR1B_Corrected=2.00] | 22.040 | 0.000 | | 1 | | ######## | ######## | ######## |
| | [HTR1B_Corrected=3.00] | 0[c] | | | 0 | | | | |
| ADHD Hyperactive | Intercept | -49.646 | 11928.318 | .000 | 1 | .997 | | | |
| | Medical_probs_corr | 59.977 | 10707.652 | .000 | 1 | .996 | ######## | 0.000 | .[b] |
| | Psychological_problems_corr | -30.278 | 6469.888 | .000 | 1 | .996 | 7.089E-14 | 0.000 | .[b] |
| | Developmental_probs_corr | -26.895 | 10206.940 | .000 | 1 | .998 | 2.087E-12 | 0.000 | .[b] |
| | Learning_disorder_corr | 4.915 | 23433.379 | .000 | 1 | 1.000 | 136.283 | 0.000 | .[b] |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | [HTR1B_Corrected=1.00] | 17.899 | 0.000 | | 1 | | ########## | ########## | ########## |
| | [HTR1B_Corrected=2.00] | -27.135 | 0.000 | | 1 | | 1.642E-12 | 1.642E-12 | 1.642E-12 |
| | [HTR1B_Corrected=3.00] | 0[c] | | | 0 | | | | |

a. The reference category is: Control.

b. Floating point overflow occurred while computing this statistic. Its value is therefore set to system missing.

c. This parameter is set to zero because it is redundant.

**Classification**

| Observed | Predicted | | | | |
|---|---|---|---|---|---|
| | Control | ADHD combined type | ADHD inattentive | ADHD Hyperactive | Percent Correct |
| Control | 17 | 0 | 1 | 0 | 94.4% |
| ADHD combined type | 1 | 1 | 1 | 0 | 33.3% |
| ADHD inattentive | 2 | 1 | 6 | 0 | 66.7% |
| ADHD Hyperactive | 1 | 0 | 0 | 1 | 50.0% |
| Overall Percentage | 65.6% | 6.3% | 25.0% | 3.1% | 78.1% |

**Observed and Predicted Frequencies**

| Learning_disorder_corr | | | | | | Frequency | | | Percentage | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Observed | Predicted | Pearson Residual | Observed | Predicted |
| .00 | .00 | .00 | .00 | GG | Control | 1 | 1.000 | .000 | 100.0% | 100.0% |
| | | | | | ADHD combined type | 0 | .000 | .000 | 0.0% | .0% |
| | | | | | ADHD inattentive | 0 | .000 | .000 | 0.0% | .0% |
| | | | | | ADHD Hyperactive | 0 | .000 | .000 | 0.0% | .0% |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 1.00 | GC | Control | 1 | .171 | 2.201 | 100.0% | 17.1% |
| | | | ADHD combined type | 0 | .111 | -.354 | 0.0% | 11.1% |
| | | | ADHD inattentive | 0 | .718 | -1.594 | 0.0% | 71.8% |
| | | | ADHD Hyperactive | 0 | .000 | .000 | 0.0% | .0% |
| 1.00 | .00 | GG | Control | 1 | 1.000 | .000 | 100.0% | 100.0% |
| | | | ADHD combined type | 0 | .000 | .000 | 0.0% | .0% |
| | | | ADHD inattentive | 0 | .000 | .000 | 0.0% | .0% |
| | | | ADHD Hyperactive | 0 | .000 | .000 | 0.0% | .0% |
| | | GC | Control | 1 | 1.000 | .000 | 100.0% | 100.0% |
| | | | ADHD combined type | 0 | .000 | .000 | 0.0% | .0% |
| | | | ADHD inattentive | 0 | .000 | .000 | 0.0% | .0% |
| | | | ADHD Hyperactive | 0 | .000 | .000 | 0.0% | .0% |
| | 1.00 | GG | Control | 8 | 7.750 | .189 | 80.0% | 77.5% |
| | | | ADHD combined type | 0 | .034 | -.185 | 0.0% | .3% |
| | | | ADHD inattentive | 1 | 1.216 | -.209 | 10.0% | 12.2% |
| | | | ADHD Hyperactive | 1 | 1.000 | .000 | 10.0% | 10.0% |
| | | GC | Control | 1 | 1.829 | -.981 | 33.3% | 61.0% |
| | | | ADHD combined type | 1 | .226 | 1.693 | 33.3% | 7.5% |
| | | | ADHD inattentive | 1 | .945 | .068 | 33.3% | 31.5% |
| | | | ADHD Hyperactive | 0 | .000 | .000 | 0.0% | .0% |
| | | CC | Control | 1 | 1.000 | .000 | 100.0% | 100.0% |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | ADHD combined type | 0 | .000 | .000 | 0.0% | .0% |
| | | | | ADHD inattentive | 0 | .000 | .000 | 0.0% | .0% |
| | | | | ADHD Hyperactive | 0 | .000 | .000 | 0.0% | .0% |
| | 2.00 | 1.00 | GG | Control | 1 | .980 | .142 | 100.0% | 98.0% |
| | | | | ADHD combined type | 0 | .001 | -.029 | 0.0% | .1% |
| | | | | ADHD inattentive | 0 | .019 | -.139 | 0.0% | 1.9% |
| | | | | ADHD Hyperactive | 0 | .000 | .000 | 0.0% | .0% |
| 1.00 | 1.00 | 1.00 | GG | Control | 0 | .539 | -.811 | 0.0% | 18.0% |
| | | | | ADHD combined type | 0 | .170 | -.424 | 0.0% | 5.7% |
| | | | | ADHD inattentive | 3 | 2.291 | .964 | 100.0% | 76.4% |
| | | | | ADHD Hyperactive | 0 | .000 | .000 | 0.0% | .0% |
| | | | CC | Control | 2 | 2.000 | .000 | 100.0% | 100.0% |
| | | | | ADHD combined type | 0 | .000 | .000 | 0.0% | .0% |
| | | | | ADHD inattentive | 0 | .000 | .000 | 0.0% | .0% |
| | | | | ADHD Hyperactive | 0 | .000 | .000 | 0.0% | .0% |
| | 2.00 | 2.00 | GG | Control | 0 | .000 | .000 | 0.0% | .0% |
| | | | | ADHD combined type | 0 | .118 | -.366 | 0.0% | 11.8% |
| | | | | ADHD inattentive | 1 | .882 | .366 | 100.0% | 88.2% |
| | | | | ADHD Hyperactive | 0 | .000 | .000 | 0.0% | .0% |
| 2.00 | 1.00 | 2.00 | GG | Control | 0 | .000 | .000 | 0.0% | .0% |
| | | | | ADHD combined type | 0 | .187 | -.479 | 0.0% | 18.7% |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | ADHD inattentive | 1 | .813 | .479 | 100.0% | 81.3% |
| | | | | | ADHD Hyperactive | 0 | .000 | .000 | 0.0% | .0% |
| | | | | GC | Control | 0 | .000 | .000 | 0.0% | .0% |
| | | | | | ADHD combined type | 0 | .663 | -1.401 | 0.0% | 66.3% |
| | | | | | ADHD inattentive | 1 | .337 | 1.401 | 100.0% | 33.7% |
| | | | | | ADHD Hyperactive | 0 | .000 | .000 | 0.0% | .0% |
| | | 4.00 | 1.00 | GG | Control | 1 | .730 | .608 | 100.0% | 73.0% |
| | | | | | ADHD combined type | 0 | .113 | -.356 | 0.0% | 11.3% |
| | | | | | ADHD inattentive | 0 | .157 | -.432 | 0.0% | 15.7% |
| | | | | | ADHD Hyperactive | 0 | .000 | .000 | 0.0% | .0% |
| | 3.00 | 1.00 | 2.00 | GG | Control | 0 | .000 | .000 | 0.0% | .0% |
| | | | | | ADHD combined type | 1 | .378 | 1.283 | 100.0% | 37.8% |
| | | | | | ADHD inattentive | 0 | .622 | -1.283 | 0.0% | 62.2% |
| | | | | | ADHD Hyperactive | 0 | .000 | .000 | 0.0% | .0% |
| 1.00 | .00 | 1.00 | 1.00 | GG | Control | 0 | .000 | .000 | 0.0% | .0% |
| | | | | | ADHD combined type | 0 | .173 | -.457 | 0.0% | 17.3% |
| | | | | | ADHD inattentive | 1 | .827 | .457 | 100.0% | 82.7% |
| | | | | | ADHD Hyperactive | 0 | .000 | .000 | 0.0% | .0% |
| | 2.00 | 3.00 | 3.00 | GG | Control | 0 | .000 | .000 | 0.0% | .0% |
| | | | | | ADHD combined type | 1 | .827 | .457 | 100.0% | 82.7% |
| | | | | | ADHD inattentive | 0 | .173 | -.457 | 0.0% | 17.3% |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | ADHD Hyperactive | 0 | .000 | .000 | 0.0% | .0% |
| 2.00 | 1.00 | 1.00 | 3.00 | GG | Control | 0 | .000 | .000 | 0.0% | .0% |
| | | | | | ADHD combined type | 0 | .000 | .000 | 0.0% | .0% |
| | | | | | ADHD inattentive | 0 | .000 | .000 | 0.0% | .0% |
| | | | | | ADHD Hyperactive | 1 | 1.000 | .000 | 100.0% | 100.0% |

The percentages are based on total observed frequencies in each subpopulation.

Figure 5.4

Regression

| Notes |
|---|
| REGRESSION<br>/MISSING LISTWISE<br>/STATISTICS COEFF OUTS R ANOVA<br>/CRITERIA=PIN(.05) POUT(.10)<br>/NOORIGIN<br>/DEPENDENT ASRS_Inattention_Diag<br>/METHOD=ENTER *HTR2A*_Corr_Reshuffled<br>SelfConcept_Impairment. |

**Variables Entered/Removed[a]**

| Model | Variables Entered | Variables Removed | Method |
|---|---|---|---|
| 1 | SelfConcept_Impairment, *HTR2A*_Corr_Reshuffled[b] | . | Enter |

a. Dependent Variable: ASRS_Inattention_Diag
b. All requested variables entered.

**Model Summary**

| Model | R | R Square | Adjusted R Square | Std. Error of the Estimate |
|---|---|---|---|---|
| 1 | .713[a] | .508 | .410 | 1.37276 |

a. Predictors: (Constant), SelfConcept_Impairment, *HTR2A*_Corr_Reshuffled

**ANOVA[a]**

| Model | | Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|---|
| 1 | Regression | 19.463 | 2 | 9.732 | 5.164 | .029[b] |
| | Residual | 18.845 | 10 | 1.884 | | |
| | Total | 38.308 | 12 | | | |

a. Dependent Variable: ASRS_Inattention_Diag
b. Predictors: (Constant), SelfConcept_Impairment, *HTR2A*_Corr_Reshuffled

**Coefficients[a]**

| Model | Unstandardised Coefficients | | Standardised Coefficients | t | Sig. |
|---|---|---|---|---|---|
| | B | Std. Error | Beta | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| 1 | (Constant) | 3.108 | 1.480 | | 2.100 | .062 |
| | *HTR2A*_Corr_Reshuffled | -.054 | .276 | -.043 | -.196 | .849 |
| | SelfConcept_Impairment | 4.601 | 1.432 | .714 | 3.214 | .009 |

a. Dependent Variable: ASRS_Inattention_Diag

Regression

| Notes |
|---|
| REGRESSION<br>/MISSING LISTWISE<br>/STATISTICS COEFF OUTS R ANOVA<br>/CRITERIA=PIN(.05) POUT(.10)<br>/NOORIGIN<br>/DEPENDENT ASRS_Pre_Diag<br>/METHOD=ENTER *HTR2A*_Corr_Reshuffled SelfConcept_Impairment. |

**Variables Entered/Removed[a]**

| Model | Variables Entered | Variables Removed | Method |
|---|---|---|---|
| 1 | SelfConcept_Impairment, *HTR2A*_Corr_Reshuffled[b] | . | Enter |

a. Dependent Variable: ASRS_Pre_Diag

b. All requested variables entered.

**Model Summary**

| Model | R | R Square | Adjusted R Square | Std. Error of the Estimate |
|---|---|---|---|---|
| 1 | .796[a] | .634 | .560 | .92269 |

a. Predictors: (Constant), SelfConcept_Impairment, *HTR2A*_Corr_Reshuffled

**ANOVA[a]**

| Model | | Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|---|
| 1 | Regression | 14.717 | 2 | 7.359 | 8.643 | .007[b] |
| | Residual | 8.514 | 10 | .851 | | |
| | Total | 23.231 | 12 | | | |

a. Dependent Variable: ASRS_Pre_Diag

b. Predictors: (Constant), SelfConcept_Impairment, *HTR2A*_Corr_Reshuffled

**Coefficients[a]**

| Model | | Unstandardised Coefficients | | Standardised Coefficients | t | Sig. |
|---|---|---|---|---|---|---|
| | | B | Std. Error | Beta | | |
| 1 | (Constant) | 1.432 | .995 | | 1.440 | .180 |
| | *HTR2A*_Corr_Reshuffled | -.216 | .186 | -.223 | -1.164 | .272 |
| | SelfConcept_Impairment | 3.905 | .962 | .778 | 4.058 | .002 |

a. Dependent Variable: ASRS_Pre_Diag

Figure 5.5

Regression

| Notes |
|---|
| REGRESSION<br>/MISSING LISTWISE<br>/STATISTICS COEFF OUTS R ANOVA<br>/CRITERIA=PIN(.05) POUT(.10)<br>/NOORIGIN<br>/DEPENDENT ADHD<br>/METHOD=ENTER Medical_probs_corr Smoker_corr Poor_sleep_corr HTTLPR_SDominant. |

**Variables Entered/Removed[a]**

| Model | Variables Entered | Variables Removed | Method |
|---|---|---|---|
| 1 | HTTLPR_SDominant, Poor_sleep_corr, Medical_probs_corr, Smoker_corr[b] | . | Enter |

a. Dependent Variable: ADHD or Control

b. All requested variables entered.

**Model Summary**

| Model | R | R Square | Adjusted R Square | Std. Error of the Estimate |
|---|---|---|---|---|
| 1 | .644[a] | .414 | .297 | .42476 |

a. Predictors: (Constant), HTTLPR_SDominant, Poor_sleep_corr, Medical_probs_corr, Smoker_corr

**ANOVA[a]**

| Model | | Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|---|
| 1 | Regression | 2.552 | 4 | .638 | 3.535 | .024[b] |
| | Residual | 3.608 | 20 | .180 | | |
| | Total | 6.160 | 24 | | | |

a. Dependent Variable: ADHD or Control

b. Predictors: (Constant), HTTLPR_SDominant, Poor_sleep_corr, Medical_probs_corr, Smoker_corr

**Coefficients[a]**

| Model | | Unstandardised Coefficients | | Standardised Coefficients | t | Sig. |
|---|---|---|---|---|---|---|
| | | B | Std. Error | Beta | | |
| 1 | (Constant) | 1.361 | .414 | | 3.283 | .004 |
| | Medical_probs_corr | -.196 | .187 | -.232 | -1.050 | .306 |
| | Smoker_corr | -.025 | .046 | -.135 | -.545 | .592 |
| | Poor_sleep_corr | -.026 | .075 | -.071 | -.347 | .732 |
| | HTTLPR_SDominant | .423 | .217 | .383 | 1.947 | .066 |

a. Dependent Variable: ADHD or Control

Figure 5.6

Regression

**Notes**

```
REGRESSION
/MISSING LISTWISE
/STATISTICS COEFF OUTS R ANOVA
/CRITERIA=PIN(.05) POUT(.10)
/NOORIGIN
/DEPENDENT ADHD
/METHOD=ENTER HTTLPR
/METHOD=ENTER Psychological_problems_corr.
```

**Variables Entered/Removed[a]**

| Model | Variables Entered | Variables Removed | Method |
|---|---|---|---|
| 1 | HTTLPR[b] | | Enter |
| 2 | Psychological_problems_corr[b] | | Enter |

a. Dependent Variable: ADHD or Control

b. All requested variables entered.

**Model Summary**

| Model | R | R Square | Adjusted R Square | Std. Error of the Estimate |
|---|---|---|---|---|
| 1 | .462[a] | .214 | .179 | .45891 |
| 2 | .489[b] | .240 | .170 | .46145 |

a. Predictors: (Constant), HTTLPR

b. Predictors: (Constant), HTTLPR, Psychological_problems_corr

**ANOVA[a]**

| Model | | Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|---|
| 1 | Regression | 1.316 | 1 | 1.316 | 6.250 | .020[b] |
| | Residual | 4.844 | 23 | .211 | | |
| | Total | 6.160 | 24 | | | |
| 2 | Regression | 1.475 | 2 | .738 | 3.465 | .049[c] |
| | Residual | 4.685 | 22 | .213 | | |

| | | | | | |
|---|---|---|---|---|---|
| Total | 6.160 | 24 | | | |

a. Dependent Variable: ADHD or Control
b. Predictors: (Constant), HTTLPR
c. Predictors: (Constant), HTTLPR, Psychological_problems_corr

**Coefficients[a]**

| Model | | Unstandardised Coefficients | | Standardised Coefficients | | |
|---|---|---|---|---|---|---|
| | | B | Std. Error | Beta | t | Sig. |
| 1 | (Constant) | 1.031 | .231 | | 4.473 | .000 |
| | HTTLPR | .281 | .112 | .462 | 2.500 | .020 |
| 2 | (Constant) | 1.127 | .257 | | 4.388 | .000 |
| | HTTLPR | .290 | .114 | .476 | 2.552 | .018 |
| | Psychological_problems_corr | -.096 | .111 | -.161 | -.865 | .397 |

a. Dependent Variable: ADHD or Control

**Excluded Variables[a]**

| Model | | Beta In | t | Sig. | Partial Correlation | Collinearity Statistics |
|---|---|---|---|---|---|---|
| | | | | | | Tolerance |
| 1 | Psychological_problems_corr | -.161[b] | -.865 | .397 | -.181 | .992 |

a. Dependent Variable: ADHD or Control
b. Predictors in the Model: (Constant), HTTLPR

## Figure 5.7

**Regression**

**Notes**

```
REGRESSION
  /MISSING LISTWISE
  /STATISTICS COEFF OUTS R ANOVA
  /CRITERIA=PIN(.05) POUT(.10)
  /NOORIGIN
  /DEPENDENT ADHD
              /METHOD=ENTER HTTLPR_SDominant
                    Psychological_problems_corr.
```

**Variables Entered/Removed[a]**

| Model | Variables Entered | Variables Removed | Method |
|---|---|---|---|
| 1 | Psychological_problems_corr, HTTLPR_SDominant[b] | . | Enter |

a. Dependent Variable: ADHD or Control
b. All requested variables entered.

**Model Summary**

| Model | R | R Square | Adjusted R Square | Std. Error of the Estimate |
|---|---|---|---|---|
| 1 | .555[a] | .308 | .246 | .44003 |

a. Predictors: (Constant), Psychological_problems_corr, HTTLPR_SDominant

**ANOVA[a]**

| Model | | Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|---|
| 1 | Regression | 1.900 | 2 | .950 | 4.907 | .017[b] |
| | Residual | 4.260 | 22 | .194 | | |
| | Total | 6.160 | 24 | | | |

a. Dependent Variable: ADHD or Control
b. Predictors: (Constant), Psychological_problems_corr, HTTLPR_SDominant

**Coefficients[a]**

| Model | | Unstandardised Coefficients | | Standardised Coefficients | t | Sig. |
|---|---|---|---|---|---|---|
| | | B | Std. Error | Beta | | |
| 1 | (Constant) | .825 | .307 | | 2.686 | .014 |
| | HTTLPR_SDominant | .604 | .197 | .546 | 3.059 | .006 |
| | Psychological_problems_corr | -.032 | .106 | -.055 | -.305 | .763 |

a. Dependent Variable: ADHD or Control

Variables Entered/Removed[a]

| Model | Variables Entered | Variables Removed | Method |
|---|---|---|---|
| 1 | HTTLPR[b] | | Enter |
| 2 | Developmental_probs_corr, Smoker_corr[b] | | Enter |

a. Dependent Variable: ADHD or Control
b. All requested variables entered.

Regression

| Notes |
|---|
| REGRESSION<br>/MISSING LISTWISE<br>/STATISTICS COEFF OUTS R ANOVA<br>/CRITERIA=PIN(.05) POUT(.10)<br>/NOORIGIN<br>/DEPENDENT ADHD<br>/METHOD=ENTER HTTLPR_SDominant Psychological_problems_corr Medical_probs_corr Developmental_probs_corr Learning_disorder_corr Smoker_corr Hypoxia_corr Poor_sleep_corr. |

**Variables Entered/Removed[a]**

| Model | Variables Entered | Variables Removed | Method |
|---|---|---|---|
| 1 | Poor_sleep_corr, Learning_disorder_corr, HTTLPR_SDominant, Psychological_problems_corr, Hypoxia_corr, Smoker_corr, Medical_probs_corr, Developmental_probs_corr[b] | . | Enter |

a. Dependent Variable: ADHD or Control
b. All requested variables entered.

**Model Summary**

| Model | R | R Square | Adjusted R Square | Std. Error of the Estimate |
|---|---|---|---|---|
| 1 | .688[a] | .474 | .210 | .45020 |

a. Predictors: (Constant), Poor_sleep_corr, Learning_disorder_corr, HTTLPR_SDominant, Psychological_problems_corr, Hypoxia_corr, Smoker_corr, Medical_probs_corr, Developmental_probs_corr

**ANOVA[a]**

| Model | | Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|---|
| 1 | Regression | 2.917 | 8 | .365 | 1.799 | .151[b] |
| | Residual | 3.243 | 16 | .203 | | |
| | Total | 6.160 | 24 | | | |

a. Dependent Variable: ADHD or Control
b. Predictors: (Constant), Poor_sleep_corr, Learning_disorder_corr, HTTLPR_SDominant, Psychological_problems_corr, Hypoxia_corr, Smoker_corr, Medical_probs_corr, Developmental_probs_corr

**Coefficients[a]**

| Model | | Unstandardised Coefficients | | Standardised Coefficients | t | Sig. |
|---|---|---|---|---|---|---|
| | | B | Std. Error | Beta | | |
| 1 | (Constant) | 1.300 | .451 | | 2.882 | .011 |
| | HTTLPR_SDominant | .433 | .242 | .391 | 1.785 | .093 |
| | Psychological_problems_corr | .120 | .142 | .201 | .846 | .410 |
| | Medical_probs_corr | -.245 | .274 | -.290 | -.894 | .385 |
| | Developmental_probs_corr | -.070 | .198 | -.119 | -.353 | .728 |
| | Learning_disorder_corr | -.510 | .430 | -.279 | -1.185 | .253 |
| | Smoker_corr | -.017 | .051 | -.089 | -.325 | .750 |
| | Hypoxia_corr | .100 | .124 | .239 | .809 | .430 |
| | Poor_sleep_corr | -.048 | .098 | -.132 | -.496 | .627 |

a. Dependent Variable: ADHD or Control

Figure 5.8

Regression

| Notes |
|---|
| REGRESSION<br>/MISSING LISTWISE<br>/STATISTICS COEFF OUTS R ANOVA<br>/CRITERIA=PIN(.05) POUT(.10)<br>/NOORIGIN<br>/DEPENDENT ASRS_Hyperactivity_Diag<br>/METHOD=ENTER HTTsnp<br>/METHOD=ENTER Psychological_problems. |

Variables Entered/Removed[a]

| Model | Variables Entered | Variables Removed | Method |
|---|---|---|---|
| 1 | HTTsnp[b] | | Enter |
| 2 | Psychological_problems[b] | | Enter |

a. Dependent Variable: ASRS_Hyperactivity_Diag
b. All requested variables entered.

**Model Summary**

| Model | R | R Square | Adjusted R Square | Std. Error of the Estimate |
|---|---|---|---|---|
| 1 | .623[a] | .388 | .327 | 2.46171 |
| 2 | .807[b] | .652 | .574 | 1.95789 |

a. Predictors: (Constant), HTTsnp
b. Predictors: (Constant), HTTsnp, Psychological_problems

**ANOVA[a]**

| Model | | Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|---|
| 1 | Regression | 38.400 | 1 | 38.400 | 6.337 | .031[b] |
| | Residual | 60.600 | 10 | 6.060 | | |
| | Total | 99.000 | 11 | | | |
| 2 | Regression | 64.500 | 2 | 32.250 | 8.413 | .009[c] |
| | Residual | 34.500 | 9 | 3.833 | | |
| | Total | 99.000 | 11 | | | |

a. Dependent Variable: ASRS_Hyperactivity_Diag
b. Predictors: (Constant), HTTsnp
c. Predictors: (Constant), HTTsnp, Psychological_problems

**Coefficients[a]**

| Model | | Unstandardised Coefficients | | Standardised Coefficients | | |
|---|---|---|---|---|---|---|
| | | B | Std. Error | Beta | t | Sig. |
| 1 | (Constant) | -2.100 | 2.335 | | -.899 | .390 |
| | HTTsnp | 4.800 | 1.907 | .623 | 2.517 | .031 |
| 2 | (Constant) | -3.000 | 1.889 | | -1.588 | .147 |
| | HTTsnp | 4.500 | 1.521 | .584 | 2.959 | .016 |
| | Psychological_problems | 3.000 | 1.150 | .515 | 2.609 | .028 |

a. Dependent Variable: ASRS_Hyperactivity_Diag

**Excluded Variables[a]**

| Model | | Beta In | t | Sig. | Partial Correlation | Collinearity Statistics |
|---|---|---|---|---|---|---|
| | | | | | | Tolerance |
| 1 | Psychological_problems | .515[b] | 2.609 | .028 | .656 | .994 |

a. Dependent Variable: ASRS_Hyperactivity_Diag
b. Predictors in the Model: (Constant), HTTsnp

Figure 5.9

Regression

| Notes |
|---|

```
REGRESSION
 /MISSING LISTWISE
 /STATISTICS COEFF OUTS R ANOVA
 /CRITERIA=PIN(.05) POUT(.10)
 /NOORIGIN
 /DEPENDENT ADHD
    /METHOD=ENTER HTTLPR_SDominant
    Developmental_probs_corr Smoker_corr
                Hypoxia_corr.
```

**Variables Entered/Removed[a]**

| Model | Variables Entered | Variables Removed | Method |
|---|---|---|---|
| 1 | Hypoxia_corr, HTTLPR_SDominant, Smoker_corr, Developmental_probs_corr[b] | . | Enter |

a. Dependent Variable: ADHD or Control
b. All requested variables entered.

**Model Summary**

| Model | R | R Square | Adjusted R Square | Std. Error of the Estimate |
|---|---|---|---|---|
| 1 | .620[a] | .384 | .261 | .43559 |

a. Predictors: (Constant), Hypoxia_corr, HTTLPR_SDominant, Smoker_corr, Developmental_probs_corr

**ANOVA[a]**

| Model | | Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|---|
| 1 | Regression | 2.365 | 4 | .591 | 3.116 | .038[b] |
| | Residual | 3.795 | 20 | .190 | | |
| | Total | 6.160 | 24 | | | |

a. Dependent Variable: ADHD or Control
b. Predictors: (Constant), Hypoxia_corr, HTTLPR_SDominant, Smoker_corr, Developmental_probs_corr

**Coefficients[a]**

| Model | | Unstandardised Coefficients | | Standardised Coefficients | t | Sig. |
|---|---|---|---|---|---|---|
| | | B | Std. Error | Beta | | |
| 1 | (Constant) | 1.132 | .359 | | 3.157 | .005 |
| | HTTLPR_SDominant | .435 | .228 | .393 | 1.909 | .071 |
| | Developmental_probs_corr | -.051 | .139 | -.088 | -.368 | .717 |
| | Smoker_corr | -.046 | .042 | -.243 | -1.098 | .285 |
| | Hypoxia_corr | -.015 | .095 | -.036 | -.159 | .876 |

a. Dependent Variable: ADHD or Control

Figure 5.10

Regression

Notes

```
REGRESSION
 /MISSING LISTWISE
 /STATISTICS COEFF OUTS R ANOVA
 /CRITERIA=PIN(.05) POUT(.10)
 /NOORIGIN
 /DEPENDENT ADHD_Type
   /METHOD=ENTER HTR1B_Corrected
       Psychological_problems_corr
Medical_probs_corr HTTLPR_SDominant.
```

**Variables Entered/Removed[a]**

| Model | Variables Entered | Variables Removed | Method |
|---|---|---|---|
| 1 | HTTLPR_SDominant, Psychological_problems_corr, *HTR1B*_Corrected, Medical_probs_corr[b] | . | Enter |

a. Dependent Variable: ADHD_Type

b. All requested variables entered.

**Model Summary**

| Model | R | R Square | Adjusted R Square | Std. Error of the Estimate |
|---|---|---|---|---|
| 1 | .677[a] | .458 | .344 | .75447 |

a. Predictors: (Constant), HTTLPR_SDominant, Psychological_problems_corr, *HTR1B*_Corrected, Medical_probs_corr

**ANOVA[a]**

| Model | | Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|---|
| 1 | Regression | 9.143 | 4 | 2.286 | 4.015 | .016[b] |
| | Residual | 10.815 | 19 | .569 | | |
| | Total | 19.958 | 23 | | | |

a. Dependent Variable: ADHD_Type

b. Predictors: (Constant), HTTLPR_SDominant, Psychological_problems_corr, *HTR1B*_Corrected, Medical_probs_corr

**Coefficients[a]**

| Model | | Unstandardised Coefficients | | Standardised Coefficients | t | Sig. |
|---|---|---|---|---|---|---|
| | | B | Std. Error | Beta | | |
| 1 | (Constant) | 3.029 | .909 | | 3.330 | .004 |
| | *HTR1B*_Corrected | -.508 | .261 | -.353 | -1.949 | .066 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | Psychological_problems_corr | -.307 | .220 | -.274 | -1.396 | .179 |
| | Medical_probs_corr | .325 | .318 | .213 | 1.021 | .320 |
| | HTTLPR_SDominant | -1.186 | .392 | -.591 | -3.028 | .007 |

a. Dependent Variable: ADHD_Type

Figure 5.11

Regression

| Notes |
|---|
| REGRESSION<br>/MISSING LISTWISE<br>/STATISTICS COEFF OUTS R ANOVA<br>/CRITERIA=PIN(.05) POUT(.10)<br>/NOORIGIN<br>/DEPENDENT Inattentive<br>/METHOD=ENTER HTTLPR_SDominant Medical_probs_corr Poor_sleep_corr *HTR2A*_Corr_Reshuffled. |

**Variables Entered/Removed[a]**

| Model | Variables Entered | Variables Removed | Method |
|---|---|---|---|
| 1 | *HTR2A*_Corr_Reshuffled, Poor_sleep_corr, HTTLPR_SDominant, Medical_probs_corr[b] | . | Enter |

a. Dependent Variable: Inattentive
b. All requested variables entered.

**Model Summary**

| Model | R | R Square | Adjusted R Square | Std. Error of the Estimate |
|---|---|---|---|---|
| 1 | .754[a] | .568 | .467 | .37364 |

a. Predictors: (Constant), *HTR2A*_Corr_Reshuffled, Poor_sleep_corr, HTTLPR_SDominant, Medical_probs_corr

**ANOVA[a]**

| Model | | Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|---|
| 1 | Regression | 3.127 | 4 | .782 | 5.599 | .005[b] |
| | Residual | 2.373 | 17 | .140 | | |
| | Total | 5.500 | 21 | | | |

a. Dependent Variable: Inattentive
b. Predictors: (Constant), *HTR2A*_Corr_Reshuffled, Poor_sleep_corr, HTTLPR_SDominant, Medical_probs_corr

**Coefficients[a]**

| Model | | Unstandardised Coefficients | | Standardised Coefficients | t | Sig. |
|---|---|---|---|---|---|---|
| | | B | Std. Error | Beta | | |
| 1 | (Constant) | .949 | .411 | | 2.307 | .034 |
| | HTTLPR_SDominant | -.658 | .196 | -.613 | -3.354 | .004 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | Medical_probs_corr | .201 | .151 | .251 | 1.333 | .200 |
| | Poor_sleep_corr | -.001 | .063 | -.002 | -.013 | .990 |
| | *HTR2A*_Corr_Reshuffled | .083 | .057 | .237 | 1.458 | .163 |

a. Dependent Variable: Inattentive

Figure 5.12

Regression

| Notes |
|---|
| REGRESSION<br>/MISSING LISTWISE<br>/STATISTICS COEFF OUTS R ANOVA<br>/CRITERIA=PIN(.05) POUT(.10)<br>/NOORIGIN<br>/DEPENDENT ADHD_C<br>/METHOD=ENTER Medical_probs_corr Psychological_problems_corr Developmental_probs_corr Learning_disorder_corr Smoker_corr Hypoxia_corr. |

Variables Entered/Removed[a]

| Model | Variables Entered | Variables Removed | Method |
|---|---|---|---|
| 1 | Hypoxia_corr, Psychological_problems_corr, Developmental_probs_corr, Smoker_corr, Learning_disorder_corr, Medical_probs_corr[b] | | Enter |

a. Dependent Variable: ADHD_C
b. All requested variables entered.

Model Summary

| Model | R | R Square | Adjusted R Square | Std. Error of the Estimate |
|---|---|---|---|---|
| 1 | .629[a] | .395 | .316 | .29887 |

a. Predictors: (Constant), Hypoxia_corr, Psychological_problems_corr, Developmental_probs_corr, Smoker_corr, Learning_disorder_corr, Medical_probs_corr

ANOVA[a]

| Model | | Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|---|
| 1 | Regression | 2.683 | 6 | .447 | 5.007 | .001[b] |
| | Residual | 4.109 | 46 | .089 | | |
| | Total | 6.792 | 52 | | | |

a. Dependent Variable: ADHD_C
b. Predictors: (Constant), Hypoxia_corr, Psychological_problems_corr, Developmental_probs_corr, Smoker_corr, Learning_disorder_corr, Medical_probs_corr

Coefficients[a]

| Model | | Unstandardised Coefficients | | Standardised Coefficients | | |
|---|---|---|---|---|---|---|
| | | B | Std. Error | Beta | t | Sig. |
| 1 | (Constant) | -.191 | .100 | | -1.904 | .063 |
| | Medical_probs_corr | .167 | .106 | .334 | 1.570 | .123 |

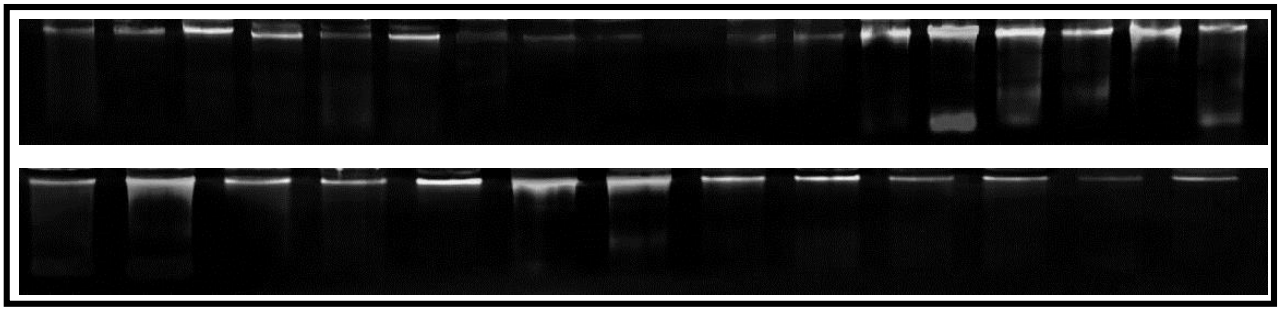
| | | | | | |
|---|---|---|---|---|---|
| Psychological_problems_corr | .067 | .063 | .161 | 1.065 | .293 |
| Developmental_probs_corr | -.027 | .058 | -.069 | -.472 | .639 |
| Learning_disorder_corr | -.098 | .087 | -.179 | -1.124 | .267 |
| Smoker_corr | .041 | .022 | .287 | 1.869 | .068 |
| Hypoxia_corr | .037 | .049 | .116 | .760 | .451 |

a. Dependent Variable: ADHD_C

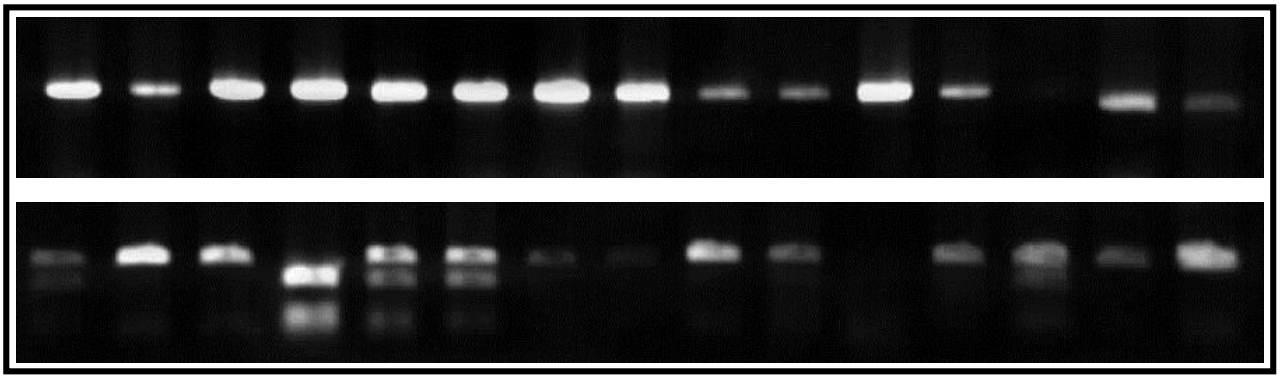
# Appendix 10

## Agarose gel electrophoresis

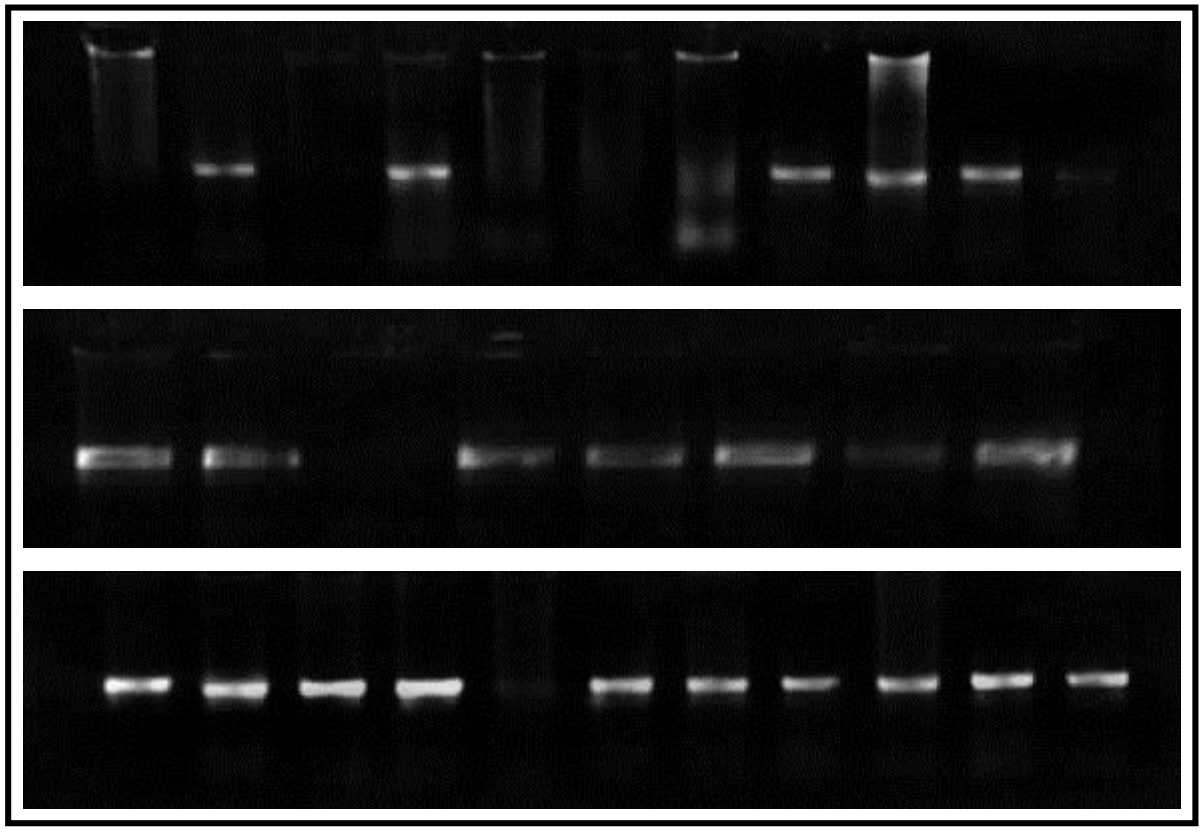
Extracted DNA, Unaffected Cohort.



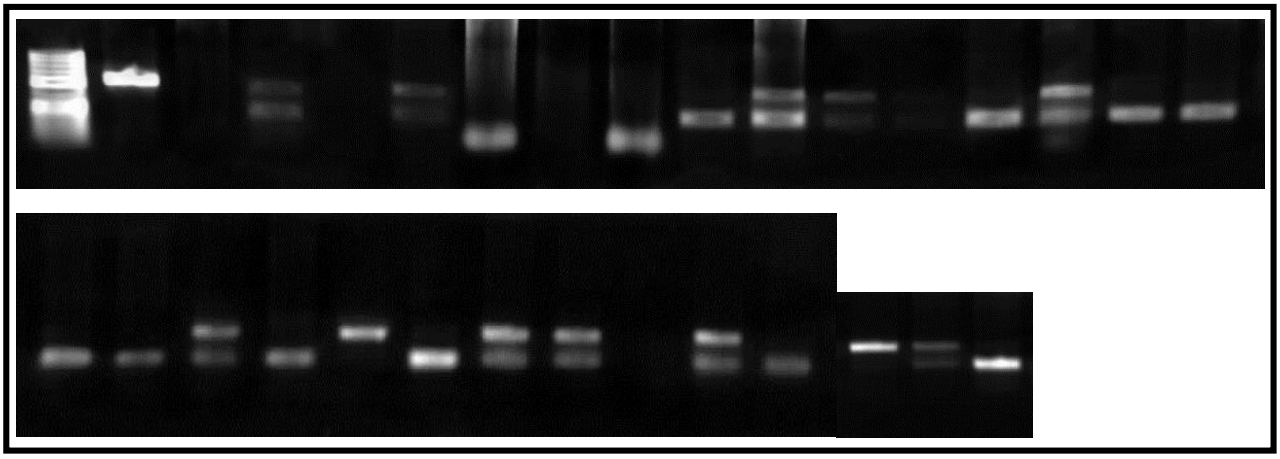
Amplified ***HTR1B*** promoter region, of approximately 548 bp in lanes 1-13 (top). Digested *HTR1B* promoter region in lanes 14 and 15 (top), and lanes 1-15 (bottom). Possible fragment lengths are 452 bp and 96 bp (G allele) and 142 bp, 310 bp, and 17 bp (C allele). (Affected Cohort)



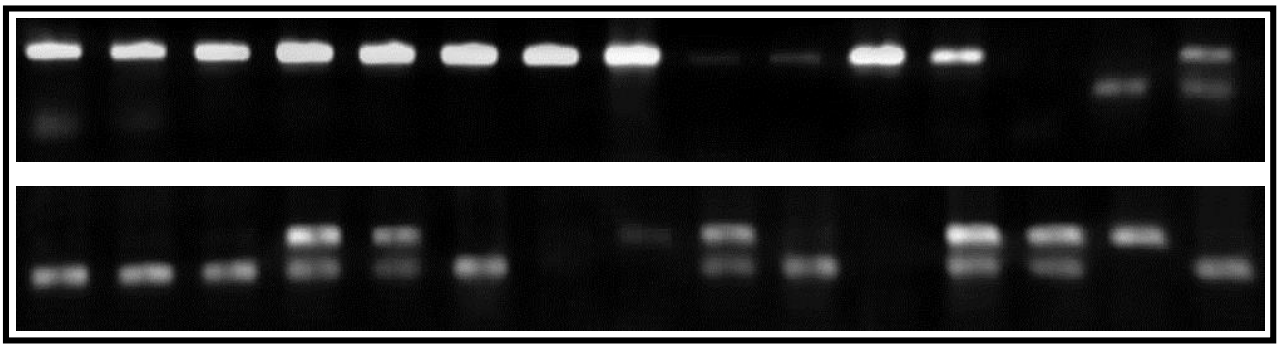
Amplified *HTR2A* promoter region, of approximately 468 bp. (Unaffected Cohort)



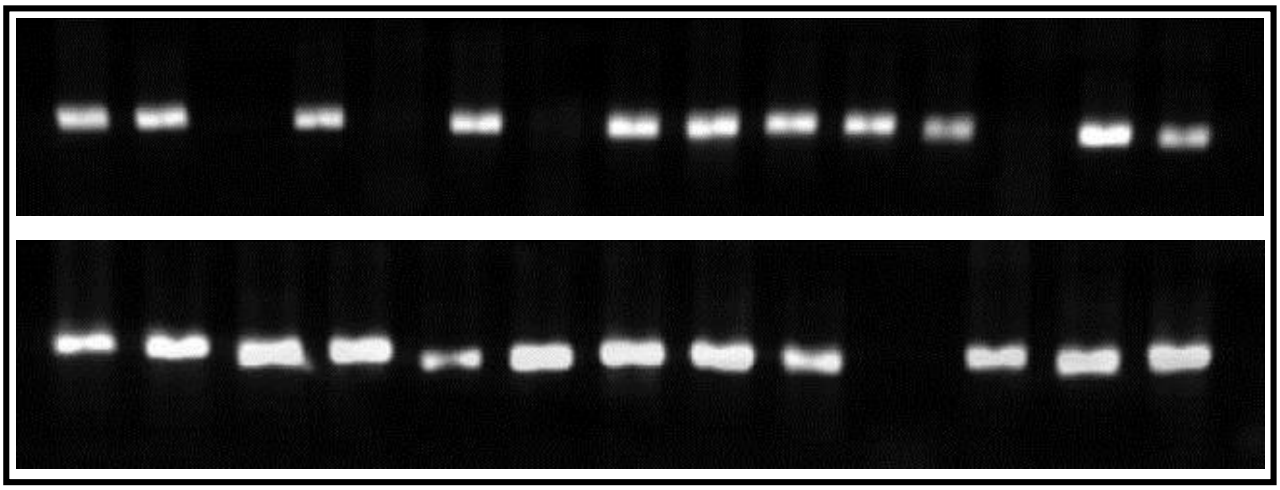
Digested *HTR2A* promoter region with the 50 bp O'GeneRuler DNA ladder (Fermentas, Thermo Scientific) in the first lane. Possible fragment lengths are 468 bp (T allele) and 224 bp, and 244 bp (C allele). (Unaffected Cohort)



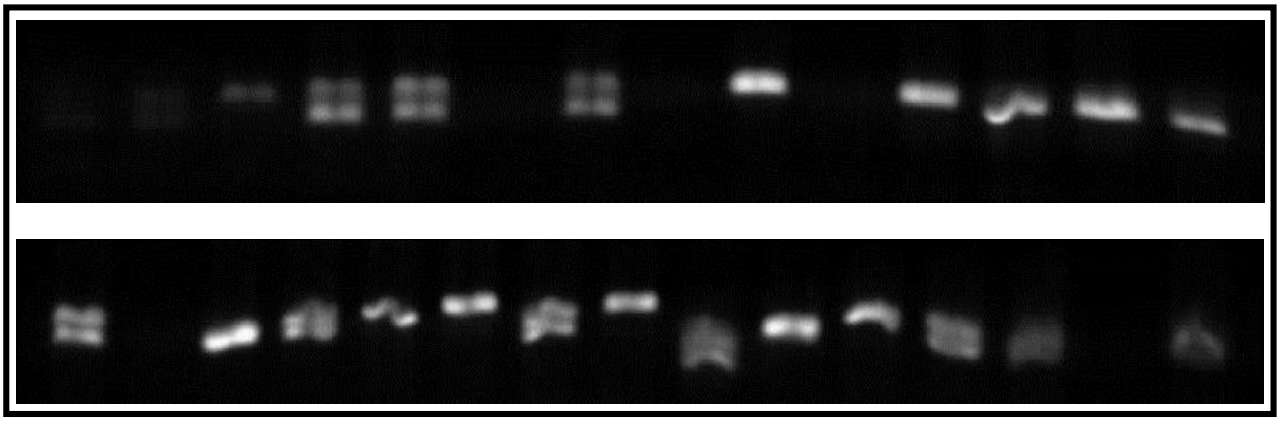
Amplified *HTR2A* promoter region, of approximately 548 bp in lanes 1-13 (top). Digested *HTR2A* promoter region in lanes 14 and 15 (top), and lanes 1-15 (bottom). Possible fragment lengths are 468 bp (T allele) and 224 bp, and 244 bp (C allele). (Affected Cohort)



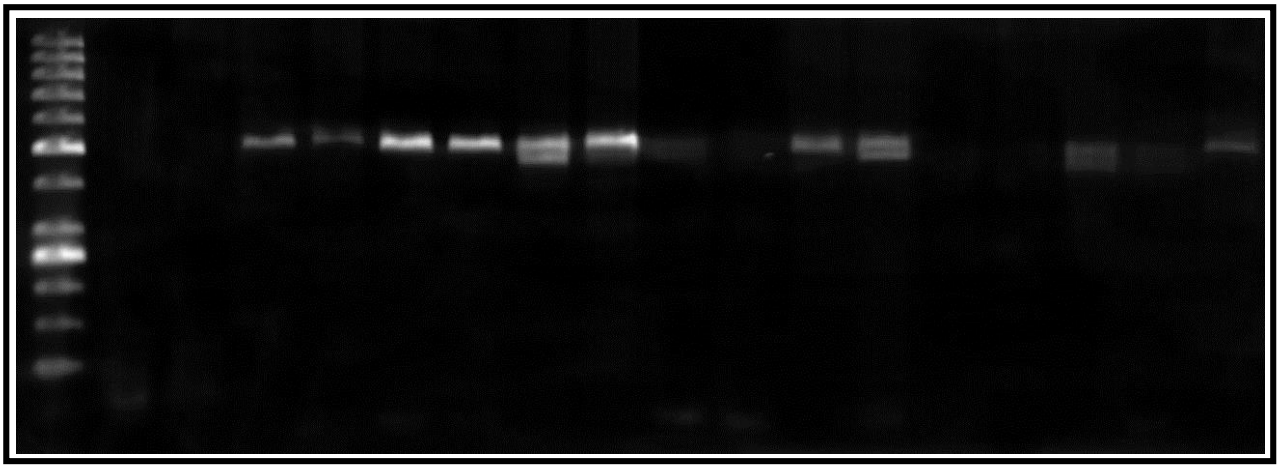
Amplified *5-HTT* SNP promoter region, of approximately 512 bp. (Unaffected Cohort)



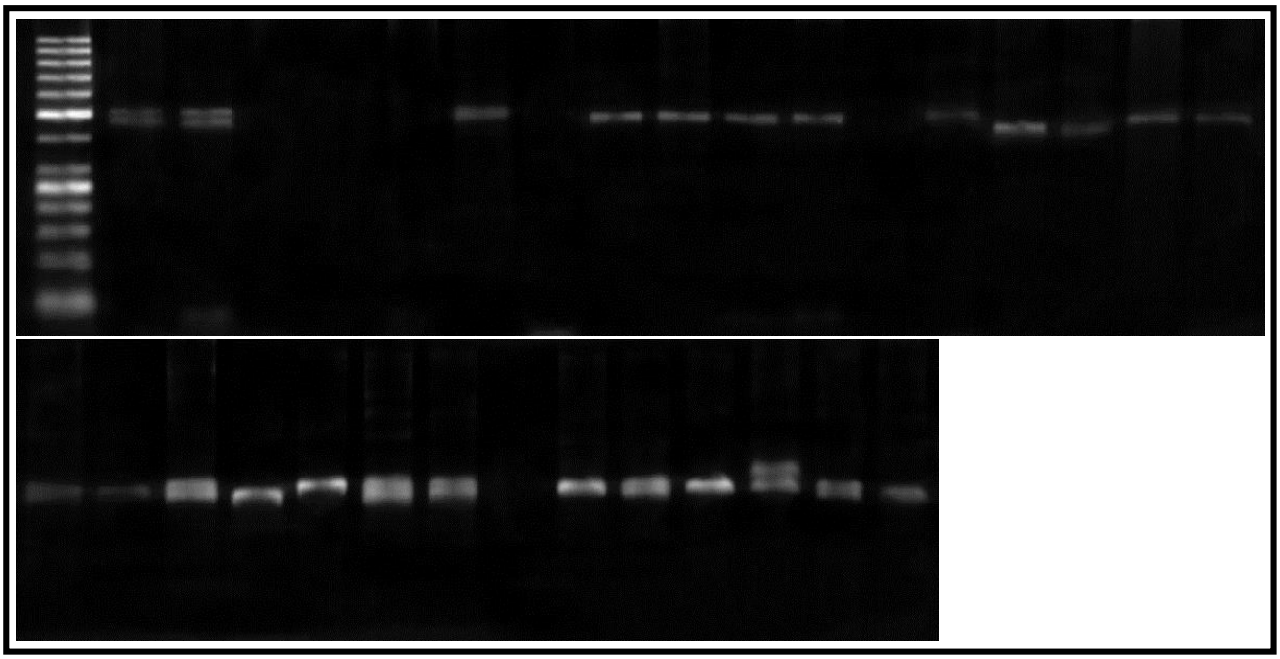
Digested *5-HTT* SNP promoter region. Possible fragment lengths are 512 bp (A allele) and 403 bp, and 109 bp (G allele). (Affected (lane 1-4) and Unaffected Cohort)



Amplified *5-HTTLPR* promoter region with the 50 bp O'GeneRuler DNA ladder (Fermentas, Thermo Scientific) in the first lane. Possible fragment lengths are 484 bp (S allele), and 528 bp (L allele). (Affected (lane 17) and Unaffected Cohort (lane 2-16)).



Amplified *5-HTTLPR* promoter region with the 50 bp O'GeneRuler DNA ladder (Fermentas, Thermo Scientific) in the first lane. Possible fragment lengths are 484 bp (S allele), and 528 bp (L allele). (Unaffected Cohort).



# Appendix 11

## Sequences

## Sequences obtained for the *HTR2A* promotor region

```
JMA4     ----------------------------TGCACCAAACAG-----GCTTA-TTTCTTCT
JMC12    ----------------------------TAAGGCTACACAG----GGCTTAATTTCTTCT
JMA1     ----------------------------TCACACCTTACCA----GGCATA-TTTCTTCT

JMA4     CCCTCTTTTTGCTACATATTAATATTG-GGAAGTTTTCCTTTGCTTTTGAGAGAAACT-G
JMC12    CC-TCCTTTTGCTACATATTAATATTG-GGAAGTTTTCCTTTGCTTTTGCCATAAAAAGG
JMA1     CCCTCTTTTTGCTACATATTAATATTG-GGAAGTTTTCCTTTGCTTTTGAGAGAAACA-G

JMA4     GAGAAATGGCCTTTTGTGCAGATTCCCATTAAGGTA-GGTAAGTGGCACTGTGGTAATTT
JMC12    GAGGAATGGCCTTTTGTGCAGATTCCCATTA-GGCCCTTTAAGAGGCACTGTGTAAATTT
JMA1     GAGAAATGGCCTTTTGTGCAGATTCCCATTAAGGCCCCTT-AGTGGCACTGTGGCAATTT

JMA4     TTTAGGCTGAAGGGTGAAGAGAGAACATAAATAAGGCTAGAAAACAGTATGTCCTC-GGA
JMC12    TTTAGGCTGAAGGGTGAAGAGAGAACATAAATAAGGCTAGAAAACAGTATGTCCTC-GGA
JMA1     TTTAGGCTGAAGGGTGAAGAGAGAACATAAATAAGGCTAGAAAACAGTATGTCCTC-GGA

JMA4     GTGCTGTGAGTGTCCGGCACTTCCATCCAAAGCCA--ACAGTGTTTGTGTCCAGAGTGGA
JMC12    GTGCTGTGAGTGTCCGGCACTTCCATCCAAAGCCA--ACAGTGTTTGTGTCCAGAGTGGA
JMA1     GTGCTGTGAGTGTCTGGCACTTCCATCCAAAGCCA--ACAGTGTTTGTGTCCAGAGTGGA

JMA4     ATTACTGACATTGGCCACATAGGCTCAGGGTGGCTAGGCACGTCTGTGGTGAT-AACTCT
JMC12    ATTACTGACATTGGCCACATAGGCTCAGGGTGGCTAGGCACGTCTGTGGTGAT-AACTCT
JMA1     ATTCCTGACATTGGCCACATAGGCTCAGGGTGGCTAGGCACGTCTGTGCTGAT-AACTTA

JMA4     GATAAACTATTAGCACTATTTTTATTTAATAGATACACCATTGAACTGGCTTATTTTCTT
JMC12    GATAAACTATTAGCACTATTTTTATTTAATAGATACACCATTGAACTGGCTTATTTTCTT
JMA1     AATAAACTATTAGCACTATTTTTATTTAATAGATACACCATTGAACTGGCTTATTTTCTT

JMA4     CAGCAGAAATATGCCACCCAGATATTATT-CAAAACCTCACATGT-GGTAGGATAAAA--
JMC12    CAGCAGAAATATGCCACCCAGATATTAGT-CCAAACCTCACATGT-GGTAGGAAAT-AGG
JMA1     CAGCAGAAATATGCCACCCAGATATTATT-CAAAACCTCACATGT-GGTAGGAAATAA-G
```

## Sequences obtained for the *HTR1B* promotor region

```
JMC26    TGTGTAAACAAACCCCGACAGGACCGGCAAGCGCTTGACCCGAGCCCAGCTGATAACCGA
JMA15    --------------------------------CTTTGCACCGGGC-CAGCTGGT-ACCGA
JMA1     ----------------------------------GGTGA-CTGAGC-CAGCTGGT-ACCGA

JMC26    CTCCCCCGGGTCCACGTCCTCGGTCACCTCTATTAACTCGCGGGTTCCCGACGTGCCCAG
JMA15    CTCCCCCGGTTCCACGTCCTCGGTCACCTCTATTAACTCGCGGGTTCCCGACGTGCCCAG
JMA1     CTCCCCCGGGTCCACGTCCTCGGTCACCTCTATTAACTCGCGGGTTCCCGACGTGCCCAG

JMC26    CGAATCCGGATCTCCTGTGTATGTCAACCAAGTCAAAGTGCGAGTCTCCGACGCCCTGCT
JMA15    CGAATCCGGATCTCCTGTGTATGTGAACCAAGTCAAAGTGCGAGTCTCCGACGCCCTGCT
JMA1     CGAATCCGGATCTCCTGTGTATGTGAACCAAGTCAAAGTGCGAGTCTCCGACGCCCTGCT

JMC26    GGAAAAGAAGAAACTCATGGCCGCTAGGGAGCGCAAAGCCACCAAGACCCTAGGGATCAT
JMA15    GGAAAAGAAGAAACTCATGGCCGCTAGGGAGCGCAAAGCAACCAAGACCCTAGGGATCAT
JMA1     GGAAAAGAAGAAACTCATGGCCGCTAGGGAGCGCAAAGCCACCAAGACCCTAGGGATCAT

JMC26    TTTGGGAGCCTTTATTGTGTGTTGGCTACCCTTCTTCATCATCTCCCTAGTGATGCCTAT
JMA15    TTTGGGAGCCTTTATTGTGTGTTGGCTACCCTTCTTCATCATCTCCCTAGTGATGCCTAT
JMA1     TTTGGGAGCCTTTATTGTGTGTTGGCTACCCTTCTTCATCATCTCCCTAGTGATGCCTAT

JMC26    CTGCAAAGATGCCTGCTGGTTCCACCTAGCCATCTTTGACTTCTTCACATGGCTGGGCTA
JMA15    CTGCGAAGATGCCTGCGGGTTCCACCTAGCCATCTTTGACTTCTTCACATGGCTGGGCTA
JMA1     CTGCAAAGATGCCTGCTGGTTCCACCTAGCCATCTTTGACTTCTTCACATGGCTGGGCTA

JMC26    TCTCAACTCCCTCATCAACCCCATAATCTATACCATGTCCAATGAGGACTTTAAACAAGC
JMA15    TCTCAACTCCCTCATCAACCCCATAATCTATACCATGTCCAATGAGGACTTTAAACAAGC
JMA1     TCTCAACTCCCTCATCAACCCCATAATCTATACCATGTCCAATGAGGACTTTAAACAAGC

JMC26    ATTCCATAAACTGATACGTTTGGA-TACACAAGTTGACTTGCCATTTGCAGTGGGGTCGC
JMA15    ATTCCATAAACTGATACGTTTTAAGTGCACCAGTTGACTTGCCATTTGCAGTGGGGTCGC
```

```
JMA1     ATTCCATAAACTGATACGTTTTAAGTGCACAAGTTGACTTGCCATTTGCAGTGGGGTCGC

JMC26    CTAAGCGACCTT-GGGGACCAAGTGGTCCGTGAGAGCCT----------------------
JMA15    CTAAGCGACCTTTGGGGACCAAGTTGTGGCTG-GGTCCACAGGTAGTTCGAATCTTCTTT
JMA1     CTAAGCGACCTTTGGGGACCAAGTTGTGTCTG-GTTCCACAGGTAGGTCGAATCTTCTTC

JMC26    ----------------------------
JMA15    CG-GGTTTTTTGAGATAATGC------
JMA1     GGGGGTTTTTTCGGAGAATGTCCCATA
```

## Sequences obtained for the *5-HTT* SNP promotor region

```
JMA10    CCTCCGGGCGTGATC-GTAACGTAGGCCTCTTGGA----ACACCTTTGCGTTT-TCTGT-
JMA11    CGCTTTGAGTCCTTC-AT-----TGGCCTCCTGGA-AGGA-AC-TTTGCGTTT-TCTGT-
JMA3     ----CCTTCCGGGTC-AT----TTGGCCTCTTGGA-AGGACAC-TTTGCGTTT-TCTGT-
JMA4     -----CGAAAGGGGC--TCGAATTGGCCTCCTGGA-AGGACAC-TTTGCGTTT-TCTGT-
JMA5     -CGGGAGGGTGCCTC-CT----TTGGCCTCCTGGA-AGGACAC-TTTGCGTTT-TCTGT-
JMA6     ---CAGGACGGTATCCAT---TTTGACCTCCTGGAAGGCACAC-TTTGCGTTTCTCTGTG
JMA7     ---AAGAACCACGTC-CT----TTGACCTCCTGGA-AGGCAAC-TTTGCGTTT-TCTGTG
JMA8     TAGTTTGGTGGCACCAAT-----TG-CTTCCGGGA----AAACCTTTGCGTTT-TCTGT-
JMA9     GTTAATGGTAGCGAC---------GGCCTC-TGGA-AGGC--CCTTTGCGTTT-TCTGT-
JMC15    GAAGTTTGGCCCGTTTAT---TTTGGCCTC-TGGA-AGGAAAC-TTTGCGTTT-TCTGT-
JMC26    ----ACAGCCACGTC-AT----TTGACCTCGTGGA-AGGA-AC-TTTGCGTTT-TCTGT-
JMC27    ----AGAACCACGAC-AT----TTGGCCTC-TGGA-AGGA-AC-TTTGCGTTT-TCTGT-
JMC29    --AAATTGTCCCGTTCAT----TGGGCCTC-TGGA-AGGA-AC-TTTGCGTTT-TCTGT-
JMC30    ---CTTGGCCGCGTCATT---TTGGCCCTCCTGGA-AGGACAC-TTTGCGTTT-TCTGT-
JMC35    --CGAGACCCGTGTCAAT----TTGGCCTCTTGGAAAGGACAC-TTTGCGTTT-TCTGT-
JMC38    --GAGGTGGCCGCTC-AT----TTGAC-TC-TGGA-AGGA-AC-TTTGCGTTT-TCTGTG
JMC45    --GGGTTGCCGGATC-AT----TTGGC-TCCTGGA-AGGACAC-TTTGCGTTT-TCTGT-
JMC46    ---AGTGCCCCCGTC-AT----TTGACCTC-TGGA-AGGA-AC-TTTGCGTTT-TCTGT-
JMC50    --------CCGGAACGAGTCATTTGACCTCCTGGA--GGACAC-TTTGCGTTT-TCTGTG
JMC51    -AAGAGAACTCTGTC-AT----TTGGCCTCTTGGAAAGAAC---TTTGCGTTT-TCTGT-
JMC58    ---CGATGCCCGGTCATT----TTGGCCTC-TGGA-AGGA-AC-TTTGCGTTT-TCTGT-
JMC59    ----CAGACGGGGATCAT----TTGGCCTCCTGGAA--GAAAC-TTTGCGTTT-TCTGT-
JMC60    ----CGTGACGGAACATT----TGGCCCTCCTGGA-AGGACAC-TTTGCGTTT-TCTGT-
JMC62    ---AGTGCCGGCGTC-AT----TTGGCCTC-TGGA-AGGA-AC-TTTGCGTTT-TCTGT-
JMC63    --AAATGGACCCGTC-AT----TTGGCCTCCTGGA--GGA-AC-TTTGCGTTT-TCTGTG
JMC64    ----ACACACGGGTCCTT----TTGGCCTCCTGGA-AGGA-AC-TTTGCGTTT-TCTGTG
JMC7     ---AGGGGACCGTTCATT----TGGCCCTCTTGGA-AGGA-AC-TTTGCGTTT-TCTGT-
JMC80    --------CCTGGCCCCTTCATTTGCCCTCCTGGAAAGAAC---TTTGCGTTT-TCTGT-
JMC8     --AAGGTGACGGGTC-AT----TTGGCCTC-TGGA--GGA-AC-TTTGCGTTT-TCTGT-

JMA10    -GCCCT-TGCCTATAC-GCACAAAAGGGGGGATGTTAAGAAGTGGAA--GGGAAGGCAGC
JMA11    TGCCCT-TGCCTATACAGCAAAAAAAAG-GCGTTGGAAGAAGTGGAACGTGGGAGGCAGC
JMA3     TGCCCT-TGCCTATACAGCACAA-CGGGAACATA-TAAGAAGTGGAACGTGGGAGGCAGC
JMA4     TGCCCT-TGCCTATACAGCACAAA-ATGAACGTT-TAAGAAGTGGAACGGGGGAGGCAGC
JMA5     TGCCCT-TGCCTATACAGCACAAAAA-GAGAGGGGTGGGAAGTGGAACGGGGGAGGCAGC
JMA6     GGCCCT-TGCCTATACAGCAAAAGAGGGGGCGTTTGGGGAAGTGGAACGGGGGAGGCAGC
JMA7     TGCCCTGTGCCTATACAGCACAAAAAGCAACATT-TAAGAAGTGGAACGGGGGAGGCAGC
JMA8     TGCCCT-TGCCTATAC-GCAAAAAAAA-AGGATT-AGAGAAGTGGAACGGGGGAGGCAGC
JMA9     TGCACT-TGCCTATAC-GCA--AAAAGGAACATTG-AAGAAGTGGA-CG-GGGAG--CGC
JMC15    TGCCCATTGCCTATACAGCAAAAAAAGGAGGGTTG-GGGAAGTGGAACGGGGGAGGCAGC
JMC26    TGCCCT-TGCCTATACAGCAAAAAAGGGAG---TTTAGGAAGTGGAACGGGGGAGGCAGC
JMC27    TGCCCT-TGCCTATACAGCA-AAAGAAGGGCGTT-TGAGAAGTGGAACGGGGGAGGCAGC
JMC29    TGCCCT-TGCCTATACAGCAAAAGAAGGGGCGTT-TAGGAAGTGGAACGGGGGAGGCAGC
JMC30    TGCCCT-TGCCTATACAGCAAAAAAGGGAGCGTTTAAAGAAGTGGAACGGGGGAGGCAGC
JMC35    TGCCCT-TGCCTATACAGCACAAAAAGGAG-ATTG-AAGAAGTGGAACGTGGGAGGCAGC
JMC38    TGCCCT-TGCCTATACAGCAAAAAAAAGGGCATT-TAAGAAGTGGAACGTGGGAGGCAGC
JMC45    TGCCCT-TGCCTATACAGCACAAAAAGGA-CATGGTAAGAAGTGGAACGGGGGAGGCAGC
JMC46    TGCCCT-TGCCTATACAGCACAAAGAGGGGCATT-TAAGAAGTGGAACGTGGGAGGCAGC
JMC50    TGCCCTGTGCCTATACAGCACAAAAA-GCTCATT-TAAGAAGTGGAACGTGGGAGGCAGC
JMC51    TGCCCT-TGCCTATACAGCACAAAAGGGA-CATTG-AAGAAGTGGAACGTGGGAGGCAGC
JMC58    TGCCCT-TGCCTATACAGCA-AAAGAGGGGCGTT-TAAGAAGTGGAACGGGGGAGGCAGC
JMC59    TGCCCT-TGCCTATACAGCACAAAAAAGGACATT-TAAAAAGTGGAACGGGGGAGGCAGC
JMC60    TGCCCTGTGCCTATACAGCACAAAAAGCAGGTTT--AAGAAGTGGAACGGGGGAGGCAGC
JMC62    TGCCCT-TGCCTATACAGCACAAAAAAGAGAATT-TAAGAAGTGGAACGTGGGAGGCAGC
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JMC63    TGCCCT-TGCCTATACAGCACAAAGAAGGACATTGGAAAAAGTGGAACGGGGGAGGCAGC
JMC64    TGCCCT-TGCCTATACAGCACAAAAGGAAGCGTT-TAAGAAGTGGAACGGGGGAGGCAGC
JMC7     TGCCCT-TGCCTATACAGCACAAAGAAGGGCGTT-AAAGAAGTGGAACGTGGGAGGCAGC
JMC80    TGCCCT-TGCCTATACAGCACAAAAAA-AAAATT-AAAGAAGTGGAACGTGGGAGGCAGC
JMC8     TGCCCT-TGCCTATACAGCACAAAAAAGGGCAGT-TAAGAAGTGGAACGTGGGAGGCAGC

JMA10    AGACAACTGAG--AAAAAAGGAAAGGAGGAGGCCCCACTCCCGTGCAGGCGCTGCCCCTT
JMA11    AGACAACTGAG-TTCAAAAAGAAAGGAGGAGGCCCCACTCCCGTGCAGGCGCTGCCCCT-
JMA3     AGACAACTGGG-TTCAT-CTGAAAGGAGGAGGCCCCACTCCCGTGCAGGCGCTGCCCCT-
JMA4     AGACAACTGTG-TTCATCAAGAAAGGAGGAGGCCCCACTCCCGTGCAGGCGCTGCCCCT-
JMA5     AGACAACTGAGAAAAAACGGGAAAGGAGGAGGCCCCACTCCCGTGCAGGCGCTGCCCCT-
JMA6     AGACAACTGAGAAAAAGGGGGAAAGGAGGAGGCCCCACTCCCGGGCAGGCGCTGCCCCT-
JMA7     AGACAACTGTG-ATCAAAATGAAAGGAGGAGGCCCCACTCCCGTGCAGGCGCTGCCCCT-
JMA8     AGACAACTGCG-ATAAAAAAGAAAGGAGGAGGCCCCACTCCCGTGCAGGCGCTGCCCCT-
JMA9     -GACA--TGCG--GGGGGGGGAAAGGAGGAGGCCCCACTCCCGTGCAGGCGCTGCCCCT-
JMC15    AGACAACTGCG-AAAATAAAGAAAGGAGGAGGCCCCACTCCCGTGCAGGCGCTGCCCCT-
JMC26    AGACAACTGA-AAAAAAAAGGAAAGGAGGAGGCCCCACTCCCGTGCAGGCGCTGCCCCT-
JMC27    AGACAACTGGG-GACAGAA-GAAAGGAGGAGGCCCCACTCCCGTGCAGGCGCTGCCCCT-
JMC29    AGACAA-TGAGAAACAAACTGAAAGGAGGAGGCCCCACTCCCGTGCAGGCGCTGCCCCTG
JMC30    AGACAACTGAGAAAAAGGAAGAAAGGAGGAGGCCCCACTCCCGGGCAGGCGCTGCCCCT-
JMC35    AGACAACTGTG-TTCAAAAGGAAAGGAGGAGGCCCCACTCCCGTGCAGGCGCTGCCCCT-
JMC38    AGACAACTGAGGAAATAAAAGAAAGGAGGAGGCCCCACTCCCGTGCAGGCGCTGCCCCT-
JMC45    AGACAACTGTG-TTCAAAAAGAAAGGAGGAGGCCCCACTCCCGTGCAGGCGCTGCCCCT-
JMC46    AGACAACTGGG-GTAAAAAGGAAAGGAGGAGGCCCCACTCCCGTGCAGGCGCTGCCCCT-
JMC50    AGACAACTGCG-ATCAT-CTGAAAGGAGGAGGCCCCACTCCCGTGCAGGCGCTGCCCCT-
JMC51    AGACAACTGGGAAACATCAAGAAAGGAGGAGGCCCCACTCCCGTGCAGGCGCTGCCCCT-
JMC58    AGACAACTGAAAAAAATAAAGAAAGGAGGAGGCCCCACTCCCGTGCAGGCGCTGCCCCT-
JMC59    AGACAACTGTG--ATAATCTGAAAGGAGGAGGCCCCACTCCCGTGCAGGCGCTGCCCCT-
JMC60    AGACAACTGAG-AACATAAGGAAAGGAGGAGGCCCCACTCCCGTGCAGGCGCTGCCCCT-
JMC62    AGACAACTGTG-TTAATAAAGAAAGGAGGAGGCCCCACTCCCGTGCAGGCGCTGCCCCT-
JMC63    AGACAACTGTG-AAAATAATGAAAGGAGGAGGCCCCACTCCCGTGCAGGCGCTGCCCCT-
JMC64    AGACAACTGCG-AACAAAATGAAAGGAGGAGGCCCCACTCCCGTGCAGGCGCTGCCCCT-
JMC7     AGACAACTGTG-TGCAT-AGGAAAGGAGGAGGCCCCACTCCCGTGCAGGCGCTGCCCCT-
JMC80    AGACAACTGTGAAACATAAAGAAAGGAGGAGGCCCCACTCCCGTGCAGGCGCTGCCCCT-
JMC8     AGACAACTGGG-ATCAT-CTGAAAGGAGGAGGCCCCACTCCCGTGCAGGCGCTGCCCCT-

JMA10    GGGGGTGAAATTCCCAAGCTTGTTGGT--TCTTCTTCCCGCC-TGGCGTTGCCGCTCTGA
JMA11    GTGGGTGAAATTCCCAAGCTTGTTGTT-CTACTCT-CACGCC-TGGCGTTGCCGCTCTGA
JMA3     GGGGGTGAAATTCCCAAGCTTGTTGGT-CTACTCTCC-CGCC-TGGCGTTGCCGCTCTGA
JMA4     GGGGGTGAAATTCCCAAGCTTGTTGGG--TTCTCTCC--GGCCTGGCGTTGCCGCTCTGA
JMA5     GGGGGTGAAATTCCCAAGCTTGTTGTT--TCTTCCCCCCGAG-GGGCGTTGCCGCTCTGA
JMA6     GGGGGTGAAATTCCCAAGCTTGTTGTTTCTCTTCTCC-CGCA-GGGCGTTGCCGCTCTGA
JMA7     GGGGGTGAAATTCCCAAGCTTGTTGTT--CCCTCTCC-CGCC-TGGCGTTGCCGCTCTGA
JMA8     GGGGGTGAAATTCCCAAGCTTGTTGGT--TTCT-TCCCCGAAATGGCGTTGCCGCTCTGA
JMA9     TGGGGTGAAATTCCCAAGCTTGTTGTTTCTAATTCACGAGCAAGGGCGTTGCCGCTCTGA
JMC15    GGTGGTGAAATTCCCAAGCTTGTTGGG---TTTCCCCCCAAACGGGGGTTGCCGCTCTGA
JMC26    GGGGGTGAAATTCCCAAGCTTGTTGTTT-TACCCTTCCGAAGAGGGCGTTGCCGCTCTGA
JMC27    GGGGGTGAAATTCCCAAGCTTGTTGGT-CCCCTCTCC-CGAC-TGGCGTTGCCGCTCTGA
JMC29    TGGGGTGAAATTCCCAAGCTTGTTGTT--TTCCTTCCCAGCC-GGGCGTTGCCGCTCTGA
JMC30    GGGGGTGAAATTCCCAAGCTTGTTGTC--CATTC-CCCCGAC-GGGCGTTGCCGCTCTGA
JMC35    GGGGGTGAAATTCCCAAGCTTGTTGGG--TACTCTCC-CGCC-TGGGGTTGCCGCTCTGA
JMC38    GGGGGTGAAATTCCCAAGCTTGTTGTTT-CCCTCTCC-AAACGTGGCGTTGCCGCTCTGA
JMC45    GGGGGTGAAATTCCCAAGCTTGTTGGT--TTCTCTCC-CGCC-TGGCGTTGCCGCTCTGA
JMC46    GGGGGTGAAATTCCCAAGCTTGTTGGT--TACTCTCC-CGCC-TGGCGTTGCCGCTCTGA
JMC50    GGGGGTGAAATTCCCAAGCTTGTTGGG--GATTCTCC-CGCC-TGGCGTTGCCGCTCTGA
JMC51    GGGGGTGAAATTCCCAAGCTTGTTGGG--GATTCTCC-CGCC-TGGGGTTGCCGCTCTGA
JMC58    GGGGGTGAAATTCCCAAGCTTGTTGGT--TTCTCTTCCCGCC-TGGCGTTGCCGCTCTGA
JMC59    GGGGGTGAAATTCCCAAGCTTGTTGGG--TTTTCTCC-CGCC-TGGCGTTGCCGCTCTGA
JMC60    GGGGGTGAAATTCCCAAGCTTGTTGGT-CTCCTCTCC-CGCC-TGGCGTTGCCGCTCTGA
JMC62    GGGGGTGAAATTCCCAAGCTTGTTGGG--TTTCCTCC-CGCC-TGGCGTTGCCGCTCTGA
JMC63    GGGGGTGAAATTCCCAAGCTTGTTGGT--TACTCTCC-CGCC-TGGCGTTGCCGCTCTGA
JMC64    GGGGGTGAAATTCCCAAGCTTGTTGGG--TTTTCTCC-CGCC-TGGCGTTGCCGCTCTGA
JMC7     GGGGGTGAAATTCCCAAGCTTGTTGGG--CCCTTTCCCCCGCA-GGGGGTTGCCGCTCTGA
JMC80    GGGGGTGAAATTCCCAAGCTTGTTGGT--TCTTCTTCCCGCC-TGGCGTTGCCGCTCTGA
JMC8     GGGGGTGAAATTCCCAAGCTTGTTGGG--TTTTCTCC-CGCC-TGGCGTTGCCGCTCTGA

JMA10    ATGCCAGCACCGGGGGGGGGGGGTGTCCCTACTGCAGCCCTCCCAGCATCCCCCCTGCAA
JMA11    ATGCCAGCACCT-AACCCC-TAATGTCCCTACTGCAGCCCTCCCAGCATCCCCCCTGCAA
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JMA3     ATGCCAGCACCT-AACCGGGTAATGTCCCTACTGCAGCCCTCCCAGCATCCCCCCTGCAA
JMA4     ATGCCAGCACCT-AACGGGGGAGGGTCCCTACTGCAGCCCTCCCAGCATCCCCCCTGCAA
JMA5     ATGCCAGCACCT-AACCCC-TAATGTCCCTACGGCAGCCCTCCCAGCATCCCCCCTGCAA
JMA6     ATGCCAGCACCT-AACCCC-TAATGTCCCTACGGCAGCCCTCCCAGCATCCCCCCTGCAA
JMA7     ATGCCAGCACCT-AACCCC-TAATGTCCCTACTGCAGCCCTCCCAGCATCCCCCCTGCAA
JMA8     ATGCCAGCACCT-AACCCC-TAATGTCCCTACTGCAGCCCTCCCAGCATCCCCCCTGCAA
JMA9     ATGCCAGCACCTAGGGGCCGGGGTGTCCCTACTGCAGCCCTCCCAGGATCCCCCCTGCAA
JMC15    ATGCCAGCACCT-AACCGGGGGAGGTCCCTACTGCAGCCCTCCCAGCATCCCCCCGGCAA
JMC26    ATGCCAGCACCT-AGCGGGGGGGTGTCCCTACTGCAGCCCTCCCAGCATCCCCCCTGCAA
JMC27    ATGCCAGCACCT-AACCCC-TAATGTCCCTACTGCAGCCCTCCCAGCATCCCCCCTGCAA
JMC29    ATGCCAGCACCT-AAGCGGGGAATGTCCCTACTGCAGCCCTCCCAGCATCCCCCCTGCAA
JMC30    ATGCCAGCACCT-AACCCC-TAATGTCCCTACTGCAGCCCTCCCAGCATCCCCCCTGCAA
JMC35    ATGCCAGCACCT-AACGGGGTAATGTCCCTACTGCAGCCCTCCCAGCATCCCCCCTGCAA
JMC38    ATGCCAGCACCT-AACCCC-TAATGTCCCTACTGCAGCCCTCCCAGCATCCCCCCGGCAA
JMC45    ATGCCAGCACCT-AACGGGGGAATGTCCCTACTGCAGCCCTCCCAGCATCCCCCCTGCAA
JMC46    ATGCCAGCACCT-AACCCC-TAATGTCCCTACTGCAGCCCTCCCAGCATCCCCCCTGCAA
JMC50    ATGCCAGCACCT-AACCCC-TAATGTCCCTACTGCAGCCCTCCCAGCATCCCCCCTGCAA
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JMC60    ATGCCAGCACCT-AACCCC-TAATGTCCCTACTGCAGCCCTCCCAGCATCCCCCCTGCAA
JMC62    ATGCCAGCACCT-AACCCC-TAATGTCCCTACTGCAGCCCTCCCAGCATCCCCCCTGCAA
JMC63    ATGCCAGCACCT-AACCCC-TAATGTCCCTACTGCAGCCCTCCCAGCATCCCCCCTGCAA
JMC64    ATGCCAGCACCT-AACCCC-TAATGTCCCTACTGCAGCCCTCCCAGCATCCCCCCTGCAA
JMC7     ATGCCAGCACCT-AACCCC-TAATGTCCCTACTGCAGCCCTCCCAGCATCCCCCCTGCAA
JMC80    ATGCCAGCACCT-AACCCC-TAATGTCCCTACTGCAGCCCTCCCAGCATCCCCCCTGCAA
JMC8     ATGCCAGCACCT-AACCCC-TAATGTCCCTACTGCAGCCCTCCCAGCATCCCCCCTGCAA

JMA10    CCTCCCAGCAACTCCCTGTACCCCTCCTAGGATCGCTCCTGCATCCCCC-ATTATCCCCC
JMA11    CCTCCCAGCAACTCCCTGTACCCCTCCAAGGATCGCTCCTGCATCCCCC-ATTATCCCCC
JMA3     CCTCCCAGCAACTCCCTGTACCCCTCCTAGGATCGCTCCTGCATCCCCC-ATTATCCCCC
JMA4     CCTCCCAGCAACTCCCTGTACCCCTCCAAGGATCGCTCCTGCATCCCCC-AATATCCCCC
JMA5     CCTCCCAGCAACTCCCTGTACCCCTCCTAGGATCGCTCCTGCATCCCCC-ATTATCCCCC
JMA6     CCTCCCAGCAACTCCCTGTACCCCTCCTAGGATCGCTCCTGCATCCCCC-ATTATCCCCC
JMA7     CCTCCCAGCAACTCCCTGTACCCCTCCTAGGATCGCTCCTGCATCCCCC-ATTATCCCCC
JMA8     CCTCCAAGCAACTCCCTGTACCCCTCCAAGGATCTCCCCTGCAACCCCA-AAAATCCCCC
JMA9     CCTCCCAGCAACTCCCTGTACCCCTCCTAGGATCGCCCCTGCACCCCCCAATTATCCCCC
JMC15    CCTCCCAGCAACTCCCTGTACCCCTCCAAGGATCGCTCCTGCACCCCCC-ATAATCCCCC
JMC26    CCTCCCAGCAACTCCCTGAACCCCTCCTAGGATCGCTCCTGCATCCCCC-ATTATCCCCC
JMC27    CCTCCCAGCAACTCCCTGTACCCCTCCTAGGATCGCTCCTGCATCCCCC-ATTATCCCCC
JMC29    CCTCCCAGCAACTCCCTGTACCCCTCCTAGGATCGCTCCTGCATCCCCC-ATTATCCCCC
JMC30    CCTCCCAGCAACTCCCTGTACCCCTCCTAGGATCGCTCCTGCATCCCCC-ATTATCCCCC
JMC35    CCTCCCAGCAACTCCCTGTACCCCTCCTAGGATCGCTCCTGCATCCCCC-ATTATCCCCC
JMC38    CCTCCCAGCAACTCCCTGTACCCCTCCTAGGATCGCTCCTGCATCCCCC-ATTATCCCCC
JMC45    CCTCCCAGCAACTCCCTGTACCCCTCCTAGGATCGCTCCTGCATCCCCC-ATTATCCCCC
JMC46    CCTCCCAGCAACTCCCTGTACCCCTCCTAGGATCGCTCCTGCATCCCCC-ATTATCCCCC
JMC50    CCTCCCAGCAACTCCCTGTACCCCTCCTAGGATCGCTCCTGCATCCCCC-ATTATCCCCC
JMC51    CCTCCCAGCAACTCCCTGTACCCCTCCTAGGATCGCTCCTGCATCCCCC-ATTATCCCCC
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JMC60    CCTCCCAGCAACTCCCTGTACCCCTCCTAGGATCGCTCCTGCATCCCCC-ATTATCCCCC
JMC62    CCTCCCAGCAACTCCCTGTACCCCTCCTAGGATCGCTCCTGCATCCCCC-ATTATCCCCC
JMC63    CCTCCCAGCAACTCCCTGTACCCCTCCTAGGATCGCTCCTGCATCCCCC-ATTATCCCCC
JMC64    CCTCCCAGCAACTCCCTGTACCCCTCCTAGGATCGCTCCTGCATCCCCC-ATTATCCCCC
JMC7     CCTCCCAGCAACTCCCTGTACCCCTCCTAGGATCGCTCCTGCATCCCCC-ATTATCCCCC
JMC80    CCTCCCAGCAACTCCCTGTACCCCTCCAAGGATCGCTCCTGCATCCCCC-ATTATCCCCC
JMC8     CCTCCCAGCAACTCCCTGTACCCCTCCTAGGATCGCTCCTGCATCCCCC-ATTATCCCCC

JMA10    CCTTCACCCCTCGC-GGAATCCCCCCTGGCCCCCCAG-AATCCCCCCTGCAGCCCTTCCG
JMA11    CCTTCACCCCTCGC-GGCATCCCCCCTGCACCCCCAG-CATCCCCCCTGCAGCCCCCCA
JMA3     CCTTCACCCCTCGC-GGCATCCCCCCTGCACCCCCAG-CATCCCCCCTGCAGCCCCCCA
JMA4     CCTTCACCCCTCGG-GGCATCCCCCCTGCACCCCCAG-CATCCCCCCTGCAGCCCCCCA
JMA5     CCTTCACCCCTCGC-GGCATCCCCCCTGCACCCCCAG-CATCCCCCCTGCAGCCCCCCA
JMA6     CCTTCACCCCTCGC-GGCATCCCCCCTGCACCCCCGG-CATCCCCCCGGCAGCCCCCCA
JMA7     CCTTCACCCCTCGC-GGCATCCCCCCTGCACCCCCAG-CATCCCCCCTGCAGCCCTTCCA
JMA8     CCTTCACCCCTCGC-GGCATCCCCCCTGCACCCCCGG-AATCCCCCCTGCAGCCCCCCA
JMA9     CTTTCACCCCTCGGGGGAATCCCCCCGGCACCCCCAG-CATCCCCCCGGCAGCCCCTCAA
JMC15    CCTTCACCCCTCGG-GGCATCGCCCCTGCACCCAAAG-AATCCCCCCTGCAGCCCCCAAA
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JMC26    CCTTCACCCCTCGC-GGCATCCCCCCTGCACCCCAAGGCATCCCCCCGGCAGCCCCCCCA
JMC27    CCTTCACCCCTCGC-GGCATCCCCCCTGCACCCCCAG-CATCCCCCCCTGCAGCCCCCCCA
JMC29    CCTTCACCCCTCGC-GGCATCCCCCCTGCACCCCCAG-CATCCCCCCCTGCAGCCCCCCCA
JMC30    CCTTCACCCCTCGG-GGCATCCCCCCTGCACCCCCAG-CATCCCCCCCTGCAGCCCTTCAA
JMC35    CCTTCACCCCTCGC-GGCATCCCCCCTGCACCCCCAG-CATCCCCCCCTGCAGCCCTTCCA
JMC38    CCTTCACCCCTCGG-GGCATCCCCCCTGCACCCCAAG-AATCCCCCCCTGCGGCGCCCCCA
JMC45    CCTTCACCCCTCGC-GGCATCCCCCCTGCACCCCCAG-CATCCCCCCCTGCAGCCCTTCCA
JMC46    CCTTCACCCCTCGC-GGCATCCCCCCTGCACCCCCAG-CATCCCCCCCGGCAGCCCCCCCA
JMC50    CCTTCACCCCTCGC-GGCATCCCCCCTGCACCCCCAG-CATCCCCCCCTGCAGCCCTTCCA
JMC51    CCTTCACCCCTCGC-GGCATCCCCCCTGCACCCCCAG-CATCCCCCCCTGCAGCCCTTCCA
JMC58    CCTTCACCCCTCGC-GGCATCCCCCCTGCACCCCCAG-AATCCCCCCCTGCAGCCCCCCCA
JMC59    TCTTCACCCCTCGC-GGCATCCCCCCTGCACCCCCAG-CATCCCCCCCTGCAGCCCTTCCA
JMC60    CCTTCACCCCTCGG-GGCATCCCCCCTGCACCCCCAG-CATCCCCCCCTGCAGCCCTTCCA
JMC62    CCTTCACCCCTCGC-GGCATCCCCCCTGCACCCCCAG-CATCCCCCCCTGCAGCCCCCCCA
JMC63    CCTTCACCCCTCGC-GGCATCCCCCCTGCACCCCCAG-CATCCCCCCCTGCAGCCCTTCCA
JMC64    CCTTCACCCCTCGC-GGCATCCCCCCTGCACCCCCAG-CATCCCCCCCTGCAGCCCCCCCA
JMC7     CCTTCACCCCTCGC-GGCATCCCCCCTGCACCCCCAG-CATCCCCCCCTGCAGCCCTTCCA
JMC80    CCTTCACCCCTGGC-GGCATCCCCCCTGCACCCCAAG-AATCCCCCCCTGCGGCCCCCCCA
JMC8     CCTTCACCCCTCGC-GGCATCCCCCCTGCACCCCCAG-CATCCCCCCCTGCAGCCCTTCCA

JMA10    GCATC-CCCCTGGACCCCTCCAAGGACCCCCCCCCGG-ATC---TTCTTATTATTTTT---
JMA11    GCATCTCCCCTGCACC---CCCAGAATCCCCCCTGC-AGC---CTTTTTTTTTTTTTCCC
JMA3     GCATCTCCCCTGCACC---CCCAGAATCCCCCCTGC-AGCCC-----TTCTTTTTCCTCC
JMA4     GCATCTCCCCTGCACC---CCCAGAATCCCCCCTGC-AGCCCTTCCATCTACTTTAT---
JMA5     GCATCTCCCCTGCACC---CCCAGAATCCCCCCTGC-AGC-CTTTTTTTTTTTTTTT---
JMA6     GCATCTCCCCTGCACC---CCCAGAATCCCCCCTGC-AGC-CCTTTTTTTTTTTTTTTTC
JMA7     GCATC-CCCCTGGACCTCTCCAAGGACCTCCCCTGCCAAC----TCTTTTTATTTTTTCC
JMA8     GAATCTCCCCTGCAAC---CCCAAAAAACCCCCTG--AAGCCTTTTTTTTTTTTTTTTT
JMA9     GAAATCCCCTTGCACCCCCCCAAGGACCCCCCG----AACCCTTTTAGTTTTTTTTTT-
JMC15    GAATCTCCCCGGAAAC---CCCAGAATGCCCCTTGC-AGC-CTTTCTATTTTTTTTG--
JMC26    GAATCTCCCCTGCACC---CCCAGAA-CCCCCCTGC-AGC--CTTTTTTTTTTTTTTTT
JMC27    GCATCTCCCCTGAACC---CCCAGAATCCCCCCTGC-AGC-CTTTCTTTTTTTTTTTT-
JMC29    GCATCTCCCCTGCACC---CCCAAAATCCCCCCTGC-AAC---TTTTTTTTTTTTTTTTC
JMC30    GCATC-CCCCTGGACCCCCCCAAGGACCCCCCCCGC-AACTTCATTAATTTTTT------
JMC35    GCATC-CCCCTGAAACTCTCCCAGGATCTCCCCTGC-AACCCCAATAATTTTTT------
JMC38    GAATCTCCCCTGAACC---CCCAGAATCCCCCTTGCAGGC-----CTTTTATATTCTTCG
JMC45    GAATC-CCCCTGGACCTACCCCAGGACCCCCCCCGCAACCTTCATTAATTTTTTTT----
JMC46    GCATCTCCCCTGCACC---CCCAAAATCCCCCCTGC-AGC-CTTTCTTTTTTTTTTTTG-
JMC50    GCATC-CCCCTGCACCTCTCCCAGGATCTCCCCTGC-AACTCCATTAATTTTTCCT----
JMC51    GCATC-CCCCTGCACCTCTCCCAGGATCTCCCCTGC-AACCCCATTTTTTTTTT------
JMC58    GCATCTCCCCTGCACC---CCCAGAATCCCCCCTG--AGC-CCTTCTATTTATTTTTT--
JMC59    GCATC-CCCCTGCACCTCTCCCAGGATCTCCCCTGC-AACTCCATTTATTTTTTTTG--
JMC60    GCATC-CCCCTGCACCCCCCCCAGGA-CCCCCCTGCAACCCCTATTTATTTTTT------
JMC62    GCATCTCCCCTGAACC---CCCAGAATCCCCCCTGC-AGCCCTTCTAGTTTTCCTTTTT-
JMC63    GCATC-CCCCTGGAACTCCCCCAGGACCCCCCCTGC-AACTTTTTTTTTTTTTTTTT--
JMC64    GCATCTCCCCGGCACC---CCCAGAATCCCCCCTGC-AGCC---TTTCTTTTTTTTTTCT
JMC7     GCATC-CCCCTGCACCTCCCCCAGGACCCCCCCTGCAACCCTTTTTAATTTTTTTTT---
JMC80    GAATCTCCCCTGAAAC---CCCGAAATCCCCCCTGC-AGCCCTTCTAATATTTTTTT---
JMC8     GCATC-CCCCTGGACCTCTCCCAGGATCCCCCGCGCAACCCCATTTTTTTTTTTTTG---
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