The Identification of Precursors in the Early Development of Attention Deficit Hyperactivity Disorder

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DOCTOR OF PHILOSOPHY

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Summary

The principal aim of this thesis was to identify precursors to symptoms of ADHD in early childhood in the context of a longitudinal study of first-born children (the Cardiff Child Development Study; CCDS). Three criteria were used to determine whether an early behaviour could be identified as a precursor. Firstly, the precursors should 'resemble the later developmental outcome'. In line with features of the disorder, informant-reported and measured high activity levels during a number of tasks (reflecting inattention and impulsivity domains) in infancy were proposed as precursors of ADHD symptoms.

Secondly, precursors needed to be associated with 'well-established risk factors for the later outcome'. Associations with familial symptoms of ADHD and perinatal risk factors were therefore explored. Parental ADHD symptoms predicted ADHD symptoms and executive task performance at 33 months and 7 years of age, but were only related to increased activity levels during a restraint condition at 6 months. Perinatal risk factors predicted toddlers and childrens' ADHD symptoms, but this was no longer significant when ODD symptoms were taken into account. Higher informant-reported activity levels at 6 months were associated with stress and smoking in late pregnancy, but measured activity levels were not related to perinatal risk.

Thirdly, the precursors should show 'continuity over time'. The relationships with later ADHD symptoms and executive functioning outcomes, measured in toddlerhood and then again at age 7 were therefore explored. Continuity over time was established for informant-reported activity levels at 6 months of age, which predicted later ADHD symptoms, even when ODD symptoms were controlled for. Infants' measured activity levels did not predict measured activity levels in toddlers, symptoms of ADHD or executive

functioning. The outcomes were more stable, with toddlers' ADHD symptoms and executive functioning significantly predicting outcomes in middle childhood.

Two additional tests were performed. The first required that the precursor added predictive power, beyond the effects of the risk factors. Only informant-reported activity levels passed this test. The second test established whether risk factors were associated with consolidation of precursor states into later symptoms of ADHD (measured using standardised change scores). Risk factors were significantly related to a move from activity levels in infancy (informant-reported and measured) to later symptoms of ADHD.

This thesis contributed to the literature by highlighting the need for clear criteria and a more consistent use of the term 'precursor'. A method for identifying precursors to ADHD symptoms in infancy was demonstrated, and showed that informant-reported (but not measured) activity levels were supported by all criteria and additional tests; except association with familial ADHD symptoms. This method for identifying precursors facilitates further prospective studies of etiological mechanism and could also inform the development of targeted prevention or intervention programmes.

Roles and Responsibilities within the Cardiff Child Development Study

The data presented in this thesis were collected in the context of a prospective longitudinal study of 332 first-born children from a community sample, the Cardiff Child Development Study (CCDS). Recruitment started in 2006 and five waves of data collection were completed before I joined the study in 2011. In this section I have outlined my roles and responsibilities since I joined the CCDS. I have been involved in data collection during the sixth wave (middle childhood assessment) of the study, but was also involved in the data-processing, coding and analysis of previous waves.

I contributed substantially to the entering of the Mother Interview, which was conducted during the early infancy home assessment (Wave 2). I was responsible for cleaning and checking the first part of this interview, which included perinatal variables (Chapter 4). I was also involved in reliability coding for a number of tasks. I also cleaned the Actigraph activity and heart rate data, which were collected at the early (Wave 2) and late infancy home assessment (Wave 3) and during the late toddlerhood laboratory assessment (Wave 5). I compared and matched up the Actigraph data, the observational videos and the timing sheet that had been completed during testing in order to extract the activity and heart rate data. For the early infancy assessment (Wave 2) I extracted data for a baseline, an attention and a restraint condition. For the late infancy visit (Wave 3) I extracted heart rate (and activity) data for a baseline period and during the teddy bear's picnic procedure (paper under review). Finally, for the late toddler assessment (Wave 5) I extracted data for a baseline, attention, restraint, frustration and peer interaction condition.

For the late toddler assessment (Wave 5), I also helped to enter questionnaire data, specifically the CBCL questionnaire used throughout this thesis and the MacArthur Bates CDI questionnaire. I have contributed to the observational coding of the data and assisted

with entering, cleaning and checking coded transcripts from the late toddler assessment (Wave 5) of the CCDS. I was the primary coder of the Whisper task and was responsible for analysing and creating the factor scores for the cognitive tasks.

During the middle childhood assessments (Wave 6) I was trained in administering interview protocols as well as child assessments and parent-child interaction tasks. My role as an interviewer involved administering questionnaires and interviewing the primary caregiver about their child (Preschool Age Psychiatric Assessment; PAPA) and their own psychological functioning (Schedules for Clinical Assessment in Neuropsychiatry; SCAN) during two 2-hour home visits. The child assessment, which occurred simultaneously, involved a battery of vocabulary, socio-cognitive, computerised and family-interaction tasks. As a child tester I was also responsible for making a DVD from the observation videos collected during the visit, which contains highlights of the visit and are given to the families as a memento. Finally, in terms of data-processing I was involved in entering paper and downloading electronic questionnaires, and I was responsible for coding the primary caregiver interviews I conducted.

CHAPTER 1.

Introduction.

1.1 Focus of the Thesis

The overarching aim of this thesis is to introduce a method for identifying precursors to ADHD symptoms in infancy and toddlerhood. To determine whether early behaviours can be considered a precursor, three previously proposed criteria of 'resemblance, continuity over time and association with well-established risk factors' will be used (Hay et al., 2014). These criteria will be tested within a developmental framework, in the context of a prospective longitudinal study of first-born children from a community sample, the Cardiff Child Development Study (CCDS). Three time points within the longitudinal study are examined within this thesis: the first year (mean 6.8 months, henceforth referred to as infancy), the third year (mean 33 months, henceforth referred to as toddlerhood) and the seventh year (mean 7.0 years or 84 months, henceforth referred to as middle childhood). Within this thesis evidence for precursor behaviours focuses on the period of infancy, since it is argued that symptoms of ADHD are already identifiable during toddlerhood and definitely during middle childhood. However, before this sample and longitudinal methods are introduced in Chapter 2, it is important to establish how the word precursor is defined in this thesis, and why these particular criteria of a precursor were chosen. Therefore, the first aim of this chapter is to introduce the concept of 'precursor' and the method, first established by Hay and Angold (1993) and further operationalised in this thesis, for testing whether early behaviours can be considered 'precursors' to later symptoms of ADHD. I will explain how each proposed criterion can be applied to the study of ADHD symptoms, after which the specific hypotheses that are tested in this thesis will be set forth.

1.2 What is a 'Precursor'?

Development has been described as a process of unfolding or triggering the expression of the information mapped by our genes. Gene-environment interactions (GxE) are further defined as genetically influenced differences in the sensitivity to specific environmental features (Rutter & Silberg, 2002). The philosophical approach most compatible with these viewpoints is ´constructivism´. This approach argues that the relationship between the initial state (in developmental terms 'conception') and the final product (an adult human being) can be understood by considering the progressive construction of information, which is a dynamic process with multiple contributing factors (Johnson, 1997). The identification of potential precursors might provide a stepping stone in this process. Rather than starting with the proposition that all young children are psychologically healthy and that disorder develops out of 'nothing', it is more useful to start with something, like a precursor condition quite early in development (Hay and Angold, 1993, p.17). However, few researchers have examined early behaviours in a systematic way with the aim of identifying precursors to psychopathology. A clear definition of the term has not been applied in the literature and the term 'precursor' is often used inconsistently. Sometimes other terms are used to describe a similar construct. Johnson and colleagues (2015) warn researchers that careful use of terminology is critical to progression in the field and unlike other authors have attempted to define the term precursor, as well as other terms carefully (see Table 1.1; Johnson, Gliga, Jones, & Charman, 2015). However, these definitions have not been applied generally across the literature. Moreover, no criteria are specified for testing whether a behaviour qualifies as one thing or should be considered something else. Table 1.2 contains a selection of research studies that have used the term ´precursor´ and have attempted to identify behaviours as precursors within the ADHD literature.

Table 1.1 Definition of terms proposed by Johnson et al. (2005, p.230).

Term	**Relation to later diagnosis**
Potential marker	Group difference in the development of children with later ADHD (or other psychopathology)
Marker/predictor	Marker with demonstration of predictive validity (e.g. sensitivity/specificity) in relation to categorical diagnosis
Precursor	Marker that indicates the approach of the disorder (i.e. is conceptually related to the core domains of difficulty)
Antecedent	Marker that precedes diagnosis and has a causal relation to later symptoms; this may be demonstrated through the downstream effects of early intervention. Marker may have little apparent surface similarity to later symptoms and may even be transitory in development.
Endophenotype	A heritable attribute that mediates between genetic and behavioural levels of explanation (e.g. Gottesman & Gould, 2003)
Protective/compensatory factor	Marker that relates to later typical development across disorders, e.g. good executive functioning skills (Johnson, 2012)

From Table 1.2 it becomes clear that up to date the validity of precursor behaviours of ADHD has not been systematically and consistently tested. Each researcher tested the construct in a different manner and this lack of consistency is certainly problematic.

Whilst it is clear that a precursors needs to be related to the later outcome in some way, in what way it needs to be related is not clearly defined by researchers in the field (see Table 1.2). These difficulties are not surprising. Developmental processes are highly complex and certain outcomes might be the result of diverse developmental pathways (*equifinality*) and/or certain predictors could be associated with various outcomes (*multifinality*) (Hirshfeld-Becker et al., 2003). Similarly, early predictors (or precursors) might be either *homotypic* (early signs that are similar to the adult form of a disorder) or *heterotypic* (early signs that are dissimilar to the adult form of the disorder; Seguin & Leckman, 2013).

Table 1.2. Examples of research studies that have attempted to identify precursors.

Authors	Precursor defined as ...	Criteria?	Precursor	Outcome
Olsen, Bates, Sandy, & Schilling (2002)	not clearly defined ´developmental antecedent'	Not explicit, they... - test if precursor predicts outcome - perform hierarchical multiple regression analyses for each outcome including all precursors	- Infant (6 months) and toddler (13 and 24 months) cognitive competence (task-based) - Infant and toddler age observed caregiver-child interaction (affectionate contact, object stimulation, verbal stimulation, restrictiveness, affection) - Toddler's observed Difficultness, Disengagement and parent-rated Resistance to Control.	Impulsivity (inhibitory and behavioural control) and Inattention (disengagement) measured with a battery of self-regulatory tasks at age 8
Allely et al. (2012)	not clearly defined ´early signs´	Not explicit, they... - test if precursor predicts outcome	Clinical observation during parent-child interaction task at 1 year	Psychopathology at age 7, various cases (ADHD *N* = 16)
Auerbach, Atzaba-Poria, Berger, & Landau (2004)	´early path markers of vulnerability to ADHD´	Not explicit, they... - test if precursors are more prevalent in risk group (fathers had >7 symptoms) than in control group	- Infant (7 months) activity levels (mothers´ report) - Infant interest in block play - Infant anger (reactivity, directed anger)	no outcome defined, only association with familial risk assessed.
Hirshfeld-Becker et al. (2002)	Not clearly defined... ´those at highest risk´ ´trait observable in early childhood´	Not explicit, they... - test if precursor relates to concurrent psychopathology and functioning - test if precursor relates to parental diagnosis (panic dis. or depression)	Behavioural measure of temperament ´behavioural disinhibition´ in children from high risk sample, aged 2-6 years old (i.e. tendency to seek out novelty, approach unfamiliar stimili and display disinhibition of speech or action)	- Concurrent disruptive behaviour disorders including ADHD and ODD - poor academic performance - psychosocial functioning
Mannuzza, Klein, Abikoff, & Moulton (2004)	Not defined.	Not explicit, they... - examined if precursor was more prevalent in ´pure´ ADHD group compared with control group and comorbid conduct problem group.	´pure´ADHD symptoms without conduct symptoms in childhood (6-12 years)	- Conduct Disorder at 10 year follow up (average age 18)
Schmid & Wolke (2014)	Not defined.	Not explicit, they... - test if precursor predicts outcome - test if prediction holds when risk factors are controlled for (perinatal, socio-economic, gender)	regulatory problems at 5, 20 and 56 months (crying, feeding and sleeping problems – interview measure) - transient (1 timepoint only) or persistent	- Intelligence at 8.5 years - observed attention and activity and ADHD diagnosis
Sullivan et al. (2015)	Not clearly defined... ´marker related to familial liability´ ´early indicator of future disorder´	Not explicit, they... - tested if precursor was asssociated with familial current and past ADHD - control for risk factors (perinatal stress, postnatal mood, education)	Conceptually relevant emotional temperament indicators – Parent reported temperament - Observed negative affect, neg. vocalisation, attention seeking and escape behaviour during still face and arm restraint paradigm	no outcome defined, only association with familal risk assessed.

Firstly, I will argue that in order to overcome these conceptual difficulties, and in order to differentiate precursors from risk factors, there needs to be some evidence for continuity of function over time. A precursor 'does not simply precede or predict later behaviours, but is also structurally, functionally or mechanistically related to the outcome' (Hay & Angold, 1993, p.14). In other words, a precursor needs to resemble the later outcome *in a meaningful way*. Nonetheless, the measurement of resemblance may itself be problematic. In psychometric theory, face validity has been shown to be an inadequate criterion for attaining confidence in a measure (Downing, 2005). In order to determine whether something 'resembles' something else, subjective judgements need to be made, and criteria for 'resemblance' are difficult to establish. These problems are even more evident within a developmental context, since similar behaviours may have different meanings at different points of development (Hay and Angold, 1993). Additionaly, even precise resemblance would be problematic, since if the precursor resembled the later outcome exactly, it would not be a precursor, but rather it could be said that the mature condition is already present (Hay and Angold, 1993). Nevertheless, to differentiate a precursor from other types of behaviour and other predictor variables, at least some similarity in function is required. This relates to issues of content validity as well as face validity; a potential precursor must represent a behaviourally relevant step towards the later behaviour. On the other hand, it is important to limit the number of behaviours that could be considered precursors or the concept of precursor would be indistinguishable from 'prior risk factor.'

To illustrate this point, it can be noted in Table 1.2 that Mannuzza et al. (2004) defined ADHD as a precursor to conduct disorder (CD). If the resemblance criterion had been applied, it would not have qualified as a precursor. Perhaps it would be better defined as a risk factor of the other (later) disorder or perhaps these two comorbid disorders simply develop at different rates. The overlap between ADHD and CD/oppositional defiant disorder

(ODD) is substantial and the relationship between these disorders complicated (as illustrated by Mannuzza et al., 2004). The aim of this thesis is to find precursors that are specific to ADHD symptoms and care must therefore be taken that findings are not obscured by factors related to CD/ODD. To account for the comorbidity between CD/ODD and ADHD the presence of comorbid ODD problems has been controlled for, where relevant. ODD symptoms were considered more relevant than CD symptoms for this age group.

Whilst the aim of the 'resemblance' criterion is not to limit the search for precursors unnecessarily, I believe it is important to set some restrictions to the construct. At the same time, it is important to take the limitations of this criterion into account and acknowledge that precursors that do not completely resemble the later outcome are theoretically possible, and that determining 'resemblance' is inherently a subjective process. Nonetheless, I have chosen to include this criterion, since it helps the researcher identify which behaviours might classify as precursors. Rather than an absolute requirement, it should be seen as a criterion that allows researchers to orientate themselves towards behaviours that might be of importance. Of course, resemblance alone is not sufficient to determine whether an early behaviour can be considered a precursor.

Secondly, it is important that the concept 'precursor' is clearly differentiated from 'causes' of disorders, i.e. its aetiology or pathogenesis and from 'risk factors' of disorders. These terms, although related, are not equivalent. Risk 'is purely a statistical concept, indicating that if X is present, Y is more likely to occur' (Hay & Angold, 1993, p.4). Many risk factors have been associated with the development of ADHD symptoms; however, thus far few aetiological/causal inferences have been made. It is not hard to understand the inherent difficulties in determining 'causes' of psychological disorders in developing systems. Few behavioural patterns are 'set in stone' and unalterable by the environment. Neuroscience has provided many examples of the plasticity of the human brain in response to

injury and the influence of ‘causes’ such as genetic and environmental factors need to be seen in a probabilistic, rather than deterministic fashion (Pennington, 2002). Given the complex nature of these interactions between genes, environment and developmental processes, it is no surprise that whilst several sophisticated causal theories of ADHD have been proposed, the field is still far from demonstrating a complete account of the disorder. This challenge is exemplified by the suggestion that a good comprehensive theory would need to ‘predict a ballet choreographed interactively over time among genotype, environment and epigenetic factors, which give rise to a particular phenotype’ (Gottesman & Gould, 2003, p.636). These issues with determining causation could be helped by identifying precursor conditions. It is therefore important to distinguish the concept ‘precursor’ from ‘cause’. The definition of a precursor is fundamentally correlational (i.e. no causal inferences can be made). A precursor simply represents a behaviour that is structurally, functionally or mechanistically predictive of the later outcome, but is neither a ‘cause’ nor a ‘risk factor’ of the outcome. Instead, it could be seen as ‘an early or immature form of some end-point pathology’ (Hay and Angold, 1993, p.32), something which if present marks actual progress towards the pathology (precursor) rather than something that only raises the probability of pathology (risk factor; Hay and Angold, 1993). One criterion that helps differentiate precursors from risk factors and helps identify a precursor as an early form of the outcome, is the requirement that a precursor is associated with risk factors in the same way as the later outcome. This criterion so far has not systematically been applied in the literature and instead one finds that the term ‘precursor’ is applied to some variables that might qualify as risk factors rather than precursor behaviours.

Thirdly, to gain more confidence in a precursor, it is essential that the precursor is predictive of the later outcome. The definitions in Table 1.2 show that all studies examined precursors which ‘preceded’ the later outcome. Whilst this might seem like an obvious

requirement, it is perhaps the most important criterion to establish. The third criterion of a precursor therefore requires that individual differences show stability over time. The only suitable approach that can be used to study individual consistency or change over time is longitudinal research. Longitudinal research strategies repeatedly test the same sample of participants across a number of ages, and in this way provide snapshots of development, usually with the intention of studying naturally occurring rather than experimentally induced changes in behaviour over time. Whilst a longitudinal study approach is more time-consuming, expensive and difficult to complete than other research strategies, it has many advantages. Most importantly, it is the only suitable approach for identifying early developmental precursors. It can also be applied for other purposes, such as identifying clusters of individuals whose symptoms follow a similar time course over development. This could be particularly relevant to the study of ADHD (see Legerstee et al., 2013; Sonuga-Barke & Halperin, 2010; Willoughby et al., 2012). A longitudinal method was therefore adopted throughout this thesis.

It must be noted that longitudinal relationships between early and later conditions are often probabilistic rather than deterministic and it is difficult to determine when a probability is sufficiently high (Hay and Angold, 1993). Clearly, deciding to what extent each criterion has been met is difficult and is characterised by a certain level of vagueness and uncertainty. Therefore, an additional test of a precursor was suggested by Hay et al. (2014), evidence that the precursor predicts the later outcome, after other well known risk factors are taken into account. This could be considered a test of the usefulness of the precursor. If a precursor does not explain any additional variance in predicting the outcome beyond that associated with the risk factors, perhaps the precursor does not add value to the prediction of the later outcome and is not worthy of further investigation. Another way of testing a precursor is by examing whether consolidation from a precursor state into a disorder is associated with well-

established risk factors. A second additional test was therefore formulated in this thesis. It was tested whether selected risk factors were associated with the continuity of precursors to later outcomes (using standardised change scores). Such a relationship would indicate that a move from a precursor state, to higher outcome scores over time, is associated with well-established risk factors of the outcome, and would thus further support the definition of the precursor as the very earliest manifestation of the outcome.

1.3 Defining the Outcome

It has become clear that within the ADHD literature the concept of a precursor has not been explored systematically. The main aim of this thesis is to demonstrate a method that allows researchers to systematically test whether an early behaviour can be considered a precursor to ADHD symptoms. However, before the criteria outlined above can be applied, it is first important to establish what ADHD is and how it has been studied up to date.

This is particularly relevant for the first criterion that needs to be met in order to identify an early behaviour as a precursor: 'resemblance' between the precursor and later developmental outcomes (Hay et al., 2014). To be able to judge whether an early behaviour resembles the later outcome, is essential to establish what ADHD looks like in its 'mature' form (i.e., in school-aged children). The next section will therefore firstly describe the clinical definition of ADHD, after which research of the core symptom domains is dealt with. Finally, some psychological theories of the underlying mechanisms will be described. This review of the literature will allow us to paint a picture of the developmental outcome: ADHD symptoms.

1.3.1 What is ADHD?

1.3.1.1 Clinical definitions of ADHD. There are many misconceptions surrounding Attention Deficit Hyperactivity Disorder (ADHD). Whilst a wealth of research has clarified

many of these misconceptions, there are still issues surrounding the definition, diagnosis and theoretical frameworks that support the construct 'ADHD'. It must firstly be noted that a behavioural cluster of hyperactivity, impulsivity and inattention is not a recent phenomenon. Recently, a chapter called 'Attentio Volubilis1' was discovered in a medical textbook published in 1775, written by German physician Melchior Adam Weikard; this text described attention disorders and is argued to be the earliest reference to ADHD, containing descriptions of distractibility, poor sustained attention and disinhibition (Barkley & Peters, 2012). The popular poems from 1844, written by German physician Heinrich Hoffman, are also often cited as an early description of ADHD-like behaviours (see Figure 1.1). Whilst these examples discredit the commonly heard sentiment that ADHD is a 'recent invention', it must be acknowledged that the definition and classification of what constitutes Attention Deficit Hyperactivity Disorder (ADHD) has changed extensively over the last 50 years with each successive revision of the Diagnostic and Statistical Manual (DSM) (Daley, 2005). The concept of ADHD at this time has developed from a 'minimal brain dysfunction' to a 'heterogeneous set of related behaviours' (Taylor, 2009). ADHD is furthermore identified as a 'developmental disorder', which is a disorder where no explicit pathology is known, but where in comparison to age-matched peers, particular difficulties in acquiring abilities or skills are found (Temple, 1992). This can be contrasted with 'acquired disorders' where skills were present, but were lost due to injury. Genetic disorders are similar to 'acquired' disorders, since a clear biological cause can be identified. The aetiology of ADHD is not well understood and whilst some evidence of early brain injury has been found, the biological substrate is still too unclear to be able to classify it as an 'acquired' or 'genetic' disorder (Temple, 1992).

[1] Translated as 'Attention Deficits'.

Fidgety Philip
Let me see if Philip can,
Be a little gentleman
Let me see, if he is able,
To sit still for once at table
But fidgety Phil,
He won't sit still…

Johnny Head-In-The-Air
As he trudged along to school,
It was always Johnny's rule
To be looking at the sky,
And the clouds that floated by…

Figure 1.1 Translated excerpts and illustration from Heinrich Hoffman's poems (1844).

Whilst the aetiology of ADHD might still be unclear, it is widely agreed that the core group of symptoms consist of inattention, hyperactivity and impulsivity (Daley, 2005). However, these symptoms of ADHD are not unique to the disorder, with many symptoms being evident in other disorders and in 'normal' behaviour as well. Currently, a diagnosis of ADHD is based upon either DSM-5 or the ICD-10 criteria. Until recently, the DSM-IV criteria divided ADHD in two main dimensions (inattention vs. hyperactivity-impulsivity) from which three subtypes emerge: ADHD-H (hyperactive-impulsive), ADHD-I (inattentive) and ADHD-C (combination of both) (Chandler, 2010, p. 39). These subtypes are defined differently in the recently updated DSM-5; however, since the research described in this thesis has used DSM-IV classifications, I will describe the DSM-IV criteria after which the changes that were made to the DSM-V will shortly be addressed. The ICD-10 classification manual uses the term 'hyperkinetic disorder' rather than ADHD, for which the cardinal features are described as impaired attention, impulsivity and over-activity along with a number of associated features (disinhibition, learning disorders and motor clumsiness). The ICD-10 also established a further classification of 'hyperkinetic conduct disorder', which includes both hyperactivity and conduct disorder. The diagnostic features of the disorder, according to these two classification systems will now be explored more closely.

1.3.1.1.1 DSM criteria. A diagnosis of ADHD, according to DSM-IV-TR criteria, is made based upon five criteria (A-E; see Table 1.3). According to these criteria a persistent pattern of either inattention or hyperactivity-impulsivity must be present for at least 6 months and must be more severe than typically observed in individuals at similar levels of development. Some impairing behaviour should already be observed before the age of 7 years and these impairments should be present in at least two settings. Finally the impairment must significantly interfere with daily functioning and should not be part of another mental disorder (APA, 2000).

The recent publication of the DSM-5 (APA, 2013) included some changes to the diagnostic criteria for ADHD, although the same 18 symptoms, divided into the same two domains are still used to diagnose the disorder, with six symptoms in one domain required. However, it was argued that diagnosing subtypes disregards the contribution of the other symptom domains and that all symptoms should be considered to derive at an overall diagnosis for the disorder; therefore rather than subtypes, the DSM-5 uses presentation specificiers that map directly onto the previously used subtypes. Furthermore, an attempt has been made to make the diagnostic criteria more applicable to other developmental periods: examples have been added to the criterion items, the onset criterion has been changed to 'several inattentive or hyperactive-impulsive symptoms were present prior to age 12' and a cut-off of five instead of six symptoms is required for adults, thus loosening the criteria in favour of adult diagnoses. Moreover, the DSM-5 now allows a comorbid diagnosis of autism spectrum disorder. Finally, cross-situational requirements have been strengthened and 'several' symptoms in each setting are now required (APA, 2013).

Table 1.3 Diagnostic criteria for ADHD according to the DSM-IV-TR (APA, 2000).

Diagnostic criteria for Attention-Deficit/Hyperactivity Disorder

A. Either (1) or (2):

(1) Six (or more) of the following symptoms of **inattention** have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

Inattention

(a) often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities
(b) often has difficulty sustaining attention in tasks or play activities
(c) often does not seem to listen when spoken to directly
(d) often does not follow through on instructions and fails to finish school-work, chores, or duties in the workplace (not due to oppositional behaviour or failure to understand instructions)
(e) often has difficulty organizing tasks and activities
(f) often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)
(g) often loses things necessary for tasks or activities (e.g., toys, school assignments, pencils, books, or tools)
(h) is often easily distracted by extraneous stimuli
(i) is often forgetful in daily activities

(2) Six (or more) of the following symptoms of **hyperactivity-impulsivity** have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

Hyperactivity

(a) often fidgets with hands or feet or squirms in seat
(b) often leaves seat in classroom or in other situations in which remaining seated is expected
(c) often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)
(d) often has difficulty playing or engaging in leisure activities quietly
(e) is often 'on the go' or often acts as if 'driven by a motor'
(f) often talks excessively

Impulsivity

(g) often blurts out answers before questions have been completed
(h) often has difficulty awaiting turns
(i) often interrupts or intrudes on others (e.g., butts into conversations or games)

B. Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before age 7 years.

C. Some impairment from the symptoms is present in two or more settings (e.g., at school [or work] and at home).

D. There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning.

E. The symptoms do not occur exclusively during the course of a Pervasive Developmental Disorder, Schizophrenia, or other Psychotic Disorder and are not better accounted for by another mental disorder (e.g., Mood Disorder, Anxiety Disorder, Dissociative Disorder, or a Personality Disorder).

Code based on type:

314.01 Attention-Deficit/Hyperactivity Disorder, Combined Type: if both Criteria A1 and A2 are met for the past 6 months
314.00 Attention-Deficit/Hyperactivity Disorder, Predominantly Inattentive Type: if Criterion A1 is met but Criterion A2 is not met for the past 6 months
314.01Attention-Deficit/Hyperactivity Disorder, Predominantly Hyperactive-Impulsive Type: if Criterion A2 is met but Criterion A1 is not met for the past 6 months

Coding note: For individuals (especially adolescents and adults) who currently have symptoms that no longer meet full criteria, 'In Partial Remission' should be specified.

1.3.1.1.2 ICD-10 criteria. The ICD-10 prefers the term 'Hyperkinetic Disorder', since the term 'Attention Deficit Hyperactivity Disorder' implies a knowledge of (not yet fully understood) psychological processes (WHO, 2000). In order to diagnose Hyperkinetic Disorder, the three core features (impaired attention, impulsivity and overactivity) need to be present in more than one situation. Symptoms should be present from an early age (before 6 years), but are commonly first recognized at the age of school entry. In preschool years, wide normal variation can be present and at this time a diagnosis should only be made if extreme levels of disturbance are present (WHO, 2000). Impaired attention is characterised by leaving tasks and activities unfinished, frequent changes in activity and loss of interest in tasks. Impulsive problems include a difficulty awaiting ones turn, interrupting or intruding on others and blurting out answers before questions have been completed. Overactivity is manifested by excessive restlessness, running and jumping around, getting up when seating is

required, excessive talkativeness and noisiness, fidgeting and wriggling. This behaviour is mostly seen in structured, organised situation and should be excessive in the context of what is expected in the situation and by comparison with other children of the same age and IQ (WHO, 2000).

It must also be noted that restlessness can sometimes be part of anxiety or depressive disorders. Symptoms can also manifest in pervasive developmental disorders and schizophrenia. In these cases hyperkinetic disorder should not be diagnosed (WHO, 2000). The ICD-10 further notes that it is sometimes difficult to differentiate hyperkinetic disorder from conduct disorder, since milder degrees of overactivity and inattention are common in conduct disorder. The diagnosis should therefore be 'hyperkinetic conduct disorder' when features of both hyperactivity and conduct disorder are present and the hyperactivity is pervasive and severe. To reiterate, this thesis focuses on ADHD symptoms only and whilst the comorbidity between disorders is interesting, an effort has been made to control for the effect of oppositional problems (which are more common at this age, and strongly related to conduct problems), in order to find precursors that are specific to ADHD symptoms.

1.3.1.1.3 ADHD symptoms in preschool children. The bulk of the research into ADHD has focused on school-aged children, and it is striking when examining the DSM-IV and ICD-10 criteria, described in the previous chapter, that these criteria reflect mainly childhood-based symptoms. This means that they might not necessarily be developmentally appropriate for other age groups. This is argued to create obstacles for the accurate assessment of signs and symptoms of ADHD in preschool (as well as in adolescence and adulthood) (Cherkasova, Sulla, Dalena, Pondé, & Hechtman, 2013). However, it must also be noted that indicators of ADHD, such as high activity levels, poor inhibitory control and a short attention span are not uncommon in healthy preschoolers, making it more difficult to distinguish clinical cases form normally developing children. Despite this, preschool children

are increasingly identified as manifesting ADHD. In this thesis, symptoms of ADHD will be measured in toddlerhood and middle childhood (in a subsample). It is therefore important to discuss the literature on ADHD symptoms in preschool children a little further.

It was noted that the DSM-IV requires that some impairment needs to be present before the age of seven years. Behavioural and disruptive problems, including ADHD, can begin in preschool, often as early as 3 to 4 years of age, and are associated with chronic and often life-long challenges, especially in those children that started displaying symptoms at an early age (Moreland & Dumas, 2008). Nonetheless, many of the behaviours associated with ADHD have been argued to be more common in early childhood (Smidts & Oosterlaan, 2007). Results in line with this from a sample of 652 normal preschoolers (3-6 years old) indicate that a prevalence of at least 40% was found in a third of all behaviours listed in a DSM-IV based parent-rated questionnaire, including a difficulty in playing quietly (54.6%), excessive talking (51.6%), difficulty engaging in tasks requiring sustained mental effort (50.1%), being on the go/driven by a motor (49.6%), responding to every extraneous stimulus (47.8%), difficulty awaiting turn (44.3%) and interrupting other people (43.3%). Some gender differences were also found with boys scoring higher than girls on 6 out of 13 inattention symptoms and 3 out of 10 hyperactivity symptoms (Smidts & Oosterlaan, 2007). This study however did not identify which children reported multiple symptoms. An American longitudinal study of 1155 children reported that 3-year-olds on average exhibited four symptoms (1.7 inattention and 2.5 hyperactive-impulsive symptoms), which reduced over time, with 3.5 symptoms at 4 years and 3 at 5 years of age (Willoughby, Pek, & Greenberg, 2012). Of these children 8.4% showed persistently high ADHD symptoms across time (*M*s 12.2, 12.8 and 12.1), 16.4% had symptoms that reduced with age (*M*s 9.7, 5.8 and 3.2), 3.5 % started with few symptoms, which increased over time (*M*s 4.3, 7.7 and 12.3) and 71.7% of children had persistently low symptoms (*M*s 1.8, 1.8 and 1.5).

A further study concluded that preschool children who exhibit six symptoms or more across multiple settings were found to be markedly different from typically developing controls (Egger & Angold, 2006). Moreover, a Canadian study found that 12.3% of children had persistent high levels of both inattentive and hyperactive-impulsive symptoms across the preschool period, whereas overall hyperactive-impulsive trajectories were high (but declining over time) in 16.1% of children (52.7% moderate and 31.2% low) and inattentive trajectories were high (but ascending over time) in 13% of the sample (58.2% moderate and 28.8% low) (Galera et al., 2011). Therefore, it can be argued that whilst symptoms of ADHD are common in preschool, prevalence rates of persistently elevated levels of ADHD are more comparable with rates found in school-aged children.

It has further been noted that in preschool children the combined subtype of ADHD is most common; hyperactivity tends to decrease with age, whereas inattention becomes more evident with age, meaning that the predominantly hyperactive-impulsive subtype is found more in preschool children and the predominantly inattentive subtype is found less (Cherkasova et al., 2013). However, the findings from Smidts and Oosterlaan's (2007) study suggest that atypical hyperactive-impulsive symptoms might be more difficult to distinguish from typical behaviours in preschoolers than inattentive symptoms, since 5 out of 10 hyperactive-impulsive behaviours were found in over 40% of the sample compared with only 2 out of 13 inattentive symptoms.

A recent study, which examined endorsement patterns of DSM-IV symptoms in a longitudinal sample of 144 children with and without ADHD from age 4 to 7 concluded that some inattention symptoms were of limited utility at age 4-5, whereas by ages 6-7 inattention items were somewhat superior at differentiating ADHD and non-ADHD children. Hyperactive-impulsive items were more frequently endorsed amongst younger children (Curchack-Lichtin, Chacko, & Halperin, 2014). It was therefore argued that some items are

not developmentally appropriate, since they represent behaviours that are not yet required of preschool-aged children (e.g. 'avoids tasks requiring sustained mental effort', 'makes careless mistakes').

Others also explored the factor structure of ADHD symptoms in 3-, 4- and 5-year old-children and found that across these ages symptoms were represented best by a one-factor model, suggesting that inattentive and hyperactive-impulsive factors might not be easily differentiated in early childhood, which is in contrast with findings from school-aged children (Willoughby et al., 2012). Finally, whilst hyperactive-impulsive symptoms reduced over time and inattention symptoms increased, it was found that the two trajectories were significantly and strongly associated with each other in preschool (from 17 months to 8 years) and predicted one another (Galera et al., 2011). Together these findings suggest that ADHD can be successfully measured in preschool children and that it can be distinguished from normative behaviours in early childhood, although caution is still needed, since diagnosis of ADHD is likely to be less accurate in preschool than in school-age children.

1.3.1.1.4 Considerations concerning diagnosis. The diagnostic manuals do not attempt to ascribe causes to the symptoms they describe, since no definite conclusions can yet be drawn as to what causes ADHD (Chandler, 2010). The importance of clearly defining the criteria of ADHD is exemplified by the finding that the prevalence rates of ADHD vary depending on the classification system used (ICD-10 criteria are more stringent than DSM-IV), and range from 2.4-19.8 percent of the normal population (Faraone, Sergeant, Gillberg and Biederman, 2003). Williams and Taylor (2005) note that when assessment methods are carefully standardized, prevalence around the world is about 5-10 %. It is worth noting that during the latter part of the twentieth century the number of cases diagnosed has steadily increased, a phenomenon that Taylor (2009) describes as an epidemic in diagnostic practice and stimulant prescribing (most notably in America) rather than in the prevalence of the

illness. In general researchers have predominantly used DSM-IV criteria to define ADHD and throughout this thesis the term 'ADHD' therefore refers to these criteria. Where ICD-10 criteria were applied, the term 'hyperkinetic disorder' will be used.

Moreover, this thesis will focus on symptoms of ADHD using a dimensional approach, rather than diagnoses. In the preschool years, ADHD can be assessed using either categorical instruments, which use diagnostic criteria to determine whether certain behaviours are present or absent, or using dimensional approaches, which places symptoms on a continuum of frequency/severity. A meta-analysis including 26 studies and 4,536 preschoolers (range 2-6 years of age, M = 3.86) found that data obtained with either categorical or dimensional measures corresponded closely, and that referred preschoolers could be successfully distinguished from non-referred preschoolers using either approach (Moreland & Dumas, 2008). However, a more recent German study of 793 children which compared the stability of ADHD symptoms from 4 to 7 years of age using a categorical and dimensional approach found that stability was high with regard to dimensional analyses, however when a categorical approach was used stability was only low to moderate (Schmiedeler & Schneider, 2014). Children who crossed the cut-off point at one assessment point did not necessarily cross this point at a next assessment. Furthermore, the symptoms of ADHD have been considered to be pathological extremes of normal behaviour and should therefore be conceptualised as existing along a continuum with normality (Chandler, 2010, p.37) as well as with other disorders. A dimensional approach, using a measure of ADHD symptoms, was therefore considered the most appropriate way of investigating the outcome in this thesis. This continuum of symptoms is studied most effectively using a longitudinal community sample. Rating scales, completed by parents or other informants who know the child well are commonly used to study symptoms of ADHD. Whilst it is expected that only a small proportion of children will exhibit a diagnosable form of ADHD, symptoms of ADHD

are expected to be more frequent and distributed normally. However, whilst symptoms of ADHD are most commonly studied using rating scales, there are limitations to these (subjective) measures. More objective measurement of the core symptom domains has been developed and various underlying mechanisms have been proposed. Research into the core symptom domains of ADHD and psychological theories of underlying mechanisms will therefore be be discussed next to show what other measures are available and might be relevant for our purposes.

1.3.1.2 The core symptom domains of ADHD. Both the DSM-IV and ICD-10 criteria agree that the core symptom domains of ADHD are overactivity, impulsivity and inattention. These three symptom domains have been researched extensively and this section will therefore discuss the main findings in the literature for each domain. The aim of this section is thus to establish what these symptom domains look like according to the latest research without attempting, at this point, to identify causal mechanisms since some of the main theories that have been proposed to explain why ADHD symptoms develop in some children, will be discussed in the next section.

1.3.1.2.1 Overactivity. Overactivity and hyperactivity are terms that are often used interchangeable; however confusion arises when the term 'hyperactivity' is used to describe children with ADHD or hyperkinetic disorder as a whole, rather than simply the core symptom domain of 'overactivity'. This section will deal with the core symptom domain of 'overactivity' as an excess of movement, which can be recorded objectively and mechanically. Overactivity can be regarded as a primary problem in children with ADHD, which cannot be reduced to inattentiveness or impulsiveness (Taylor, 1998). It is regarded as a trait-like characteristic that can be observed across settings and situations. This activity can be measured in various ways, such as with actometers strapped to the body, stabilimeter chairs and interruption of ultrasonic beams around the room. However, relatively little

research has been done in so mechanical a way and this in part is due to the definition of overactivity in clinical practice. The items in both the DSM-IV and the ICD-10 are mostly defined by the situation, since the overactivity is regarded as inappropriate in certain situations. This definition is problematic and makes it very difficult to distinguish it from impulsive behaviour. In fact, the DSM-IV uses the 'hyperactive-impulsive type' as a separate classification or subtype of ADHD rather than viewing overactivity as a separate problem, for which different brain mechanisms might be the underlying cause.

When activity levels are objectively measured, children with a diagnosis of ADHD are found to exhibit increased activity in comparison with controls. Good discrimination between ADHD and comparison groups has been found using actometers, which measure the number of movements made by a child (Teicher, Ito, Glod, & Barber, 1996). Actometers measure the number of movements only, whereas actigraphs are able to also take the magnitude and size of these movements into account. A study, which measured truncal activity with an actigraph for a week across different naturalistic situations, found that children with ADHD make more movements in most situations, including sleep. Only in a few settings (unstructured free play and lunchroom activities), no significant differences in activity levels were found in comparison with normal controls (Porrino et al., 1983). Activity levels could distinguish children with ADHD and controls in this study independently from a measure of inattention (scores on a continuous performance test). Others have also found that activity levels did not relate significantly to CPT measures of attention or impulsivity (Reichenbach, Sharma, & Newcorn, 1992), suggesting that overactivity is a separate characteristic of ADHD and should be researched independently.

Another study found that compared to controls, children with ADHD showed increased activity, as measured with an actigraph worn on the nondominant wrist, during an afternoon testing session, but no differences were found during a morning testing session

(Dane, Schachar, & Tannock, 2000). Previous findings also suggested that during classroom activities children with ADHD are more active in the afternoons compared to the mornings (Dane et al., 2000). It thus appears that activity is produced as a function of the context or situation in which it is recorded. Activity is furthermore found to decrease in novel situations, whereas familiarity is associated with heightened overactivity. This is in line with the fact that behavioural problems are more evident in situations that are less reinforcing or unrewarding (Dane et al., 2000). Activity levels are thus not consistently elevated, but are found to be increased under conditions of low environmental stimulation (Wood, Asherton, Rijsdijk, & Kunsti, 2009). This situational specificity seems to also depend on task structure, with hyperactivity being more apparent in tasks that require a high degree of self-regulation. However, when few behavioural restrictions are present, it is more difficult to distinguish children with ADHD from normal controls (Barkley, 1998).

Furthermore, this study found that activity levels were increased in both the inattentive subtype and the combined subtype of ADHD, and did not differ between these two groups, suggesting that these subtypes are not as distinct in overactivity as is suggested by the DSM-IV (Dane et al., 2000). Another study measured waist and leg movements using an actigraph and found that the number of movements was able to distinguish children with ADHD and controls, whilst the cumulative intensity of the movements could distinguish the two groups even better (Wood et al., 2009). The intra-individual variability (IIV) of the intensity of the movements was also able to discriminate between children with ADHD and controls, but the IIV of the number of movements was not. Furthermore, it was found that unaffected siblings and controls differed in their mean and IIV of the intensity of movement, but not in their number of movements, suggesting a shared familial vulnerability of overactivity (Wood et al., 2009). In this study leg and waist movements showed a similar ability to distinguish groups, however others have found differences depending on what part

of the body is examined with low inter-correlations between different body parts (Taylor, 1998).

Inattention and impulsivity are considered to persist into adulthood, whilst hyperactivity is assumed to lessen with age. Gross motor overactivity is observable in children; however in adulthood this symptom is assumed to change into difficulties with fidgeting and a sense of restlessness. Research using an infrared motion tracking system during a computer-based working memory task found that adult ADHD patients showed a higher number of micro-events compared to controls, which was more pronounced as the testing progressed. Higher levels of hyperactivity were further linked to increased cognitive deficits in ADHD, but not in control subjects (Lis et al., 2010). Others used actigraph data for a period of 7 days and found higher levels of motor activity in adults with ADHD both during the day and during the night (Boonstra et al., 2007), suggesting that whilst directly observable motor activity might decrease, objective measures show that higher levels of hyperactivity do persist into adulthood. Increased ankle activity has even been found in adults with a history of childhood ADHD that have since remitted, whilst for measures of executive attention (working memory and effortful control) no differences between remitted ADHD adults and controls were found (Halperin et al., 2008). Persisters however differed from controls in both activity levels and executive control, and the authors suggest that in remitters improvements in prefrontally mediated executive functions might be able to compensate for more entrenched deficits in non-executive functions, mostly supported by subcortical regulatory systems (Halperin et al., 2008). These findings highlight the entrenched nature of overactivity and suggest that it might represent a prime candidate to be identified as a precursor. It is likely that overactivity might be observed early in development, prior to the the full emergence of the disorder.

1.3.1.2.2 Impulsivity. Impulsivity is often defined as 'acting without reflecting', which can be understood as an over-rapid responsiveness, sensation seeking, excessive attraction to immediate reward, a failure to plan ahead or a failure of inhibition (Taylor, 1998). Impulsive behaviour can thus be described as any motivated or goal-directed behaviour which is initiated prior to the time at which all available information has been evaluated (Rubia, Oosterlaan, Sergeant, Brandeis, & van Leeuwen, 1998).

Unlike overactivity, it is more difficult to measure objectively whether impulsive behaviours are present in children. Research often uses the concept of inhibitory control, which is the process involved in withholding a planned response, interrupting a response that has been started, protecting an ongoing activity from interfering activities and delaying a response (Barkley, 1997). Several tasks have been used to measure inhibitory control and therefore indirectly measure impulsivity. The stop signal paradigm requires participants to respond as quickly and accurately as possible to a task unless a stop signal (often auditory) is given. Worse inhibition and longer stop signal reaction times (SSRTs) have repeatedly been found for children with ADHD as well as aggressive children with ODD or CD (Oosterlaan, Logan, & Sergeant, 1998; Rubia et al., 1998), but not for children with ADD only (Overtoom et al., 2002). ERP recordings have further shown that positive amplitudes in time with SSRTs when inhibition was successful were smaller for children with ADHD, whilst also showing less brain activity during error processing (Overtoom et al., 2002). Methylphenidate has been found to improve performance of hyperactive children on the stop signal task (Tannock, Schachar, Carr, Chajzyk, & Logan, 1989).

A similar task is the go-no-go task, where participants are presented with frequent 'go-signals' and less frequent 'no-go-signals', so that responses need to be either executed or inhibited. Similar results are found with this task where children with ADHD perform more poorly than controls (Rubia et al., 1998). A meta-analysis showed that hyperactive children

and controls differed significantly on mean RTs, errors of commission and the standard deviation of RT (Metin, Roeyers, Wiersema, van der Meere, & Sonuga-Barke, 2012). Event rates were furthermore shown to influence performance on this task. Children with ADHD are unable to adjust their activation levels sufficiently, so that slow event rates lead to underactivation and thus inattention in these children. The meta-analysis showed that slow event rates were associated with slower RTs, whilst faster event rates resulted in more impulsive errors of commission (Metin et al., 2012).

Anti-saccade tasks represent another popular way of measuring inhibitory control. People have a natural tendency to look towards a stimulus whenever it appears; this is called a pro-saccade. During the anti-saccade task, participants are instructed to inhibit this automatic saccade and instead look in the opposite direction (i.e. to make an anti-saccade). Children with ADHD (both on and off medication) are found to make more directional errors during the anti-saccade task (Mostofsky, Cooper, Kates, Denckla, & Kaufmann, 2001). Memory-guided saccade tasks have also been used, where subjects were cued where to look, but instructed to delay their eye-movement towards the remembered position for a short period of time. All children with ADHD showed difficulties in inhibiting the response during the delay period by making significantly more anticipatory errors, whilst unmedicated ADHD children had longer latencies than either medicated ADHD children or controls (Mostofsky et al., 2001).

The continuous performance task (CPT) has also been used as a measure of inhibitory control, although it is more often used to measure sustained attention. During this task, participants observe a long sequence of targets over the course of 10-30 minutes, where only a small amount of targets requires a response. However, several version of the CPT exist, which differ in stimuli, event rate and signal probability. Conners' CPT requires participants to respond frequently (high signal probability) and withhold their response only occasionally.

A prepotent motor response is established this way that must be inhibited (Huang-Pollock, Karalunas, Tam, & Moore, 2012). Children with ADHD are found to make more errors and have more variable RTs on this task, whilst as time on the task progressed the ADHD group showed further increases in errors of commission and more variable RTs (Epstein et al., 2003). Errors of commission are likely to increase with time as the prepotent motor response becomes more established and reveal an impulsive response style, since they result from a failure to inhibit this prepotent response.

Another common way of investigating impulsivity is through the reaction of hyperactive children to immediate or delayed reward. Using a delay of gratification paradigm, it is found that children with ADHD are more likely to respond for a small, but immediate reward than for a larger, but delayed reward. In fact, children with ADHD are not as good at tasks in which a response needs to be delayed or withheld for a specific amount of time (Gordon, 1979). Researchers have found that whilst in general hyperactive children will more likely choose an immediate smaller reward rather than a larger delayed reward, this preference could be manipulated by controlling the amount of time that the child had to wait. When a post-reward delay was included after the small, immediate reward, so that the overall waiting time was constant for either reward, hyperactive children would choose the large, delayed reward (Sonuga-Barke, Taylor, Sembi & Smith, 1992). Hyperactive children are further found to adopt a fast response style, which favours errors (a fast guess strategy), when completing cognitive tasks, which might also reflect delay-aversive behaviours (Rubia et al., 1998).

Finally, during the Matching Familiar Figures Test (MFFT) children are required to select a target drawing from a set of five distracters. Children with ADHD are found to behave more impulsively during this task, responding more quickly and making more errors than comparison children (Sonuga-Barke, Houlberg, & Hall, 1994). However, delay

minimisation might play a role here as well, since children are found to only respond more quickly if they were able to reduce the total length of a session this way. If trial length was controlled, similar reaction times were found for ADHD and comparison children (Sonuga-Barke et al., 1994).

1.3.1.2.3 Inattention. Whilst it might seem that the meaning of the term 'attention' is obvious, since it a common everyday word, its precise meaning needs further clarification. Attention refers to a complex array of cognitive-behavioural processes involved in the reduction and selection of information and in behavioural response control (Tannock, 2003). The concept provides a bridge between behaviour and cognition and offers the possibility of a direct translation from brain dysfunction into a behavioural presentation (Taylor, 1998). Attentional processes develop over time and form an important part of the intelligence quotient (IQ). Since attention is something that is required for almost all daily tasks, it is not surprising that there is marked continuity between normal and abnormal levels of (in-) attention.

The ability to concentrate is dependent on how interesting the task is and motivation is thus likely to interact with attention (Taylor, 1998). Deficiencies are most easily detected in boring and uninteresting tasks (resembling school work). In fact, children with ADHD are often first diagnosed when they go to school, since they are not able to focus their attention on their schoolwork or teacher/parent. The subtypes used in the DSM-IV allow children to be diagnosed with ADHD based upon other problems, whilst the ICD-10 requires inattention to be present. Any research study that uses the DSM-IV concept of ADHD needs to take into account that this group can consist of both children who do show an attention deficit and children who do not, thus blurring results and making findings less reliable (Barkley, 2001). Sample heterogeneity could also obscure an actual distinction, since it is quite possible that non-hyperactive children with an abnormality in their attention are neuro-psychologically

different from children with both inattention and overactivity/impulsivity (Taylor, 1998). A recent international study (Toplak et al., 2012) found that a hierarchical general factor model with two specific factors (inattention and hyperactivity/impulsivity) fitted data using several instruments from a sample of 1373 ADHD children and 1772 siblings better than alternative single factor or correlated factor models. Within this model, the variance of inattentive symptoms from several measures could consistently be explained better by the inattention specific factors compared to the general ADHD factor, whereas the variance in hyperactivity/impulsivity symptoms could better be explained by the general factor than the hyperactivity/impulsivity specific factor. Therefore, whilst this study supports a unitary construct of ADHD, it does highlight the relatively independent character of inattention symptoms (Toplak et al., 2012). Nonetheless, it must be noted that this study contained a sample with primarily combined type symptoms of ADHD, limiting its conclusions regarding primarily inattentive children.

ICD-10 and DSM-IV criteria of inattentiveness do seem to have some concurrent validity, since they significantly predict inattentive behaviours as measured by behavioural observation and detailed behavioural interview accounts. Attention is often behaviourally defined in terms of overt action, such as on task behaviour (i.e. visual fixation to task-relevant stimuli) (Tannock, 2003). The behaviours that are often seen are a reduced length of time spent on a toy or task presented by the examiner, an increase in the number of orientations away from a centrally presented task and more rapid changes between activities (Taylor, 1998). When comparing controls with children with attention deficit disorder, it was found that task-irrelevant activities and short sequences of activity on tasks were more common in children with attentional problems (Milich, Loney, & Landau, 1982). Furthermore, correlations from 0.4 to 0.6 have been found between an independent psychiatric judgement and task-irrelevant activities, including visual orientations away from visually presented

material (Taylor, 1998). An epidemiological study of 7-year-old boys showed that boys with attention problems 6 months later had more off-task behaviour and more visual orientations towards irrelevant aspects of the environment than comparison children (Taylor, Sandberg, Thorley, & Giles, 1991).

Attention however can also be described in terms of cognitive processes that operate through neural networks in order to self-regulate sensory input, motor output and emotion in the service of internal goals (Posner & Rothbart, 1998). Whilst the DSM-IV and ICD-10 classifications rely on a definition of the construct of attention in terms of a single dimension, it is clear from neuropsychological research that several different components of attention exist (Barkley, 2001). The diagnostic manuals focus mainly on sustained attention and its associated resistance to distraction; however it is likely that other disorders exist for other components of attention. Barkley (2001) argues that 'all inattention is not ADHD, and that ADHD is not simply (or even) impaired attention'. Indeed, when four different types of attention deficits (sustained, selective, orienting and executive attention) were examined within the same sample, it was found that different children with ADHD revealed diverse combinations of deficits, suggesting a heterogeneity of attention deficits within the ADHD population (Tsal, Shalev, & Mevorach, 2005). Whilst more classifications are likely to exist, three major sub-functions are usually distinguished, namely sustained attention or vigilance, selective attention and executive attention. These three classifications will now be discussed briefly.

1.3.1.2.3.1 Sustained attention. Sustained attention refers to control of attention over time, in the sense of 'energy' or 'cognitive resources'. Sustained attention is viewed as a continuous process during which resources are depleted by having to maintain focused attention over time (Tannock, 2003). In other words, it is the ability to stay alert during a task and this has been found to be the most prevalent deficit of children with ADHD compared

with executive, selective and orienting attention deficits (Tsal et al., 2005). The right fronto-parietal network has repeatedly been found to mediate sustained attention processes. These processes are commonly measured using the Continuous Performance Test (CPT), mentioned in the previous section (section 1.3.2). A meta-analysis of 47 studies using a CPT (Huang-Pollock et al., 2012) showed that children with ADHD are more likely to make errors of commission and omission as well as having increased reaction times (RT) and more variation in RT. This slower RT could be explained by a slower rate at which these children are able to accumulate or uptake information from a stimulus in order to make a choice (slower drift rate). At the same time, large numbers of fast RTs were found in ADHD, which might reflect a failure to consider speed-accuracy trade-offs. Children with ADHD also had more difficulties detecting targets (i.e. decreased perceptual sensitivity) and the analysis also reported performance over time effects with error rates of children with ADHD increasing to a greater extent over time compared with controls (Huang-Pollock et al., 2012). This means that children diagnosed with ADHD are less capable of maintaining a vigilant state than controls.

1.3.1.2.3.2 Selective attention. Selective attention refers to the ability to attend to relevant stimuli and ignore irrelevant stimuli (Tannock, 2003). This type of attention can also be referred to as orienting attention, i.e. the selection of information from sensory input, and this type of attention is located primarily in the superior parietal, temporal parietal junction, frontal eye fields and superior colliculus (Posner, 2008). With age there appears to be an improvement in the ability to resist distraction, since the presence of irrelevant distracting information has a disproportionate effect on younger children. It seems that as cognitive abilities develop as children get older, the filtering mechanism might work better, but their knowledge and understanding about what is likely to be relevant in a given situation might also have improved (Taylor, 1998). The flanker test is often used as a measure of selective

attention. For this task participants are required to respond to one of two possible targets appearing at the centre, while ignoring two flanking distracters that are either congruent or incongruent to the target (Tsal et al., 2005). Children with ADHD make more errors to incongruent stimuli during this task than control children (Jonkman et al., 1999). Another task for which selective attention is required is a feature and conjunction search task. A target needs to be detected on the basis of either one (feature) or two (conjunction) dimensions. Children with attention difficulties are found to struggle mostly when searching for a conjunctive target in a high density background display, suggesting an inability to restrict visual attention in order to process relevant information and ignore distracting information (Shalev & Tsal, 2003).

1.3.1.2.3.3 Executive attention. Executive attention refers to control of cognitive processes in general, rather than biasing visual-spatial processing toward the selection of certain stimuli (this is also referred to as central executive, supervisory attention and effortful control) (Tannock, 2003). This type of attention accounts for how we allocate attention, regulate effort and concentration and plan for complex sequential activities (Ruff & Rothbart, 1996). In other words, executive attention is responsible for the control and organisation of behaviour as well as regulating thoughts and behaviour. This occurs both at the conscious and the subconscious level. It involves processes that can either facilitate action and thus counteracting inhibitory mechanisms that are at work or processes that can inhibit action in the face of facilitatory processes (Ruff & Rothbart, 1996). It can therefore also be defined as the mechanisms involved in resolving conflict among thoughts, feelings and responses (Posner, 2008). The concept is closely related to 'executive functions' (see section 1.3.1.3) and deficits in these functions are argued to affect self-regulatory capabilities, which are often found to be impaired in ADHD.

Some of the self-regulatory capabilities that are affected by deficits in executive attention are working memory, planning and inhibitory control. These functions are located primarily in the prefrontal cortex, the anterior cingulate, the lateral ventral and the basal ganglia (Posner, 2008). Deficit in inhibitory control are strongly related to impulsive behaviour and tasks such the stop signal task and the go-no-go task were therefore described in section 1.3.1.2.2. Another aspect of behavioural inhibition however, called interference control is argued to protect the decision making process from interference of external stimuli and often measured using the Stroop Task (Stroop, 1935). During the Stroop task participants are required to either read colour words in black, name the colour of variously coloured squares or name the colours of incongruent colour words as fast as possible. In this last task, the automatic word reading response can interfere with the naming of the colour of the words and interference scores can be calculated using various methods. An initial meta-analysis (van Mourik, Oosterlaan, & Sergeant, 2005), using Golden's interference score, found lower word reading and colour naming scores, but absent or very small differences in interference scores of children with ADHD compared to controls. However, the same study suggested that interpretation of the data is strongly affected by which method is used to calculate the interference score, since it found large differences in effect size when using 'Golden's method' compared to 'difference' interference scores. A more recent meta-analysis addressed this issue by calculating more reliable 'ratio' scores and found that 12 out of 18 studies showed that healthy controls are more resistant to interference compared with patients with ADHD, with effect sizes varying between -0.95 to 2.31 (Lansbergen, Kenemans, & van Engeland, 2007).

1.3.1.3 Psychological theories of ADHD. The previous sections have described the features of ADHD without any attempt at explaining the symptoms that are associated with the construct. This section will explore the underlying mechanisms of ADHD symptoms in

order to further establish the picture that is unfolding of 'what ADHD looks like'. However, it must be noted that some features of ADHD make the development of a good theory particularly challenging. Firstly, ADHD is a developmental disorder with a heterogeneous set of associated symptoms and differences in diagnostic practice make it difficult to interpret and generalise from research findings. Secondly, the various subtypes as well as the common presence of comorbid problems are underresearched and this makes it extremely difficult to identify possible underlying mechanisms. Given the complexity of the disrupted behaviours found in ADHD, it is not surprising that the various pathways leading up to this disruption are also likely to be complex (Pennington, 2002). A good psychological theory of ADHD should be able to account for the psychological and physiological mechanisms that underlie the disorder, whilst not ignoring the developmental processes that enable the establishment of these mechanisms.

Until recently, theories of ADHD were divided between those that viewed ADHD as the consequence of some kind of psychological dysfunction or deficit [i.e. theories of inhibitory deficits (Logan, 1981; Gray, 1987; Quay, 1997; Barkley, 1997) and/or the cognitive energetic model (Sergeant, Oosterlaan, & van der Meere, 1999)]; and those that viewed ADHD in a more functional manner, e.g. as the result of atypical motivational processes that are influenced over time by environmental and biological factors [i.e. the dynamic developmental theory (Sagvolden, Aase, Johansen, & Russell, 2005) and the delay aversion hypothesis (Sonuga-Barke, 1994)]. For a more detailed description of these theories, see Appendix 1. These theories have all tried to explain the origins of ADHD in terms of a single underlying dysfunction. However, in most cases, research studies have found group deficits with modest effect sizes and a substantial overlap between ADHD and non-ADHD samples with some ADHD children performing in the normal range (Nigg et al., 2005). It has been noted that to a certain extent these theories are complementary rather than contradictory.

Since diagnoses are made based on behavioural symptoms rather than underlying dysfunctions, it is likely that no one-to-one match between clinical and neuro-bio-psychological characteristics of ADHD can be found (Sonuga-Barke, 2003). Instead it is suggested that multiple causal pathways that are mediated by differing processes might underlie the same disorder. Multiple pathway models consider ADHD to be an umbrella construct with clinical value, which incorporates multiple potentially dissociable, but overlapping cognitive profiles (Castellanos et al., 2006).

1.3.1.3.1 The dual pathway model. Sonuga-Barke (2002) has proposed a *dual pathway model* of ADHD that attempts to integrate several theories. He suggests that there are two possible routes between biology and ADHD behaviour, namely via a pathway that describes ADHD as executive dysfunction and/or a pathway that describes the disorder as a delay averse motivational style. These two seemingly opposing models are reconciled in the dual pathway model, which explains both theoretical accounts in terms of the relationships between *neuro-biological*, *psychological* and *symptomatic* levels of analysis (Sonuga-Barke, 2003), whilst allowing for developmental interaction between cognitive and motivational characteristics where symptoms may have an aggregating effect on each other.

The 'executive dysfunction' pathway is caused primarily by inhibitory deficits and dysregulation of cognition, action and cognitive-energetic state. Theories included in this part of the model are Sergeant's cognitive-energetic model and Barkley's hybrid model of executive functions, since both theories characterise ADHD as an executive function disorder. These executive dysfunctions lead to a failure to engage with the environment appropriately (i.e. ADHD). The motivational 'delay aversion' pathway suggests that a biologically mediated preference for immediate reward leads to a psychological dislike of delay, which is moderated by cultural factors, such as negative parental responses that further deepen the association between delay and negative consequences.

Sonuga-Barke (2003) proposes that whilst the two pathways are seemingly distinct, a neurobiological account that explains the interplay between cortical and sub-cortical brain regions might be able to provide a bridge between the two models. Two brain circuits that connect the cortex with the basal ganglia and thalamus and in this way help regulate psychological processes necessary for action, thought and emotion are of particular interest. A dorsal executive circuit connects the prefrontal cortex via a dorsal striatal route with the subcortical regions and is involved in the executive control of thought and action, whilst a ventral striatal circuit, connecting frontal regions via the ventral striatum with subcortical regions and also the amygdala is implicated in the maintenance of reward orientated action. Dopamine is argued to be involved in ADHD and plays a key neuro-modulating role in both of these circuits. Sonuga-Barke (2003) thus suggest that an executive circuit, modulated by meso-cortical and nigro-striatal dopamine and an reward circuit, modulated by meso-limbic dopamine, make up the neuro-biological bases for psychological processes that lead to executive dysfunction and delay aversion respectively, therefore increasing the plausibility of the dual pathway model.

There is some further evidence to support the dual pathway account of ADHD. When executive dysfunction (stop signal task) and delay aversion (choice delay task) were examined within the same study, it was found that stop signal reaction time and choices of small immediate rather than larger delayed rewards were not associated with each other, however ADHD group membership was related to performance on either task (Solanto et al., 2001). The combination of the two tasks allowed accurate classification of 90% of the ADHD children, which suggests that the executive dysfunction pathway and the delay aversion pathway can be dissociated from each other, but that they are both associated with the ADHD outcome. A second study of preschool children with ADHD also demonstrated independent associations between ADHD and a composite of executive functions (containing measures of

working memory, planning, set-shifting and impulse control) on the one hand and ADHD and delay sensitivity on the other hand (Sonuga-Barke, Dalen, & Remington, 2003). There is also evidence to suggest that subtypes are associated with different pathways, for example inattention is associated with deficits in executive functioning, working memory and academic achievement, whilst hyperactivity/impulsivity is more closely related to dysfunctioning reward mechanisms (Coghill, Nigg, Rothenbergen, Sonuga-Barke, & Tannock, 2005).

Finally, the addition of a third pathway to the model was suggested recently (Sonuga-Barke et al., 2010). Children with ADHD are found to perform more poorly on timing tasks and functional magnetic resonance imaging (MRI) has revealed alterations in the temporal processing circuits in ADHD (Rubia, Halari, Christakou, & Taylor, 2009). Temporal processing deficits further share some neural components, such as the basal ganglia, with executive dysfunction and delay aversion. In order to test this new model, nine tasks were completed by ADHD probands, their siblings and a comparison group[1]. A principal components analysis on the data revealed four factors, representing inhibitory deficits, temporal processing deficits, the negative effect of imposed delay (delay negative) and a preference for the large delayed reward (delay positive) respectively. On all four components children with ADHD performed more poorly than siblings and comparison subjects. Within the group of ADHD children, over 70 percent showed only one deficit and overlap between deficits was not greater than that expected by chance. This suggests that different subgroups of children are affected by only one domain and that the three domains can be separated. In addition, some familial effects were discovered with siblings scoring more poorly than comparison subjects on temporal processing and delay task. Furthermore siblings of probands

[1] Executive Dysfunction was measured using the Stop Signal, Go/No-Go and a Stroop-like interference task, Delay Aversion tasks included the Maudsley Index of Delay Aversion, the Delayed Frustration Task and a Delayed Reaction Time task, and Temporal Processing deficits were measured using a Time Discrimination, Tapping and Time-anticipation task.

with impairments in inhibition and timing were found to show impairments in the same domain with no other deficits, suggesting a familial basis might underlie inhibitory and timing deficits, but evidence is weaker for delay aversion (Sonuga-Barke et al., 2010).

1.3.1.3.2 'Hot' versus 'cool' executive functions. An alternative multiple pathway account of ADHD that distinguishes between 'hot' and 'cool' executive functions has been proposed by Castellanos et al. (2006). It is fairly similar to Sonuga-Barke's model in that it contains an 'executive/cognitive' pathway and a motivational/affective pathway. Purely cognitive aspects of executive functioning located mainly in the dorsolateral prefrontal cortex, which are used during abstract, decontextualised problems, can be considered 'cool'. The more affective aspects of executive functioning located mainly in the orbital and medial prefrontal cortex, which are used during motivational and reward related processing, can be characterised as 'hot'. This model suggests that inattention symptoms are related to deficits in 'cool' executive functions, whilst hyperactivity/impulsivity symptoms are associated with deficits in 'hot' executive functions. It is suggested that some children with ADHD exhibit deficits in primarily 'hot' executive functions (hyperactive/impulsive subtype), some present with 'cool' deficits and others might manifest both types of deficits (Castellanos et al., 2006).

1.3.1.3.3 Distinct developmental pathways based upon temperamental traits. Nigg, Goldsmith and Sachek (2004) propose that several developmental pathways can be distinguished based upon two temperamental traits, which they define as effortful control (regulation) and reactivity (negative approach/anger vs. positive approach/exuberance). Their proposed model attempts to account for the heterogeneity within ADHD samples as well as common comorbidities. Problems in effortful control early in life are argued to lead to ADHD without comorbidity (particularly the inattention-disorganisation dimension). Positive approach tendencies form a second pathway towards ADHD, which is characterised by reward dysfunctions. Negative approach tendencies (anger proneness) are linked to

externalising problems and conduct problems, but ADHD might develop as a secondary problem in this subgroup of children. Other types of reactivity (extreme low anxiety versus fearful, withdrawing) are associated with an extremely antisocial subtype with comorbid ADHD versus a subtype characterised by anxious impulsivity. These pathways need to be further developed and longitudinal research is needed to further examine possible temperamental precursors and their relation with the development of ADHD.

1.3.1.3.4 Implications. The theoretical models of ADHD suggest that several mechanisms (i.e executive dysfunction, inhibitory deficits and/or delay aversion) might play an underlying role in the disorder. These underlying mechanisms might have their roots in early childhood and in fact, important developmental tasks of preschoolers involve learning to regulate behaviour, control impulses and attend in response to situational demands (von Stauffenberg & Campbell, 2007). The first five years of life are crucial for the development of the 'executive control network', with the most rapid changes occurring in prefrontal structures and their connectivity during this period (Rothbart & Posner, 2001). Two normative developmental periods are identified with simple skills developing in the first three years (i.e. holding a representation in mind; using a rule to inhibit a motor response) and most children mastering simple delay tasks between 22 and 33 months of age (Garon, Bryson, & Smith, 2008). During a second developmental period, characterised by developmental spurts occurring between three and five years, more complex executive skills emerge that require the integration of the simpler skills (for example, interference control) and an increased amount of shared variance between the different components of executive functions is found in this period (Garon et al., 2008). Early indicators of poor behavioural inhibition and inattention could therefore be studied as possible behavioural measures of ADHD symptoms from around 33 months onwards. For example, a study of 156 children between 3 and 5.5 years of age found that their scores on various tasks were represented best by two factors

(executive dysfunction and delay aversion respectively) and that both factors were significantly associated with concurrent ADHD symptoms (Sonuga-Barke et al., 2003). In order to validate the informant reports of ADHD symptoms, this study will also explore some cognitive measures, designed to assess levels of 'behavioural regulation' and 'cognitive flexibility' in toddlers. These measures are likely to be related to ADHD symptoms, and will function as a behavioural outcome measure, i.e. an indicator of ADHD symptoms in toddlers. Similarly, in middle childhood, several executive functioning tasks will be used as a behavioural outcome measure.

1.3.1.4 Conclusion. It is hoped that the reader will have gained a clear idea of what ADHD is and how researchers have attempted to explain its characteristics. Is has become clear that the diagnostic criteria used to define ADHD have had a huge impact on the way in which the disorder is researched. The literature further indicated that various mechanisms might play a role and that many neural networks might be involved in ADHD. It has become clear that single underlying factors are not sufficient to account for all cases of ADHD. Given the considerable heterogeneity within samples of ADHD subjects, it is more realistic to propose that several pathways to the disorder exist.

This section has also helped to define the outcome further. In line with the literature, not only informant-reports of ADHD symptoms in toddlerhood and middle childhood will be explored, but behavioural measures of underlying mechanisms will also be explored as indicators of the disorder. Figure 1.2 shows an overview of the outcome as measured in this thesis. In toddlerhood it is expected that behavioural regulation and cognitive flexibility, measured using several cognitive task will be related to ADHD symptoms, and in middle childhood a test-battery of executive function tasks will be used in addition to informant-reports. Finally, it is important to keep in mind that the precursors that will be explored in this thesis need to resemble the outcome, i.e. the diagnostic criteria, the core features of ADHD

and the underlying mechanisms. Adherence to the first criterion of 'resemblance' between the precursor and later developmental outcome will therefore be based upon the picture painted in this section and upon consideration of the developmental periods when different ADHD-relevant phenomena are emerging. For example, activity levels can be ascertained in infancy; executive control may not be evident until the toddler years and may therefore be best seen as a feature of ADHD rather than a precursor to it.

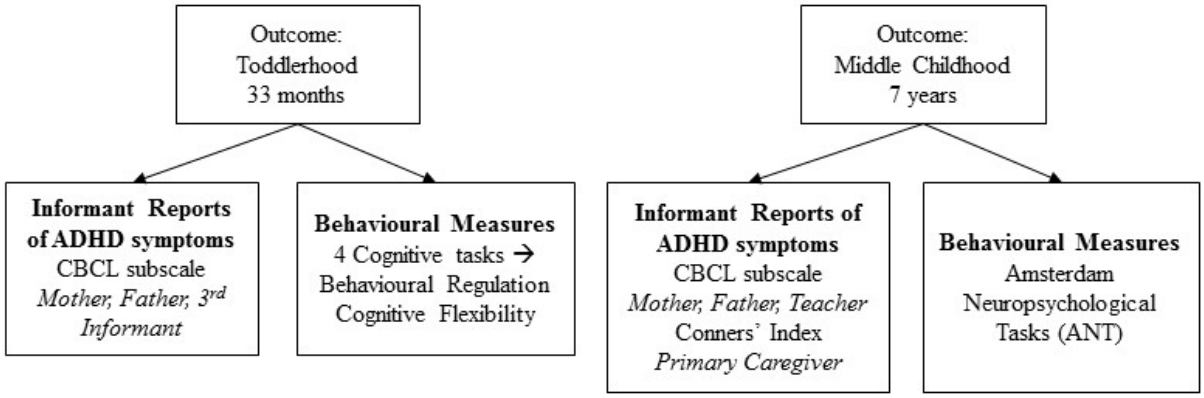


Figure 1.2 Outcome variables used in this thesis.

1.4 Risk Factors for ADHD

Now that the reader has gained understanding of what ADHD in its mature form looks like, the literature on risk factors for childhood ADHD will be considered. In order to assess whether precursor meet the second criterion, which requires that precursors are associated with risk factors in the same way as the later outcome, it is important to establish which risk factors have consistently been associated with ADHD symptoms. Only those risk factors that are considered to be well-established in the literature will be used in this thesis to test the second criterion of a precursor.

The aetiology of ADHD is complex with several genetic and non-genetic factors independently contributing to the development of the disorder (Faraone et al., 1995; Nikolas

et al., 2011; Thapar, Cooper, Eyre, & Langley, 2013). Two areas of risk have been identified in the literature most consistently. Firstly, it is suggested that genetic vulnerability plays a role in the aetiology of ADHD, since relatives of children with ADHD are at an increased risk for the disorder (Faraone et al., 1995). Familial studies indicate that ADHD runs in families; however, it is not clear from family studies alone whether this risk is due to genetic or environmental factors.

A second area of risk that has been suggested to place children at risk for developing ADHD symptoms is that of intrauterine and perinatal circumstances. It is known that complications during this period can have a detrimental effect on brain development. In fact, brain damage, resulting from brain infections, trauma or other injuries or complications during pregnancy or delivery, has long been proposed to be the main cause of ADHD (Barkley, 2006). However, the literature on obstetric complications is characterised by inconsistent findings and whilst associations with ADHD have repeatedly been found, it is clear that birth and pregnancy complications do not constitute a single cause of ADHD (Chandler, 2010). The aim of this section is to review the evidence up to date with regards to familial and perinatal risk factors. This will allow us to determine which risk factors should be associated with our precursor candidates.

1.4.1 Familial Risk Factors of ADHD

1.4.1.1 Genetic evidence. Familial studies of ADHD are concerned with patterns of inheritance and are aimed at identifying whether ADHD is more common in biological relatives of patients than in relatives of unaffected participants (Chandler, 2010). The literature on ADHD has repeatedly documented a higher prevalence of ADHD as well as other psychological disorders, including conduct, oppositional defiant, anxiety and affective disorders in the parents and other relatives of children with ADHD (Tannock, 1998). Twin studies have compared the concordance rate of monozygotic (MZ) twins (who share 100

percent of their genes) with that of dizygotic (DZ) twins (who share on average 50 percent of their genes). It has repeatedly been found that if one twin has been affected by ADHD, the other twin is more likely to also display ADHD if they are MZ twins, compared with DZ twins (Eaves et al., 1997; Goodman & Stevenson, 1989; Hay et al., 2007; Kan et al., 2013; Kuntsi et al., 2005; Larsson, Lichtenstein, & Larsson, 2006; Larsson et al., 2013; Polderman et al., 2007; Rhee, Waldman, Hay, & Levy, 1999; Rietveld et al., 2004) and a review of 21 twin studies concluded that there is a high genetic component to ADHD (Bennett, Levy, & Hay, 2007).

On average twin studies provide heritability estimates around .80 (range .50 to .98) (Tannock, 1998), which tells us the variance of a characteristic in a population that is accounted for by genetic influence (Chandler, 2010). Despite higher prevalence rates of boys, there do not appear to be gender differences in terms of heritability estimates (Rietveld et al., 2004; Kan et al., 2013). More specifically, the studies suggest that the liability for ADHD is best explained by additive rather than non-additive genetic influences, meaning that the liability is influenced by multiple alleles from different loci that 'add up'. Furthermore, the twin studies consistently find that the remaining variance is accounted for by unique environmental effects that are specific to an individual, not shared across siblings, and that shared environmental effects are negligible (Nikolas & Burt, 2010). Despite common criticisms that the design of twin studies leads to underestimates of environmental influences (Burt, 2010), it is clear that genetics contribute to the emergence of ADHD symptoms. These genetic influences likely correlate (i.e. gene-environment correlation (see Knafo & Jaffee, 2013) and interact with environmental factors (e.g. Li & Lee, 2012).

Furthermore, longitudinal twin studies have shown that stability of ADHD over time (also known as ADHD persistence) is influenced by genetic factors and this stability is similar for boys and girls (Kan et al., 2013; Larsson, Larsson, & Lichtenstein, 2004; Rietveld

et al., 2004; Thapar, Langley, Owen, & O'Donovan, 2007). Genetic influences therefore appear to be more important in cases of persistent ADHD and less so in cases that remit before adolescence (Larsson et al., 2006). A recent longitudinal twin study however found that whilst heritability of ADHD symptoms is relatively stable during childhood, it decreases from childhood to adulthood, with an increase in environmental variance (Kan et al., 2013). Subtype-specific genetic effects over time on the primarily hyperactivity-impulsive type and the primarily inattentive type of ADHD have also been observed (Larsson et al., 2006). A meta-analysis of both twin and adoption studies concluded that heritability estimates were high for both the inattentive and the hyperactive-impulsive type (71% and 73% respectively) (Nikolas & Burt, 2010). Others have found evidence that cognitive impairment can also be explained by familial influences (Holmes et al., 2002; Kuntsi et al., 2006; Kuntsi et al., 2010; Kuntsi et al., 2014). Another twin study measured hyperactivity objectively by using actigraph data and found a much lower heritability estimate (36%) and a larger proportion of the variance was explained by shared (39%) and child specific environmental effects (25%) (Wood, Saudino, Rogers, Asherson, & Kuntsi, 2007).

In support of the results from twin studies, adoption studies have shown that ADHD was more prevalent in biological first and second degree relatives of hyperactive (non-adopted) children compared with the adoptive relatives of adopted children with ADHD (Alberts-Corush, Firestone, & Goodman, 1986; Cantwell, 1975; Cunningham, Cadoret, Loftus, & Edwards, 1975; Morrison & Stewart, 1973; Sprich et al., 2000). A further adoption study, which compared 332 adopted sibling pairs, found that biologically related siblings scored more similarly on the CBCL attention problems scale than unrelated siblings (van den Oord, Boomsma, & Verhulst, 1994). It is argued that since adoptive children share their genes with their biological parents/siblings only, any similarities between the child and the

biological parent/sibling can be attributed to genetic effects. Whilst there are limitations to both twin and adoption studies, these studies do suggest that ADHD runs in families.

Further support for the influence of genetics on ADHD comes from molecular genetic studies that have linked ADHD to various polymorphisms. Whole-genome linkage studies of ADHD have reported some significant linkage; however these results are at a very early stage and need further investigation and replication (Banaschewski, Becker, Scherag, Franke, & Coghill, 2010; Stergiakouli & Thapar, 2010; Thapar et al., 2007). Similarly, genome-wide association studies (GWAS) of ADHD have only recently started to emerge, and reports of associations with several polymorphisms need further replication (Poelmans, Pauls, Buitelaar, & Franke, 2011; Banaschewski et al., 2010; Lesch et al., 2008; Neale et al., 2008; Stergiakouli & Thapar, 2010). Functional candidate gene studies have tried to clarify how a genetic vulnerability contributes to the development of ADHD. Genes involved in dopaminergic transmission have received special attention, and the 7-repeat allele of the dopamine receptor D4 gene (DRD4; Faraone et al., 1999; Faraone, Doyle, Mick, & Biederman, 2001; Faraone et al., 2005; Gizer, Ficks, & Waldman, 2009; Li, Sham, Owen, & He, 2006; Maher, Marazita, Ferrell, & Vanyukov, 2002), and the 10/10 dopamine transporter D1 gene (DAT1) are particularly associated with ADHD (Auerbach et al., 2010; Gizer et al., 2009). More tentative associations have been found between ADHD and the DRD1, DRD2, DRD3 and DRD5 gene (Banaschewski et al., 2010; Gizer et al., 2009; Lowe et al., 2004; Maher et al., 2002), serotonin (5-HTTLPR; Curran, Purcell, Craig, Asherson, & Sham, 2005; Gizer et al., 2009; Kent et al., 2002) and nor-adrenaline transporter genes (Thapar et al., 2007) and the MAO-A gene (Banaschewski et al., 2010). Finally, the val-allele of the Catechol-O-Methyl Transferase (COMT) gene has been associated with increased dopamine clearance in the prefrontal cortex and worse neurocognitive task performance (Diamond, Briand, Fossella, & Gehlbach, 2004; Meyer-Lindenberg, & Weinberger, 2005). Whilst no

direct association with ADHD has been found, the val/val genotype consistently has been associated with conduct disorder symptoms and antisocial behaviour in those with ADHD (Stergiakouli & Thapar, 2010). These results are interesting, given that many of the neuropsychological deficits associated with ADHD are argued to be the result of a dysfunctioning dopamine system.

It is likely that the presence of several genetic risk factors increases the risk of ADHD and interactions between several risk genes have been reported (Auerbach et al., 2010). However, the effect of each of these specific genes is likely to be very small and it is more realistic to argue that specific 'risk-genes' contribute to the development of ADHD through gene-environment correlation as well as gene-environment interactions rather than suggesting that any gene has a direct effect on ADHD.

1.4.1.2 Environmental risk associated with parental ADHD. It must be clarified that adult ADHD not only contributes to the development of ADHD in children through a genetic vulnerability, but could also create a less than optimal parenting environment, which is argued to influence the aetiology of ADHD. Their own symptoms make it more difficult to provide calm, consistent and clear parenting in structured settings, which has been found to be especially important for the needs of children with ADHD (Sonuga-Barke, Daley, & Thompson, 2002). Symptoms of ADHD in parents have been related to increased laxness, lower levels of involvement, monitoring and positive parenting and increased levels of inconsistent and permissive parenting (Chronis-Tuscano et al., 2008; Harvey, Danforth, McKee, Ulsazek, & Friedman, 2003; Murray & Johnston, 2006). Specifically, the discipline strategies of fathers with high levels of ADHD are found to be more over-reactive or authoritarian compared with fathers without ADHD symptoms (Arnold, O'Leary, & Edwards, 1997). Family and marital functioning has also been found to be affected by adult

ADHD, especially when mothers were affected (Minde et al., 2003; Agha, Zammit, Thapar, & Langley, 2013)

The influence of parental ADHD symptoms can be either negative or positive. Reactions to ADHD symptoms in children differ for all parents, but it has been found that parents with adult ADHD may be either unusually tolerant or unusually sensitive and reactive to these symptoms (Weiss, Hechtman, & Weiss, 2000). Moreover, particular parenting strengths associated with adult ADHD are enthusiasm, boundless energy and playfulness, whilst difficulties such as attention deficits and impulsive behaviour in parents are likely to influence parenting negatively (Weiss, Hechtman, & Weiss, 2000). Goodness of fit between mother and child might play a role here (Thomas & Chess, 1977). Child ADHD has been found to affect parenting negatively, and it was found that mothers who were low in ADHD themselves displayed less positive involved parenting, whilst mothers who scored high on ADHD were less affected by their child's ADHD symptoms and displayed more warmth and positivity (Psychogiou, Daley, Thompson, & Sonuga-Barke, 2008). In contrast, others have found an association between maternal ADHD and less positive parenting and more negative parenting of their children with ADHD (Chronis-Tuscano et al., 2008).

Parental 'adult' ADHD symptoms have also been associated with more severe ADHD and inattention symptoms and increased conduct problems in children, when compared to children whose parents had childhood-only ADHD or no ADHD (Agha et al., 2013). These findings were not replicated by Biederman, Faraone and Monuteaux (2002), who found that persistent and remitted ADHD in parents increased the risk for ADHD in children compared with no ADHD in parents, but found no difference in risk between children for persistent and remitted ADHD in parents (despite an association of persistent but not remitted ADHD with a disruptive family environment). Parental ADHD symptoms have also been shown to affect the effectiveness of parent training programmes for ADHD (Sonuga-Barke et al., 2002;

Harvey et al., 2003). Adult ADHD might therefore not only affect the aetiology of ADHD, but also impact on treatment and outcome later in life, especially when parents are involved in the delivery of interventions.

1.4.1.3 Conclusion. It can be concluded that the literature strongly supports a genetic contribution to ADHD. Despite some limitations of familial, twin and adoption studies, the evidence makes it clear that ADHD runs in families and that genetics play a strong role in its aetiology, although it must be noted that parental ADHD might also have an environmental effect on the development, outcome and treatment of ADHD. Some specific risk genes have been associated with ADHD, but the effects of these genes are very small and likely affect ADHD through interaction with environmental factors. Taken together, the literature suggests that in order to test our precursor behaviours on the second criterion, familial symptoms of ADHD can be considered as a well-established risk factor of ADHD (also see Figure 1.3). Despite the fact that the study design used in this thesis is not genetically informative, parental symptoms of ADHD can be considered as a 'familial' risk factor (regardless whether their effect is genetic, environmental or a combination of both).

1.4.2 Perinatal Risk Factors of ADHD

Intrauterine and perinatal circumstances have been of particular interest, given their links with early brain development. Damage to (pre)frontal areas produce similar symptoms as observed in children with ADHD and smaller cerebral volumes have been found in boys with ADHD (Castellanos et al., 2002; Mostofsky et al., 2002). Anatomic brain magnetic resonance imaging (MRI) furthermore revealed that MZ twins with ADHD had significantly smaller caudate volumes compared to their unaffected twin, which is consistent with a selective vulnerability of the striatum to adverse prenatal environmental factors (Castellanos et al., 2003). This study also demonstrates that familial effects alone cannot explain all cases

of ADHD. The higher prevalence of the disorder amongst boys is also in line with this hypothesis, since the male embryo is more vulnerable and the male foetus is therefore at greater risk of death or damage from obstetric problems prior to birth than the female (Kraemer, 2000). However, the literature on obstetric complications is characterised by inconsistent findings and it is hard to infer causal effects at this stage. However, evidence might be sufficient to define several areas of perinatal adversity as risk factors (i.e. a factor that raises the probability of pathology) of ADHD symptoms.

1.4.2.1 Exposure to toxins in utero. A number of environmental toxins, present during pregnancy, have been associated with symptoms of ADHD. One of the most consistent findings is prenatal exposure to maternal smoking (Barkley, 2006; Biederman et al., 2002; Galera et al., 2011; Linnet et al., 2003; Milberger, Biederman, Faraone, Chen & Jones, 1996; Milberger, Biederman, Faraone & Jones, 1998). However, maternal smoking is often associated with high-risk families (i.e. younger mothers, lower social class, higher rates of prenatal exposure to alcohol/drugs and parental history of ADHD and conduct problems). Findings from studies that investigate whether prenatal smoking represents a causal intrauterine effect are somewhat inconsistent. Whilst several studies have found small, but independent effects of smoking, after controlling for possible confounds, and suggest a dose-response-like association with symptoms of ADHD (Biederman, Monuteaux, Faraone, & Mick, 2008; Kotimaa et al., 2003; Linnet et al., 2003; Thapar et al., 2003), other findings suggest that this association may be explained by genetic or other confounding effects. Paternal smoking during pregnancy showed an association of a similar magnitude to maternal smoking (Langley, Heron, Davey-Smith, & Thapar, 2010) and the effect of prenatal exposure to smoking was found in genetically related mother-child pairs, but not in unrelated mother-child pairs conceived through artificial reproduction techniques (Thapar et al., 2009). A nationwide Swedish population study of 813,030 children used cousin and sibling data to

control for unmeasured familial confounding and concluded that whilst maternal smoking during pregnancy predicted ADHD in offspring at a population level, this effect was due to familial confounding (Skoglund, Chen, D'Onofrio, Lichtenstein, & Larsson, 2014). Nevertheless, since the literature consistently shows that smoking during pregnancy is associated with an increased probability of ADHD, it can safely be defined as a risk factor for ADHD symptoms.

Maternal alcohol consumption during pregnancy has further been associated with an increased risk of ADHD (Aronson, Hagberg, & Gillberg, 1997; Linnet et al., 2003; Mick, Biederman, Faraone, Sayer, & Kleinman, 2002); however, findings across studies are inconsistent. A systematic review of the literature noted that 4/9 studies supported the contribution of prenatal alcohol exposure; however none of these studies controlled for familial risk (Linnet et al., 2003). Indeed, when confounding variables were accounted for, it was found that a maternal familial risk of alcoholism (presence of two alcoholic sisters), but not prenatal exposure to alcohol was associated with ADHD (Hill, Lowers, Locke-Wellman, & Shen, 2000). A weakness of this study was however, that prenatal alcohol exposure occurred mostly in the high familial risk group, which makes it difficult to distinguish between genetic, environmental or interaction effects. In view of the inconsistent evidence, alcohol use during pregnancy will not be considered a risk factor in this thesis.

Another important toxic effect on the foetus might be caused by prenatal stress. The release of cortisol into the intrauterine environment is thought to affect neurodevelopment of the serotonergic system during late gestation (Rice et al., 2009). An alternative mechanism might be the reduction of uteroplacental blood flow, resulting from the increase in cortisol and catecholamines present during maternal stress or a combination of these mechanisms (de Weerth & Buitelaar, 2005). Maternal stress has previously been linked with several psychological problems (schizophrenia, social behaviour and depression), alterations in foetal

motor activity and heart rate patterns (van den Bergh et al., 2005) and several studies have suggested small, but significant associations with disturbances in attention and activity (Linnet et al., 2003; van den Bergh et al., 2005). Hyperactivity and inattention in 4- and 8-year-old boys was predicted by anxiety in late pregnancy (O'Conner et al., 2002; O'Connor et al., 2003). Others found that high levels of anxiety in the first half of pregnancy (12-22 wks), but not later in gestation, were associated with ADHD symptoms, externalizing problems and anxiety in 8-9 year old children (van den Bergh & Marcoen, 2004), with ADHD symptoms in 7 year olds (Rodriguez & Bohlin, 2005) and resulted in more impulsive reactions by adolescents in an encoding task and lower scores on two intelligence scales (van den Bergh et al., 2005). Stress in utero will therefore be considered as a perinatal risk factor in this thesis.

Finally, viral infections during pregnancy might play a role, since the season in which a child is born has been related to ADHD, with births in September being overrepresented in groups with ADHD (Mick, Biederman, & Faraone, 1996). Other prenatal toxins, which have been associated with ADHD are cocaine, pesticide, polychlorinated biphenyls (PCBs) and lead exposure (Lehn et al., 2007; Rauh et al., 2006; Sagiv et al., 2010; Schantz, Widholm, & Rice, 2003). These findings require further replications and in this thesis these toxins are therefore not considered to be well-established risk factors of ADHD.

1.4.2.2 Complications during pregnancy and delivery. Several other features of pregnancy have been (inconsistently) associated with an increased risk of ADHD; these are (pre-)eclampsia (Claycomb, Ryan, Miller, & Schnakenberg-Ott, 2004; Hartsough & Lambert, 1985), nausea towards the end of pregnancy (Martin, Wisenbaker, & Huttunen, 1999) and the mother's obesity and overweight prior to pregnancy (Rodriguez et al., 2008, Rodriguez, 2010). Mothers of children with ADHD were also found to be younger, when they delivered the child than control mothers; however, this might be the result of an interaction, since it is

argued that pregnancy complications are more likely to occur amongst young mothers (Barkley, 2006). These findings require further replication and cannot yet be defined as well-established.

Similarly, complications during delivery cannot be considered as well-established risk factors. The literature often remains inconclusive with some researchers finding an effect and others failing to find a link. Some studies did find significant associations between symptoms of ADHD and several complications, including the presence of delivery complications (Claycomb et al., 2004), a longer time between onset of labour and birth (Claycomb et al., 2004;), unusually short or long labour, foetal distress, forceps delivery and toxaemia or eclampsia (Hartsough & Lambert, 1985; Minde, Webb, & Sykes, 1968), emergency caesarean sections (Gurevitz et al., 2014), neonatal complications and early contractions (Amor et al., 2005). Moreover, a longitudinal study, which assessed the medical and neurological status of 5 perinatal groups of infants (full term, healthy preterm, medical preterm, neurological preterm and small for gestational age preterm) found that lower gestational age, lower birth weight, male gender, higher neonatal risk, abnormal medical and neurological status at 18 and 30 months and lower socioeconomic status were all related to high activity and poorer attention at 4 years of age (McGrath et al., 2005). Exactly how these factors might influence later behavioural problems is unknown and caution needs to be taken when interpreting these findings, since the fact that problems occur during labour might be the result of other (unknown) risk factors (Chandler, 2010). These risk factors will therefore not be considered any further in this thesis.

1.4.2.3 Gestational age and birth weight. Finally, prematurity (gestational age below 37 weeks; Bhutta, Cleves, Casey, Cradock, & Anand, 2002; Schothorst & van Engeland, 1996) and low birth weight (< 2500 grams) (Breslau et al., 1996; Galera et al., 2011; Hultman et al., 2007; Nichols & Chen, 1981; Sykes et al., 1997; Szatmari, Saigal,

Rosenbaum & Campbell, 1993; Willoughby et al., 2012) have been associated with ADHD. Birth weight appears to be one of the most consistent findings and was up to 3 times more common in children with ADHD than controls (Mick, Biederman, Prince, Fischer, & Faraone, 2002). However, birth weight might be affected by other risk factors, such as maternal smoking, alcohol use, ADHD and socio-economic status (SES). A recent comparison between MZ, DZ and unrelated discordant pairs however, demonstrated a negative relationship between birth weight and attention problems (other symptoms of ADHD were not assessed in this study), which was the same across these groups and consistent across preterm- and term-born children (Groen-Blokhuis, Middeldorp, van Beijsterveldt, & Boomsma, 2011). This suggests that the effect of birth weight cannot be attributed to prematurity, genetic factors and other maternal factors, and supports a causal effect instead. Exactly how birth weight would 'cause' attentional problems remains unclear; the authors argue that birth weight differences might reflect differential nourishment in utero, leading to impaired neurodevelopment (Groen-Blokhuis et al., 2011). This would also be in line with the programming hypothesis, which states that foetal adaptation to an unfavourable intrauterine environment permanently increases susceptibility to chronic diseases or disorders later in life (Barker, 1998, 2004; Linnet et al., 2003). Given the strong evidence, birth weight will be considered a risk factor of ADHD symptoms in this thesis.

1.4.2.4 Conclusion. It appears safe to conclude that more adversity experienced in infancy is related to symptoms of ADHD (Lehn et al., 2007) and that environmental risk factors, present during the vulnerable period of development prior to and around birth, can have a strong impact on children's behaviour. In this thesis, only well-established risk factors are considered. Whilst other factors might also have an impact on the development of ADHD symptoms, in order to test our precursor behaviours on the second criterion, only smoking

and stress during pregnancy as well as birth weight will be considered as perinatal risk factors (see Figure 1.3).

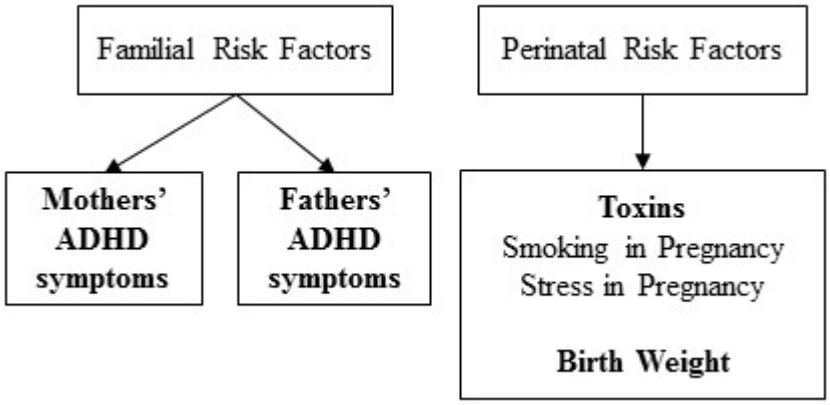


Figure 1.3 Risk factor variables used in this thesis.

1.5 Assessing Stability of Individual Differences over Time

The final criterion of a precursor requires stability of individual differences over time. Firstly, research that has looked at the stability of ADHD symptoms and behavioural measures of ADHD symptoms over time will be discussed, after which studies of earlier behaviours and their association with ADHD symptoms over time will be examined. Together this literature will provide us with a framework, which will allow us to apply the criteria of a precursor to the study of ADHD symptoms.

1.5.1 Stability of ADHD Symptoms from Early to Middle Childhood

It was shown in section 1.3.1.4 that ADHD can successfully be measured in preschool children and that it can be distinguished from normative behaviours in early childhood. Moreover, the longitudinal consistency of ADHD symptoms in preschool over time has been

established repeatedly. Children between 4 and 6 years of age who were diagnosed using DSM-IV criteria were nearly all found to still meet these criteria at follow-up three years later and experienced greater functional impairment than comparison children, which was not accounted for by confounding variables (Lahey et al., 2004). Similarly, a checklist of 18 DSM-IV based ADHD symptoms showed substantial stability across time at 3, 4 and 5 years of age (Willoughby et al., 2012). Furthermore, symptoms of ADHD measured at 54 months, first grade and third grade have been found to be moderately correlated and therefore relatively stable across time (von Stauffenberg & Campbell, 2007). Finally, a meta-analysis of preschool studies found that early disruptiveness (which included aggressive as well as ADHD symptoms) tends to be stable over time, with large effect sizes for both categorical and dimensional measures of preschool disruptive behaviour, and a large effect size was also found for the five studies that measured ADHD separately (Moreland & Dumas, 2008).

1.5.2 Stability of Executive Control from Toddlerhood to Middle Childhood

There is also evidence to suggest that toddler's performance on cognitive tasks is related not only concurrently to ADHD symptoms, but shows stability over time. This evidence will now be discussed.

Firstly, a study administered an age-appropriate CPT, Delay of Gratification Task (DGT) and Stroop Test at 54 months of age, and found that behavioural inhibition (CPT commissions and the DGT) and inattention (CPT omissions), but not the Stroop test, were modestly related to both concurrent and later symptoms of ADHD in first grade (6-7 years old), over and above the longitudinal stability in ADHD symptoms (von Stauffenberg & Campbell, 2007). In contrast, in third grade (8-9 years old) ADHD symptoms were predicted by the DGT, whilst CPT commissions were longitudinally predictive from 54 months to third grade (8-9 years old) in girls only (von Stauffenberg & Campbell, 2007). Moreover, lack of

inhibitory control, measured at 5 years of age with the go/no-go task, was found to predict later ADHD symptoms at 8 years, although more strongly for boys than girls, and this influence was independent from the contribution of concurrent executive functioning at 8 years (Berlin et al., 2003). Poor inhibition at age 5 in boys, but not girls was significantly related to poor executive functioning at age 8, specifically verbal and non-verbal working memory and the regulation of arousal, whilst executive functions in boys but not girls were also concurrently related to ADHD symptoms at age 8 (Berlin et al., 2003). The time that children were able to resist touching an appealing toy at 4 years of age furthermore was associated with an ADD diagnosis at 9 years of age (Marakovitz & Campbell, 1998). Furthermore, both interference control and prepotent response inhibition, but not working memory at 5 years of age, were associated with concurrent and 2-year longitudinal symptoms of ADHD (Brocki, Nyberg, Thorell, & Bohlin, 2007).

In the Dutch Generation R study several domains of executive functions at 4 years of age were significantly related to ADHD symptoms at 5 years of age; global executive composite, r = .53; inhibition r = .58, shifting r = .21; emotional control r = .36; working memory r = .49; planning/organisation r = .38 (Ghassabian et al., 2013). Finally, a meta-analysis of 25 studies explored the relationship of various basic deficits in the preschool period and concurrent and subsequent ADHD symptoms, as well as the strength of these relationships in relation to children's age (Pauli-Pott & Becker, 2011). A strong relation with inhibitory control/response inhibition was found (weighted mean effect size, r = .29), with three studies finding prediction to school-age ADHD symptoms and larger effects found in younger children. Delay aversion tasks were also strongly related (r = .38) to concurrent and later ADHD symptoms (2 longitudinal studies), with stronger relations found in younger children. Whilst the majority of studies looking at the interference control component of response inhibition did not find association with ADHD symptoms, the weighted mean effect

size was significant (r = .26) and larger effect sizes were found with an increase in age. Similarly, individual studies of working memory revealed non-significant associations with ADHD symptoms, but the weighted mean effect size was significant (r = .18). Finally, aspects of vigilance/arousal (measured using CPTs), including error rates and variability of reaction time were associated with ADHD symptoms (r = .27), and this effect was stronger in older samples. In line with the normative developmental processes described above, more basic deficits in inhibitory control and delay aversion in younger children were more strongly associated with ADHD symptoms than more complicated tasks involving interference control and vigilance (Pauli-Pott & Becker, 2011). However, most studies that have investigated early deficits in relation to ADHD used samples with rather broad age ranges and further research with less variability in age is needed to replicate findings and more accurately estimate age-specific associations with ADHD. It can be concluded that there is some evidence for longitudinal consistency of ADHD symptoms in preschool, as well as for cognitive correlates of ADHD symptoms.

1.5.3 Prediction from Precursor Behaviours in Infancy to Later ADHD Symptoms in Childhood

Whilst ADHD has become one of the most commonly studied childhood disorders, it is not well understood what early indicators might signal for the emergence the disorder, and what the early developmental course looks like. Fewer researchers have explored the time period prior to 3 years of age, and even fewer have tested whether behaviours observed in this period meet the criteria assessed within this thesis. This is the time period where precursors might be identified, since symptoms of ADHD are not fully established yet before toddlerhood. This section will discuss some examples of studies that, with some limitations, have attempted to identify behaviours that might be precursors to ADHD. This review of the

literature has led to the choice of potential precursors to be tested in this thesis, as seen in the next section.

Firstly, temperament traits can be identified very early in life, and some researchers have attempted to link these traits to the development of ADHD symptoms. There are many models of temperament, but most agree that temperament traits are constitutionally-based individual differences in reactivity and self-regulation, which are relatively consistent across situations and stable over time (Rothbart & Bates, 1998; Thomas & Chess, 1977). In one theoretical perspective, infants' temperament is captured by six dimensions, including fearful distress/inhibition, irritable distress, attention span and persistence, activity level, positive affect/approach and rhythmicity (Rothbart & Bates, 1998).

A research study of temperamental traits assessed during a home-visit before 8 weeks of age using the Neonatal Behavioural Assessments Scales found that state organisation difficulties (irritability, state lability and self-quieting ability) differentiated children at familial risk for ADHD and a comparison group significantly, whilst activity levels were marginally higher in the at-risk group (Auerbach et al., 2005). This study also found that at-risk infants showed significantly more neurodevelopmental immaturity than comparison infants. However, stability over time of these difficulties was not assessed. Moreover, specificity to symptoms of ADHD is not examined. It is likely that a 'difficult' temperament is also predictive of conduct disorder. In this thesis applying the 'resemblance' criterion will help to avoid identifying risk factors that might be relevant to other disorders as well, rather than precursor behaviours that are specific to ADHD symptoms.

This limitation should also be kept in mind when considering other studies that have linked a 'difficult' temperament to symptoms of ADHD later in life. A 'difficult' temperament, as evaluated at 5 months using parent questionnaire, predicted high trajectories of ADHD symptoms as measured over time from age 1½ to 8 (Galera et al., 2011). Similarly,

a retrospective study, which used detailed clinical records from the Israeli well-baby-care infrastructure, found that compared to controls, children who later developed ADHD were more likely to show a 'difficult' (defined as restless, irritable, easily frustrated and nervous, with difficulties postponing immediate satisfaction) temperament as reported by parents at 9 and 18 months of age with 62% and 47% of children with ADHD characterised as 'easy' vs. 90% and 81% of those in the control group (Gurevitz, Geva, Varon, & Leitner, 2014). This study also found a significant reduction in head growth rate from birth to 18 months, as well as a mild delay in motor, speech and language development at 9 months and 18 months in the ADHD group, but not in the comparison group (Gurevitz et al., 2014). Similarly, a German study of 319 children (Becker, Holtmann, Laucht, & Schmidt, 2004) found that children with multiple regulatory problems[1] at 3 months of age presented significantly more hyperkinetic problems between the ages of 2 to 11 years than children without these problems. A recent re-analysis of this data suggests a moderation effect of the DRD4 genotype (collected at age 15), since the relationship between regulatory problems and later ADHD symptoms was only found in children with the DRD4-7 risk (Becker et al., 2010). It is clear, that whilst these studies have examined whether these behaviours predict ADHD symptoms, they have not systematically applied other criteria. Whilst these findings are interesting, they should not be taken as evidence that a difficult temperament or regulatory difficulties qualify as precursors to ADHD symptoms.

A further longitudinal study (Olson et al., 2002) examining the relationship between precursors in infancy and toddlerhood and later impulsive and inattentive behaviour used laboratory tasks at ages 6 and 8, which reflected three main dimensions of self-regulatory

[1] Three regulatory problem factors were specified (based on temperamental and behavioural problems measured using interview and observational data): irritability, hypo-reactivity (slow-to-warm-up) and regulatory problems of somatic functioning (sleep, feeding and digestive problems). Isolated regulatory problems in infancy could be regarded as 'transitory' and were not related to any long-term outcomes (Becker et al., 2004).

competence in childhood: inhibitory control, behavioural control and disengagement[1]. Disengagement as indexed by unoccupied 'wandering' during a two-hour home visit at 24 months of age predicted lower inhibitory control and more disengagement in childhood, but other temperamental traits at 6, 13 and 24 months of age were not related to later outcomes (Olson et al., 2002). Whilst it might be argued that disengagement might resemble symptoms of inattention, this study did not assess other criteria of a precursor, such as association with well-known risk factors, or associations with later ADHD symptoms. The conclusions that can be drawn from this study with regards to precursors are therefore limited.

1.5.4 Implications for identifying precursors to ADHD

These findings indicate that longitudinal evidence of association with ADHD symptoms exists for a variety of measures/behaviours prior to the emergence of ADHD symptoms in toddlerhood, including activity levels, a difficult temperament, negative affect, regulatory (state organisation) problems and disengagement. It must be noted that findings are not consistently replicated, since not all studies have found a relationship between infant temperament and later child impulsivity and inattention (Olson, Bates, Sandy, & Schilling, 2002). Moreover, these findings do not necessarily indicate that the third criterion of a precursor (stability of individual differences in precursor behaviours over time) is met for these behaviours. It needs to be noted that this criterion does not imply all longitudinal stability of individual differences across constructs, but should be applied within related constructs specified by the resemblance criterion. Moreover, none of the studies have systematically applied the other criteria of precursors, or tested the usefulness/added value of the precursor behaviour in predicting ADHD symptoms. The aim of this thesis is to

[1] Inhibitory control was defined as reflective and accurate performance during cognitive tasks; behavioural control reflected an ability to stay on task and away from 'forbidden' toys during an academic-like task and disengagement represented distractibility and tuning out behaviours.

demonstrate a method, which allows researchers to identify whether behaviours can be considered precursors to ADHD. This will be demonstrated by limiting the investigation to infants' activity levels.

The potential precursor that will be explored is high activity levels in infancy as measured by multiple informants' reports on the activity-subscale from the Infant Behaviour Questionnaire (IBQ; Rothbart, 1981) and directly measured by an Actigraph Actitrainer during a baseline, attention and restraint condition are explored as a potential precursor (see Figure 1.4). It was shown in section 1.3.1.2.1 that directly measured activity levels could distinguish children with ADHD and controls in most situations. Differences were more difficult to establish in unstructured free play and lunchroom activities (Porrino et al., 1983), during morning sessions or novel situations (Dane et al., 2000), whereas familiarity or tasks that require high degrees of self-regulation make hyperactivity more apparent (Barkley, 1998). Moreover, overactivity was shown to persist into adulthood, even when symptoms were no longer present (Halperin et al., 2008). These findings highlight the entrenched nature of overactivity and suggest that it might be observed prior to the emergence of the disorder. Thus activity levels meet the first criterion of resemblance to a key symptom of ADHD. Adherence to the criterion of 'resemblance' remains a subjective judgement, but at least some similarity of function can be established between activity levels in infancy and ADHD symptoms later in life, and therefore the criterion of 'resemblance' allows us to identify homotypic continuity over time.

Furthermore, by directly measuring activity levels during various tasks, it is possible to examine how early activity levels may relate to the other core symptom domains of inattention and impulsivity. It is of interest to see whether infants with higher than average activity levels suppress activity during the attention task and show even higher activity when their behaviour is physically restrained.

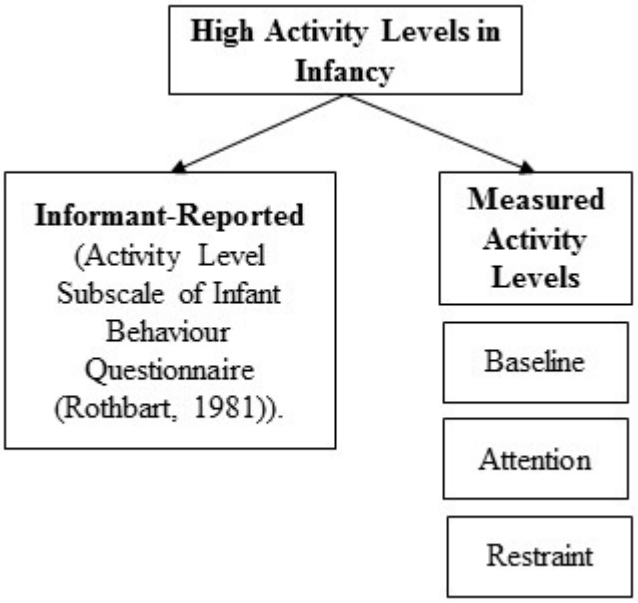


Figure 1.4 Precursor variables used in this thesis.

In order to assess whether these precursors meet the final criterion, which requires stability of individual differences over time, it is important to determine whether physical activity levels is indeed a stable characteristic of individual children over time. Stability of individual differences over time would be established if activity levels in infancy significantly predict measured activity levels in toddlerhood, as well as significantly predict ADHD symptoms as reported by informants in toddlerhood and middle childhood, and significantly predict correlates of ADHD symptoms (see Figure 1.5.l).

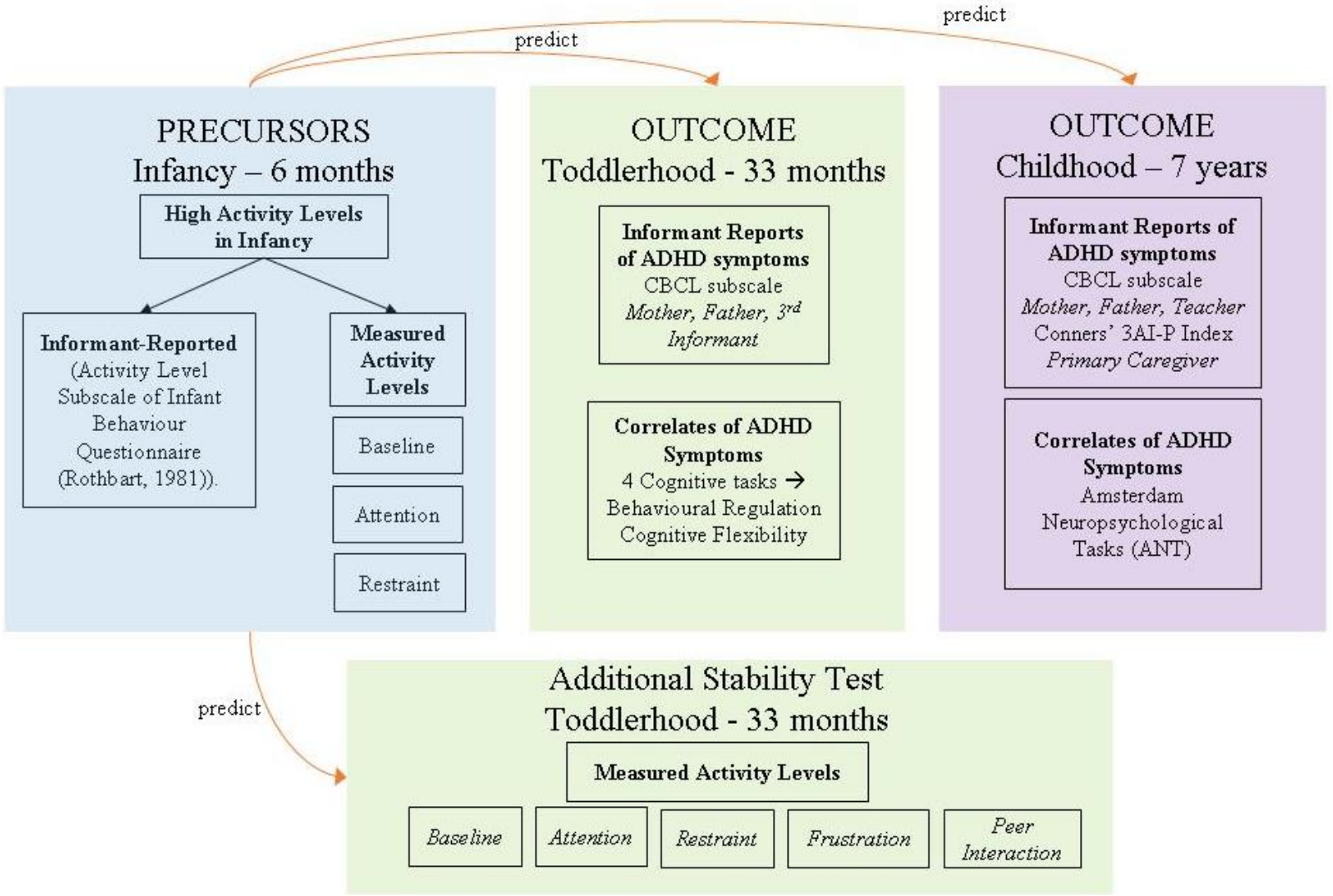


Figure 1.5 Assessment of stability of individual differences from the proposed predictor in infancy to relevant outcomes in toddlerhood and middle childhood over time.

1.6 Plan for the Thesis

1.6.1 Criterion 1: Identify a Potential Precursor to ADHD and its Measurement in the Context of the Longitudinal Design of the Cardiff Child Development Study (CCDS).

Before any hypotheses are tested, it is important to introduce the method used throughout this thesis. Chapter 2 will introduce the longitudinal design, the behaviour in infancy that is hypothesised to qualify as a precursor to ADHD symptoms on the grounds of resemblance to the later symptom of overactivity, and the ADHD-relevant outcome variables in toddlerhood and middle childhood (see also Figure 1.5).

1.6.2 Criterion 2: Assess Whether Activity Levels during Various Tasks in Infancy are Associated with Well-Established Risk Factors of ADHD Symptoms in Later Childhood.

To test whether the precursors adhere to the second criterion of similar association with well-established risk factors of the outcome, Chapter 3 and 4 will examine associations between precursor behaviours and various risk factors. The longitudinal dataset will be used to replicate previously reported associations of risk factors with the ADHD symptoms.

It was discussed above that familial risks associated with ADHD are well established (Faraone et al., 1995). Therefore, Chapter 3 will firstly establish whether mothers´ and fathers´ symptoms of ADHD predict the proposed precursor, higher activity levels in infancy. To replicate previous findings, associations between parental symptoms of ADHD and the ADHD-relevant outcome variables will be examined, whilst controlling for ODD symptoms and social risk factors. My hypothesis is that parental ADHD symptoms will be significantly associated with the outcome and with the precursor behaviours. This would be evidence that

the second criterion for determining an early behaviour as a precursor is met with regard to familial risk factors.

It has also been shown that intrauterine and perinatal risk factors such as exposure to smoking and stress in pregnancy, as well as low birth weight have repeatedly been associated with ADHD (Chandler, 2010). Therefore, a second test of the second criterion will be dealt with in Chapter 4. Firstly, it is hypothesised that smoking and stress in pregnancy as well as low birth weight is associated with the precursor behaviours. Again, to replicate earlier findings, similar associations are tested with the ADHD-relevant outcome variables. Similar associations would count as evidence that the second criterion for determining an early behaviour as a precursor is met with regard to perinatal risk factors.

1.6.3 Criterion 3: Test the Stability of Individual Differences in Activity Levels over Time and Prediction to other ADHD-Relevant Outcome Variables.

In order to identify continuity in individual differences over time, the three time periods of infancy, toddlerhood and middle childhood will be explored in Chapter 5. Firstly, it will be examined whether individual differences in high activity levels in infancy predict similarly high activity levels in toddlerhood. It must be noted that children´s motor skills develop rapidly over this time period and that toddlers will therefore be more active than infants. Nonetheless, it is hypothesised that individual differences should be consistent over time, in that very active infants are expected to develop into more active toddlers.

Next, it is hypothesised that individual differences in activity levels in infancy will predict informants´ reports of ADHD symptoms in toddlerhood and in middle childhood. Similarly, it is hypothesised that activity levels in infancy will predict children's later behavioural regulation and cognitive flexibility in toddlerhood and middle childhood. Associations between high activity levels in infancy and 1) toddlers' activity levels, 2)

informant-reported symptoms of ADHD in toddlerhood and middle childhood, and 3) measures of behavioural regulation and cognitive flexibility in toddlerhood and middle childhood would support the hypothesis that these behaviours represent early precursors of ADHD symptoms and correlates.

1.6.4 Follow-up Analyses.

1.6.4.1 Does the identification of precursor add predictive power? Test whether precursors in infancy predict later ADHD symptoms, beyond the contribution of socio-economic, familial and perinatal risk factors. In order to test whether the hypothesised precursors adds value, Chapter 5 will establish whether activity levels in infancy meet the criterion for a predictor and adds predictive power, beyond the effects of the risk factors that are associated with both the precursor and the later outcome (see Hay et al., 2014). It is hypothesised that when the precursors in infancy are added to a regression model in a second step, after risk factors are accounted for, additional variance will be explained by these precursors.

1.6.4.2 Are well-established risk factors associated with consolidation into disorder? Test associations with the continuity from precursor to outcome. In order to test whether the continuity from precursor to outcome is associated with well-established risk factors, standardised change scores will be calculated and correlated with risk factors in Chapter 5. It is hypothesised that risk factors are associated with a move towards higher standardised scores.

The findings that address each criterion will be discussed in Chapter 6, which will conclude whether high activity level in infancy really does meet the theoretical criteria to be a precursor to ADHD-relevant outcomes in toddlerhood and middle childhood.

CHAPTER 2.

Introducing the Cardiff Child Development Study.

2.1 Introduction

2.1.1 Aim of the Chapter

The main aim of this chapter is to introduce the longitudinal data from the Cardiff Child Development Study (CCDS) and the general methods used throughout this thesis. Firstly, the precursor behaviour set out in the previous chapter will be described more thoroughly. It was explained that activity levels in infancy were collected in two ways: through informants' (parents and a third informant) reports of infants' activity levels and by directly measuring activity levels using an Actigraph Actitrainer device during various tasks that relate to the other core symptom domains of inattention and impulsivity. In this chapter the method used to collect these data and descriptive statistics of the precursor variables will be examined.

Secondly, the outcome variables will be further introduced. As discussed in Chapter 1, the outcomes in this thesis will be explored in toddlerhood (at a mean of 33 months of age) and in middle childhood (at a mean of 7 years of age). At each time point both informant reports´ of children´s behaviour and directly measured behavioural tasks were included. In toddlerhood, measured Actigraph data are also included to establish whether individual differences in high activity levels in infancy predict similarly high activity levels in toddlerhood. However, it is important to note that these activity level variables in toddlerhood are not proposed to represent additional precursor behaviours. Instead, they are included to

test the stability of the construct of activity level over time. The method used to collect these data and their descriptive statistics will also be explored in this chapter.

The importance of controlling for co-occurring ODD symptoms was also discussed in the previous chapter. The aim of this thesis is to find precursors that are specific to ADHD symptoms, and ODD symptoms are therefore controlled, when relationships between precursors and outcomes are explored. In addition, social risk factors will be examined and controlled for where appropriate. This chapter will introduce these control variables and again descriptive statistics will be presented.

2.1.2 Hypotheses

Since the CCDS recruited a community sample, it is expected that precursor behaviours, as well as ADHD outcome variables, will be normally distributed. During infancy, it is hypothesised that informant-reported activity levels are significantly correlated with directly measured activity levels. It is of interest to see whether infants with higher than average activity levels as rated by the informants suppress activity during the attention task and show even higher activity when their behaviour is physically restrained. Activity levels are expected to correlate significantly across the various tasks.

In toddlerhood and middle childhood, it is hypothesised that informant-reported symptoms of ADHD are significantly correlated with concurrent measures of behavioural regulation and cognitive flexibility. More specifically, in line with the meta-analysis results from Pauli-Pott and Becker (2011), it is expected that simple measures of these executive function skills (which are first consolidated around 33 months) are more strongly related to informant-reported ADHD symptoms during toddlerhood, whereas in middle childhood more complex executive function skills (which develop a little later) are expected to be related more strongly to informant-reported ADHD symptoms.

2.2 Method

2.2.1 Participants

2.2.1.1 Recruitment. Throughout this thesis participants were drawn from the Cardiff Child Development Study (CCDS), which is a prospective longitudinal study of first time parents and their infants in Wales, funded by the Medical Research Council. Between the 1st November 2005 and the 31st July 2007, 332 first-time expectant women were recruited from prenatal clinics in hospitals and general practice clinics in two National Health Service (NHS) Trusts: Cardiff and Gwent, South Wales. Efforts were made to maximise the representativeness of the sample by including prenatal clinics for specialist medical problems and outreach services for vulnerably housed individuals.

Suitable families were identified with the help of clinic receptionists, and subsequently first time expectant women were approached by researchers at the hospital or clinics. A brief explanation about the nature of the CCDS was provided and a DVD was available to show those families who expressed an interest. A leaflet with further details was given to those families that expressed interest, and these families were asked to provide their contact details. During a follow-up telephone call, an administrator arranged an appointment with those families that decided to take part in the CCDS, which was scheduled for the third trimester of pregnancy.

2.2.1.2 Follow-up samples. Following initial recruitment, participants were followed up in five waves and a sixth follow-up wave is currently underway. For this thesis, available data from the first, second and fifth waves of the CCDS were used and data from a subsample were selected from the sixth wave (see Figure 2.1). In the first antenatal wave of the study 332 expectant mothers took part, whilst 288 fathers took part. Twelve families withdrew between pregnancy and the early infancy assessment, either because they found it too much

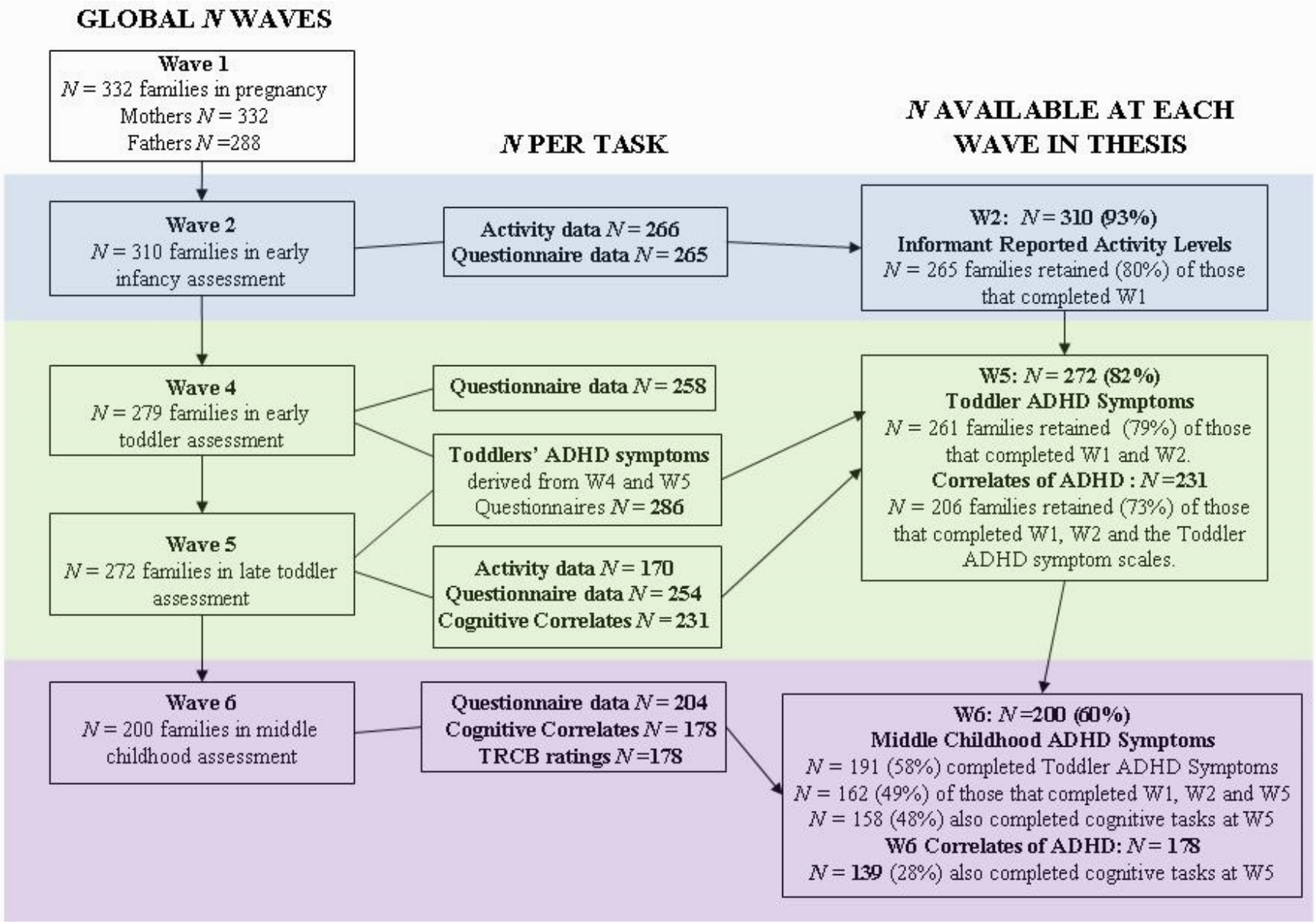


Figure 2.1 Number of participants included at each wave of data-collection wave (left hand side) and those for which data at each wave were available (right hand side).

of a time commitment or because they did not like their child being videotaped, resulting in a sample of 320 children (96%) that were seen at least once after birth. During the early infancy assessment (Wave 2: *M* age = 6.6 months post partum, *SD* = 0.9) 310 participants were followed up (93% of the original sample). At the early toddler assessment (Wave 4: *M* age = 20.6 months, *SD* = 2.3) 279 families (84% of the original sample) were followed up. Finally, the late toddler assessment assessment (Wave 5: *M* age = 33.6 months, *SD* = 2.5) was completed by 272 participants (82% of the original sample).

The CCDS is currently recruiting participants for a sixth wave of data collection (Wave 6: *M* age = 7.03 years, *SD* = 0.31). This chapter therefore focuses on a preliminary sample of 200 families[1] (60.2 % of the original sample) for which at least one questionnaire from a primary caregiver (191 mothers, 5 fathers, 3 grandmothers and a grandfather) was available at the time of writing. At this time additional questionnaires were completed for these families by 124 fathers and teachers completed 140 questionnaires. Tester Ratings of Child Behaviour (TRCB) were completed by child testers for 182 of the 200 families.

2.2.1.3 Demographic characteristics. No evidence of selective refusal was found since postal codes of families who asked to learn more about the study but did not decide to participate were found to represent the entire range of socio-economic categories. Families who did participate provided information on their demographic characteristics during the antenatal assessment. This included information on mothers' and fathers' age, ethnicity, marital status, social class and educational level. Mothers' and fathers' highest scoring occupation of the past or present was used to determine participants' social class according to the Standard Occupational Classification 2000 (SOC2000; Elias, McKnight, & Kinshott, 1999). The CCDS sample was found to be representative of the general population in all demographic factors, as shown by comparisons with the Millennium Cohort Study (K.

[1] This subsample was selected based on the available data, since data collection for the middle childhood assessment was ongoing at the time of writing.

Kiernan, personal communication, April 2009). The demographic characteristics of the initial sample, as well as the samples that completed the second and fifth wave are summarised in Table 2.1.

Table 2.1 Demographic characteristics of the full CCDS sample and the follow-up samples during the second and fifth wave of data collection.

Variable		**Wave 1** ***N*=332**	**Wave 2** ***N*=310**	**Wave 5** ***N*=272**	**Wave 6** ***N*=200**
Mother's age at birth	*Mean (range)*	28.15 (16-43)	28.52 (16-44)	28.82 (16-41)	28.64 (16-42)
Father's age at birth	*Mean (range)*	30.85 (16-57)	31.10 (16-57)	31.63 (16-57)	31.66 (16-57)
Child gender	*Female*	142 (42.8 %)	135 (43.5%)	120 (44.3%)	88(43.9%)
	Male	186 (56.0 %)	175 (56.5%)	151 (55.7%)	112(56.1%)
Languages at home	*Bilingual*	27 (8.1 %)	27 (8.7%)	23 (9.1%)	17 (8.5%)
	Not bilingual	304 (91.6 %)	282 (91.3%)	230 (90.6%)	183 (91.5%)
Mother's ethnicity	*British*	292 (88.0 %)	275 (88.7%)	242 (89.0%)	179 (89.5%)
	European	11 (3.3 %)	11 (3.5%)	9 (3.3%)	6 (3.0%)
	Asian	5 (1.5%)	5 (1.6%)	5 (1.8%)	3 (1.5%)
	South East Asian	1 (0.3 %)	1 (0.3%)	1 (0.4%)	1 (0.5%)
	Mixed Race	2 (0.6 %)	2 (0.6%)	2 (0.7%)	1 (0.5%)
	Other	4 (1.2 %)	4 (1.3%)	4 (1.5%)	2 (1.0%)
Mother's social class	*Middle Class*	169 (50.9 %)	164 (52.9%)	150 (55.1%)	113 (56.5%)
	Working Class	163 (49.1 %)	146 (47.1%)	122 (44.9%)	87 (43.5%)
Mother's highest educational qualification	*None*	17 (5.1%)	13 (4.2%)	12 (4.4%)	10 (5.0%)
	< 5 GCSE (A-C)*	55 (16.6%)	50 (16.1%)	39 (14.3%)	28 (14.0%)
	5 + GCSE (A-C)*	46 (13.9%)	39 (12.6%)	34 (12.5%)	28 (14.0%)
	A-levels	39(11.7%)	35 (11.3%)	29 (10.7%)	21 (10.5%)
	UG degree	93 (28.0%)	91 (29.4%)	83 (30.5%)	56 (28.0%)
	PG degree	82 (24.7%)	82 (26.5%)	75 (27.6%)	57 (28.5%)
Stable partnership	*Yes*	300 (90.4%)	283 (91.3%)	235 (92.5%)	184 (92.0%)
	No	32 (9.6%)	27 (88.7%)	19 (7.5%)	16 (8.0%)

2.2.2 Procedure

All procedures of the CCDS were approved by the Cardiff University School of Psychology Research Ethics Committee and the NHS Multi-Centre Research Ethics Committee. For this project five 'waves' of data collection were completed, whilst a sixth wave is currently being completed. At each stage a mixture of interview, questionnaire and observational data was collected. Data were collected at the participants' home during the first, second, fourth and sixth wave, whilst at the third at fifth wave families attended the Social Development Laboratory at the School of Psychology, Cardiff University. This thesis includes data from the first, second, fifth and sixth wave, for which the procedures will now be explained.

2.2.2.1 Wave 1: Antenatal assessment. The first wave of data collection targeted mothers who were in the third trimester of their first pregnancy. Families were visited at home by two research assistants, who provided them with a complete description of the study after which written informed consent was given before beginning the antenatal assessment. Families gave further informed consent for the audio recordings of the interviews, which were conducted at the home with mothers and fathers, each in separate rooms. If the biological father did not live with the mother, efforts were made to visit the father separately. The interviews covered the following topics: socio-demographic characteristics, employment, social support, psychopathology (past and present problems) and familial history of mental health problems. Mothers and fathers were then asked to complete a set of questionnaires, which were left with them along with stamped addressed envelopes. These questionnaires covered the following topics: general health, lifestyle, life events, relationship quality, fertility history, behavioural history and substance use. A small compensation and thank-you gesture for their participation was given to families at the end of the visit in the form of a £20 gift voucher.

2.2.2.2 Wave 2: Early infancy assessment. At a target age of 6 months (*M* = 6.55, *SD* = 0.82) home-visits took place, with one or two researchers visiting the families. The two-hour visit consisted of a mother interview and a behavioural observation of the infant and mother (or primary carer), for which informed consent was obtained at the beginning of the visit. Again a packet of questionnaires for the mother, father and a significant other (a family friend or relative) was left with the families along with stamped addressed envelopes. The Infant Behaviour Questionnaire (IBQ; Rothbart, 1981), which is used in the current chapter, was included at this stage in this packet of questionnaires. A small compensation and thank-you gesture for their participation was given to families at the end of the visit in the form of a £20 gift voucher.

2.2.2.3 Wave 5: Toddler laboratory assessment. At a target age of 33 months (*M* = 34.94, *SD* = 5.85), parents and children were invited into the Social Development Laboratory to take part in another part of the study, which involved a cognitive testing session as well as an assessment of peer interaction that consisted of a simulated birthday party. These lab visits always included three separate families, who were invited to take part at the same time. It was standard procedure that if one of the families arrived late, the birthday party, which required all three families to be present and provided the major dependent variable for the study, would receive precedence over the cognitive testing session. This meant that some children did not complete all of the cognitive tasks, which were administered in random orders to avoid excessive missing data on particular tasks. The individual cognitive assessment took place in separate small testing rooms with their accompanying parent(s) and/or guardian(s) present and lasted approximately 25 minutes. During the assessment parents were asked to complete the CBCL, included in this chapter, as part of a range of other questionnaires, whilst their child was tested. Completed questionnaires were collected at the end of the lab visit, however uncompleted questionnaires, including in a packet for the mother, father and a

significant other (a family friend or relative) were provided for them to take home along with stamped addressed envelopes. Families were compensated for travel expenses and a small acknowledgement and thank-you gesture for their participation was given to families at the end of the lab visit in the form of a £20 gift voucher.

2.2.2.4 Wave 6: Middle childhood assessment. At a target age of 7 years (*M* = 7.03, *SD* = 0.31) home visits were conducted, with two or three researchers visiting the families. The assessments took place over two 2-hour visits, during which an interviewer administered questionnaires and conducted two semi-structured interviews with the primary caregiver: the Preschool Age Psychiatric Assessment (PAPA) and the Schedules for Clinical Assessment in Neuropsychiatry (SCAN: Wing et al., 1990) interview. At the same time a child tester administered a battery of age appropriate tasks (See Table 2.2). If younger siblings were present during the visit, an additional research assistant was available to keep them occupied during the testing. Siblings were encouraged to join in during the family interaction tasks. Five of the Amsterdam Neuropsychological Tasks (ANT; completed using a laptop and mouse; De Sonneville, 1999) were used in this chapter (see section 2.2.3.4.3 for a detailed description of these tasks).

Informed consent was obtained at the beginning of the first visit. During the first visit the primary caregiver (95.5% mothers) was asked to complete a questionnaire, which included the CBCL and Conners' Scales of ADHD. These questionnaires were completed on an iPad to ensure quick data-processing. Further questionnaires were left after the first visit for the mother and father to complete, along with stamped addressed envelopes. Research assistants were asked to pick these up at the start of the second visit. Additionally, after consent and contact details were obtained during the first visit, children's school teachers were contacted and asked to complete a questionnaire, which contained the Teacher Report Form (TRF). At the end of each visit, a small compensation and thank-you gesture for their

participation was given to the families in the form of a £20 gift voucher (for both the parents and the child). Teachers were given a £10 book voucher.

Table 2.2 Tasks administered by child testers during the middle childhood home visits.

Visit 1	**Tasks**
Warm-up task	*Chairs*
ANT tasks	*Baseline Speed**
	*Set Shifting**
	*Delay Frustration**
Socio-cognitive tasks	*Machiavellian intelligence*
	Theory of Mind
	Social problem-solving
	Deception
Emotional labelling and understanding task	
Puppet-conflict task	
Family interaction Tasks	*Bop-it game*
Imaginary computer game	
Visit 2	**Tasks**
ANT tasks	*Identification of facial emotions*
	*Working Memory**
	*Pursuit**
British Picture Vocabulary Scale	
Pretend play task	
Family interaction Tasks	*I-Spy*
	Simon Says
	Etch-a-Sketch
Pretend play task	

*Tasks explored in this Thesis.

2.2.3 Measures

2.2.3.1 Social Risk Index. A social risk index was created to avoid multicollinearity in subsequent analyses, since demographic variables were significantly inter-correlated. This index reflects the additive risk of five factors: a working class status (as defined by the Standard Occupational Classification 2000), mother's lack of basic educational qualifications (defined as not having obtained 5 GCSE's at grades A* to C or equivalent CSE or 'O' level grades), the mother being a teenager (≤ 19 years of age) at the time of the child's birth, the

parents not living in a stable relationship and the parents not being legally married. This risk index showed an acceptable level of internal consistency (α = .74).

2.2.3.2 Wave 2: Early infancy assessment. For this chapter various measures of infants' activity levels were collected during a home visit, when infants were six months old.

2.2.3.1.1 Informant-reported activity level in infancy. The 'activity level' subscale of the Infant Behaviour Questionnaire (IBQ; Rothbart, 1981), which consists of 17 items, was used as a questionnaire measure of the child's gross motor activity, including movement of arms and legs, squirming and locomotor activity (Items are displayed in Table 2.3). The IBQ was completed by at least one informant in 265 families of the 310 families who were assessed at Wave 2 (250 mothers, 207 fathers and 207 significant others who knew the child well). Internal consistency of this scale was confirmed with alpha coefficients ranging from .83 to .87 across informants (median α = .84). Mothers' reports were significantly associated with fathers' reports, r (204) = .53, p < .001, and with the third informant, r (194) = .33, p < .001, with fathers' and third informants' reports also significantly correlated, r (168) = .29, p < .001. Mplus 7 (Muthén & Muthén, 2012) was used to construct factor scores from the three informants' ratings. A confirmatory factor analysis using a Maximum Likelihood estimator with robust standard errors (MLR) to allow for deviations from normal distributions of the indicators was conducted. The resulting factors scores were analogous to standardised scores, with the mean and variance of the factor variables constrained to be 1 and 0 respectively. The resulting factor explained 68, 40 and 15% of the variance in mothers', fathers' and third informants' ratings respectively.

Table 2.3 Items included in the activity level subscale of the Infant Behaviour Questionnaire (Rothbart, 1981).

	Never	Very Rarely	Less Than Half the Time	About Half the Time	More Than Half the Time	Almost Always	Always	NA
During feeding, how often did the baby:								
4. lie or sit quietly?*	☐	☐	☐	☐	☐	☐	☐	☐
5. squirm or kick?	☐	☐	☐	☐	☐	☐	☐	☐
6. wave arms?	☐	☐	☐	☐	☐	☐	☐	☐
During sleeping, how often did the baby:								
13. toss about in the crib?	☐	☐	☐	☐	☐	☐	☐	☐
14. move from the middle to the end of the crib?	☐	☐	☐	☐	☐	☐	☐	☐
15. sleep in one position?*	☐	☐	☐	☐	☐	☐	☐	☐
When being dressed or undressed during the last week, how often did the baby:								
23. wave his arms and kick?	☐	☐	☐	☐	☐	☐	☐	☐
24. squirm and/or try to roll away?	☐	☐	☐	☐	☐	☐	☐	☐
When put into the bath water, how often did the baby:								
30. splash or kick?	☐	☐	☐	☐	☐	☐	☐	☐
31. turn body and/or squirm?	☐	☐	☐	☐	☐	☐	☐	☐
When placed on his/her back, how often did the baby:								
65. lie quietly?*	☐	☐	☐	☐	☐	☐	☐	☐
66. wave arms and kick?	☐	☐	☐	☐	☐	☐	☐	☐
67. squirm and/or turn body?	☐	☐	☐	☐	☐	☐	☐	☐
When place in an infant seat or car seat, how often did the baby:								
70. wave arms and kick?	☐	☐	☐	☐	☐	☐	☐	☐
71. squirm and turn body?	☐	☐	☐	☐	☐	☐	☐	☐
72. lie or sit quietly?*	☐	☐	☐	☐	☐	☐	☐	☐

* NB: reverse scored

2.2.3.1.2 Measured activity level. Children's activity levels were objectively measured using the ActiGraph ActiTrainer (Manufacturing Technology, Inc, MTI). Several studies have established the validity and reliability of this device (de Vries, Bakker, Hopman-Rock, Hirasing, & van Mechelen, 2006; Eisenmann et al., 2004; Fairweather, Reilly, Grant, Whittaker, & Paton, 1999; Puyau, Adolph, Vohra, & Butte, 2002; Trost et al., 1998). The ActiGraph ActiTrainer contains an activity monitor with a built-in accelerometer, which

records accelerations ranging in magnitude from 0.05 to 2 G's. The output from the accelerometer is digitized by an Analog to Digital Converter (ADC) at the rate of thirty times per second (30 Hertz (Hz)) and the signal then passes through a digital filter, which band-limits the accelerometer to the frequency range of 0.25 Hz to 2.5 Hz. These limits allow detection of normal human motion, whilst motion from other sources is rejected. For this study, each motion sample was initially summed over a specified epoch of 15 seconds. Young children tend to perform physical activity in short bursts rather than in prolonged bouts (Bailey et al., 1995) and short epochs are therefore recommended. Previous studies have used 15 seconds epochs successfully when examining activity levels in preschool children (e.g. Pate, Almeida, McIver, Pfeiffer, & Dowda, 2006; Pate, Pfeiffer, Trost, Ziegler, & Dowda, 2004).

The ActiGraph ActiTrainer has dimensions of 8.6 cm by 3.3 cm by 1.5 cm and weighs approximately 1.8 ounces. The device was packaged in a plastic enclosure and attached to the infants' left leg with a Velcro strap. The collected data were downloaded via the integrated USB plug, stored in ASCII format and subsequently converted into a Microsoft Excel file with the Actilife Software. The data were cleaned and total activity scores were calculated for 30 second epochs. It was confirmed that time did not affect activity levels significantly and a mean activity score was calculated for each condition.

Activity data for *baseline, attention task* and *restraint task* periods were collected during the early infancy home visit. At the start of the behavioural observation of the infant the Actigraph Actitrainer was attached to the infant by the experimenter. A baseline period of activity data was collected for approximately 3 minutes. Activity data were also collected during two tasks, one designed to elicit attention and the other to reflect an emotional challenge. These tasks were adapted from the 'toy interest game' and the 'car seat' tasks

described in the Laboratory Temperament Assessment Battery (Lab-TAB) manual (Goldsmith & Rothbart, 1999).

Figure 2.2 Turtle toy used to elicit attention during the 6 month assessment.

For the *attention* task the child was presented with an age-appropriate turtle toy, which emits sound and light when manipulated (see Figure 2.2). The examiner positioned the toy in front of the child and said "Look what I have for you to play with. Let me show you how it works." The examiner pressed the toy so that sound and light were emitted and then left the child undisturbed for 3 minutes, whilst parents were asked to not interfere with the child's play throughout the task.

Finally, for the emotional challenge task, a *restraint in a car seat* task was used as a challenge that might induce distress in some children, although not all children were expected to show distress in this type of situation. It was expected that being restrained might elicit anger or frustration in some infants and the use of a car seat provided ecological validity, given that their use is widespread and required by law. A car seat was placed on the floor in front of the camera. Parents were asked to place the infants in the car seat and strap them into the seat, whilst standing to the side of the seat in order not to obstruct the camera. The researcher stood to the side and slightly behind the car seat and once the child was strapped

in, the parent was asked to stand next to the researcher, whilst the child was left in the car seat for 30 seconds. Parents were instructed that if they felt that their child became too distressed, they could end the procedure at any point. The entire session was video-recorded by the experimenter for later observation and coding.

2.2.3.3 Wave 5: Thirty-three month assessment. Actigraph measures of toddlers' activity levels were collected during the lab-visit, when toddlers were a mean of thirty-three months old (M = 34.94, SD = 5.85). Age-appropriate measures of executive functions were also taken at this stage using various tasks, and parents and a third informant who knew the infant well completed a questionnaire that assessed possible symptoms of ADHD.

2.2.3.3.1 Measured activity. Activity levels, measured using the ActiGraph Actitrainer, were assessed during an individual cognitive assessment, which represents a relatively formal situation that might be encountered in a school environment, and during peer interaction at a simulated birthday party, which is ecologically more similar to a situation that might be encountered within the home environment. At the start of the afternoon of testing, an Actigraph Actitrainer was attached to the toddler by an experimenter. A *baseline* period of activity data were then collected for approximately 3 minutes and the actigraph was not removed until the end of the birthday party, so that activity data was recorded for all the completed tasks. Activity levels were thus collected for an *attention* task (Tower of Cardiff Planning task, described under the executive function task section 2.2.3.2.3) and two *emotional challenge* tasks, including a 'Restraint task' and a 'Frustration task'. Both tasks consisted of a challenge that might induce distress in some children, although not all children were expected to show distress in this type of situation.

2.2.3.3.1.1 Restraint task. During the 'Restraint task' parents were asked to strap their child into a small wooden seat, which was placed in front of a small table. Activity data were then collected for 30 seconds, whilst the child remained in the seat. If the child refused the

straps, no pressure was placed upon them and the straps were left unfastened. A large number of children refused the straps; therefore a second task, designed to elicit feelings of frustration, was included in the current investigation.

Figure 2.3 The toy space aliens 'Doog' and 'Moog' that were used for the Frustration task.

2.2.3.3.1.2 Frustration task. This task consisted of the experimenter presenting the child with a toy 'space alien' called 'Moog' (see Figure 2.3), which started dancing after the experimenter pressed the top of its head. The child was then given an identical toy 'space alien' called 'Doog' and asked to make it dance too. The batteries of this toy had been taken out, which meant that whatever the children tried to do, they were not able to make the toy dance. The child was given 2 trials and activity data were collected for the entire duration of this task.

2.2.3.3.1.3 Peer Interaction. After the individual cognitive assessments were completed, all three families attended a simulated birthday party. This paradigm was designed to be an emotionally arousing setting that was ethically acceptable. This took place in a large furnished observation room, designed to resemble a sitting room in a child's home, which was fitted with video-recording equipment, and a one-way mirror, through which experimenters were able to observe the families. During the 'birthday party' two costumed

characters, a birthday lady and a teddy bear, played out a picnic scenario, during which the toddlers were encouraged to interact with the characters. After the picnic scenario was completed, the three families were left in the observation room for 20 minutes during which toddlers' free play was observed. Parents had been instructed to act as they normally would at an actual birthday party where they did not know all the other parents. The birthday party and 20 minutes of peer interaction were filmed using two wall-mounted cameras, which were controlled from behind a one-way mirror. Throughout the birthday party ActiGraph Actitrainers were attached to the toddlers and a sample of 5 minutes of activity was collected from the free play period, which was used as a measure of activity during peer interaction.

2.2.3.3.2 Toddlers' symptoms of ADHD. The widely used and repeatedly validated Child Behaviour Checklist for toddlers (CBCL version 1.5 to 5 years; Achenbach & Rescorla, 2000) was administered at 33 months of age (Wave 5). This is a standardised questionnaire for parents, which requires them to rate 100 items on behavioural and emotional problems exhibited by their children on a 3-point scale. The ADHD subscale consists of 6 items and scores can range from 0 to 12. Items include: (1) cannot concentrate, cannot pay attention for long, (2) cannot sit still, restless, or hyperactive, (3) cannot stand waiting, wants everything now, (4) demands must be met immediately, (5) gets into everything, and (6) quickly shifts from one activity to another. The CBCL has previously been used at age 3 as a measure of ADHD symptoms in a twin study and a moderate degree of stability in symptoms from age 3 to 7 was found (Rietveld et al., 2004), suggesting that symptoms of ADHD can be detected at the early age of 33 months. It therefore appears justified to use the ADHD symptoms scale on the CBCL as a measure of early symptoms of ADHD.

The CBCL was completed by at least one informant in 254 families (240 mothers, 176 fathers and 182 family members or family friends who knew the child well). The internal

consistency of this scale was confirmed with alpha coefficients of .73 for maternal, .74 for paternal and .75 for third informants' ratings. Mothers' reports were significantly associated with fathers' reports, r (168) = .42, $p < .001$, and with the third informant, r (172) = .49, $p < .001$, with fathers' and third informants' reports also significantly correlated, r (150) = .31, $p < .001$.

The questionnaires that were completed at 33 months of age also included a 'Developmental Milestones Questionnaire'. This questionnaire included 3 ADHD items, namely 'Restless, overactive, cannot stay still for long', 'Constantly fidgeting or squirming' and 'Is easily distracted, concentration wanders'. These items were rated as either 'not true (0)', 'somewhat true (1)' or 'certainly true (2)' and scores could range from 0 to 6. At 33 months the scale was completed by at least one informant in 243 families (228 mothers, 178 fathers and 180 third informants). The scale showed good internal consistency with alpha coefficients at 33 months of .74, .78 and .76 for maternal, paternal and third informants' ratings respectively. In order to maximise the sample size for this scale, scores from an identical questionnaire collected during a previous wave (Wave 4; *M* age = 20.6 months, *SD* = 2.27) were used to impute missing scores at 33 months. At 21 months the scale had been completed by at least one informant in 243 families (235 mothers, 189 fathers, 194 third informants). The scale showed good internal consistency with alpha coefficients at 21 months of .76 for maternal, .77 for paternal and .72 for third informants' ratings. Mothers' reports at this age were significantly associated with fathers' reports, r (186) = .41, $p < .001$, and with the third informant, r (186) = .37, $p < .001$, with fathers' and third informants' reports also significantly correlated, r (159) = .24, p = .002. Imputing predicted scores resulted in a sample size of 284 families (276 mothers, 220 father, 237 third informants) for the Developmental Milestones ADHD symptom scale.

Mplus 7 (Muthén & Muthén, 2012) was used to construct toddler age ADHD factor scores based on the three informants' ratings on the Developmental Milestones and CBCL questionnaires. This resulted in latent factor scores being available for a total of 286 families (86.1% of the initial sample), since Mplus 7 uses Full-Information Maximum Likelihood methods (FIML) which allow factor scores to be computed based on all available information (thus including cases where only 1 informant provided a rating). A confirmatory factor analysis, using a Maximum Likelihood estimator with robust standard errors (MLR) to allow for deviations from normal distributions of the indicators, was conducted which included these 6 indicators and 3 latent factors (see Figure 2.4). The resulting factors scores were analogous to standardised scores, with the mean and variance of the factor variables constrained to be 1 and 0 respectively. The toddler age ADHD factor explained 54.6% and 79.8% of the variance in the latent CBCL and Developmental Milestones factor respectively, whilst explaining 77.4, 31.2, 21.6, 81.3, 27.0 and 35.8% of the variance in mothers', fathers' and third informants' reports of these two respective scales. Standardised path coefficients are presented in Figure 2.4.

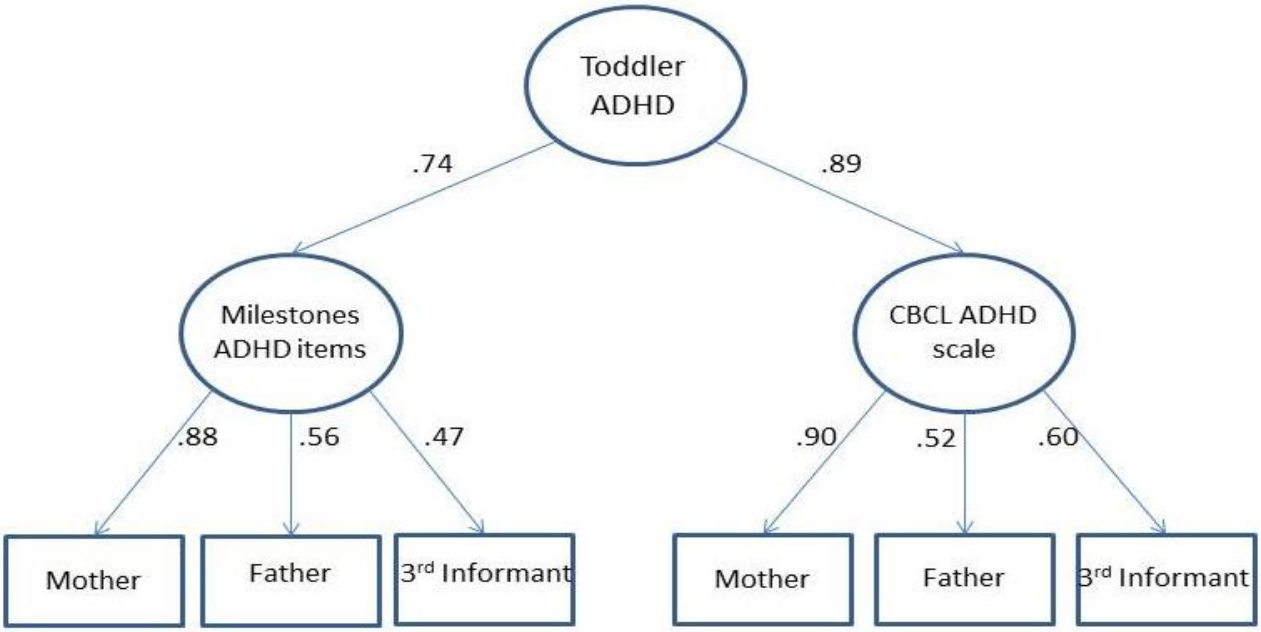


Figure 2.4 Structural model used to construct Toddler ADHD factor scores with standardised path coefficients.

2.2.3.3.3 Age-appropriate executive function tasks. During the individual cognitive assessment children were presented with a battery of cognitive and social communicative tasks, which were given in several random orders. The entire session was video-recorded by the experimenter for later observation and coding. Four age-appropriate executive function tasks were also used for the current investigation, including the 'Tower of Cardiff Planning task', 'Raisin task', 'Whisper task' and 'Big Bear, Little Bear task'. Two additional 'Imitation tasks' were used to analyse the factor structure of the cognitive tasks at this wave of data collection.

2.2.3.3.3.1 Tower of Cardiff Planning task. During this task, which was designed for the purpose of the study, the child was presented with a plastic pillar with plastic rings of various sizes. The pillar is narrower at the top than at the base, which affords stacking the rings in a graduated order. Thus the rings would normally be placed in an order from large to small (Figure 2.5, left hand side image); however, in this case the experimenter gave the child

an example of an unusual tower that the toddler was subsequently asked to copy (Figure 2.5, right hand side image).

Figure 2.5 Pillar and rings used for the tower task, stacked in the conventional order (left) and experimental order (right).

This task requires planning the order in which to select rings to put on the tower. Children were given two trials and the responses of the toddler were scored as '0' if no tower was built at all, '1' if the tower did not resemble the experimenter's tower and was not the conventional tower, '2' if the child built the conventional tower (i.e. with the rings being placed in an order from large to small) and '3' if a tower identical to the experimenter's tower was built. A subsample of 57 participants (25%) was used in order to establish inter-rater reliability. Perfect inter-rater reliability was found with an intra-class correlation of 1.00. Activity data were collected throughout the duration of this task.

2.2.3.3.3.2 Raisin task (Kochanska, et al., 1996). The Raisin task is a delay of gratification task, which was adapted from the original 'Snack Delay' task, in which a child was required to wait to retrieve an M&M from under a see-through cup (Kochanska et al., 1996). Poor performance on this task in preschoolers has been found to be predictive of behavioural problems from age 5 to 8 (Kim et al., 2013). Furthermore, children with ADHD

have repeatedly been found to perform worse on tasks that involve delays, in line with the delay aversion theory of ADHD (Sonuga-Barke, 2003). For this task a bell, a plastic box and three raisins were used (see Figure 2.6).

Figure 2.6 Raisins, plastic box and bell used during the 'Raisin' task.

The experimenter placed a raisin underneath a plastic box after which the child was instructed not to touch or eat the raisin until the bell rings. The child was given three trials. The child's response for each trial is scored as either 0 if the child eats the raisin before the experimenter rings the bell, 1 if the child touches the bell, box or raisin, but does not eat the raisin and 2 if the child does not eat the raisin and does not touch the bell, box or raisin during the trial. Total scores were corrected for the number of trials that the child completed. Intra-class correlations were calculated for a random selection of 57 participants (25%) in order to establish inter-rater reliability. Good inter-rater reliability was found with an intra-class correlation of 0.96.

2.2.3.3.3.3 Whisper task (adapted from a similar task used by Kochanska et al., 1996). This task was taken from a battery designed to measure inhibitory control and originally required the child to whisper the names of 10 cartoon characters that were presented on cards (Kochanska et al., 1996). During the adapted task children were presented

with a toy farmyard, which was made up of a large plywood base, painted as a yard with a pond and vegetable patch (See Figure 2.7).

Figure 2.7 Toy farmyard and plastic farm animals used during the 'Whisper' task.

Four side walls and a roof could be used by the experimenter and child to build a toy barn. Common farm animals were used as toys, including a horse, donkey, cow, calf, sheep, lamb, chicken, duck, pig and goat. The experimenter presented the child with a toy farm and instructed the child to 'wake up' 10 plastic farm animals by naming each animal in turn, and whisper 'good morning' very softly to them. Each trial consisted of waking up a farm animal and the child's response to each trial could be coded as 'shout', 'normal voice', 'low vocal sound' or 'whisper', which was scored as 0, 1, 2 or 3 respectively. Total scores were corrected for the number of trials that the child completed. A subsample of 56 (25%) participants was used in order to establish inter-rater reliability. Good inter-rater reliability was found with an intra-class correlation of 0.98.

2.2.3.3.3.4 Big Bear Little Bear task. This task is an adaptation from the baby Stroop task (Hughes & Ensor, 2005), which is used as a measure of interference control. This in turn was an adaptation of the original Stroop task (Stroop, 1935) which requires participants to

either read colour words in black, name the colour of variously coloured squares or name the colours of incongruent colour words as fast as possible. Children with ADHD symptoms have been found to perform more poorly on this task, possibly as a result of deficient inhibitory control, which fails to protect the decision making process from interference of external stimuli.

Figure 2.8 The Big Bear, Little Bear picture and corresponding cups and spoons.

Children were presented with a large picture of two bears, a big bear and a little bear. Two spoons (a big spoon and a small spoon) as well as two cups (a big cup and a small cup) were also used (see Figure 2.8). The experimenter showed the child the large picture of two bears and explained to the child that big bear liked to use a small spoon and a small cup, whilst little bear prefers a big spoon and a big cup. The child was subsequently asked to place the four items with the correct bear during four trials (i.e. the small spoon and cup belonged to big bear and the large spoon and cup belonged to little bear). Children's responses could be coded as 'no response', 'conventional response' (incorrect) or 'correct response'. Scores ranged between 0 and 4, depending on how often the correct response was given. A

subsample of 57 (25%) participants was used in order to establish inter-rater reliability. Good inter-rater reliability was found with an intra-class correlation of 0.99.

2.2.3.3.3.5 Imitation tasks. During an 'Imitation of Intentional Actions' task a toy bus with shapes of various sizes that fitted into similarly shaped slots in the bus was presented to the child. The child was allowed to play with the bus any way they wanted for a minute, after which the experimenter took a shape and placed in it in the corresponding slot, whilst saying 'Oops, I didn't mean to do that'. Subsequently, the experimenter took a shape and wedged it in one of the slots so that it stood up in the slot, whilst saying 'There'. The child was given the opportunity to imitate the action of the experimenter, after which the procedure was repeated once more. The tasks thus consisted of 4 trials, 2 affordance trials (i.e. where the correct shape was placed in the correct slot) and 2 intentional trials (i.e. where the shape was wedged into a slot). Scores were calculated by adding up the number of times the child imitated the intentional action of the experimenter (range 0-2). A subsample (25.6% of participants) was coded by an independent observer and good inter-rater reliability was found with an intra-class correlation of 0.96.

Secondly, for the 'Imitation of Novel Use of Familiar Objects' task (adapted from Hay, Murray, Cecire, & Nash, 1985) the children were shown a party hat and a plastic toy banana. They were given the opportunity to play with it for a minute after which the experimenter demonstrated two unusual actions for each object by putting the party hat on the child's foot as if it was a shoe and using it as a trumpet by blowing into it and making trumpet sounds, whilst the banana was used as a comb and as a telephone. The child was given the opportunity to imitate these actions after each demonstration. This task therefore consisted of 4 trials and scores were calculated by adding up the total number of times the child imitated the action of the experiment (range 0-4).). A subsample (25 % of participants)

was coded by an independent observer and good inter-rater reliability was found with an intra-class correlation of 0.89.

2.2.3.3.3.6 Construction of composite scores. A principal components analysis, using Varimax Rotation with Kaiser Normalisation, was performed on the scores from six cognitive tasks. Three factors were accounting for 59.1 percent of the variance (see Table 2.4 for factor loadings). The first factor loaded heavily on the 'Raisin task' score and the 'Whisper task' score, suggesting that this factor represented behavioural regulation. The 'Bus task' and the 'Hat-Banana task' were associated with a second factor, therefore representing an imitation factor. A third factor was associated more with the 'Tower task' score and the 'Big Bear Little Bear task' score, suggesting that this factor represented cognitive flexibility. The fact that these tasks did not relate to the imitation factor supports this construct further since children were not simply imitating the experimenter, but rather using 'problem-solving' skills to resolve these tasks. Only the behavioural regulation factor scores and the cognitive flexibility factor scores, derived from this principal components analysis, are used as variables of interest in subsequent analyses throughout this thesis. All four tasks were completed by 212 children; however mean imputation for missing values allowed factor scores for 231 children to be calculated.

Table 2.4 Factor loadings for principal components analysis of six cognitive tasks.

	Factor 1 Behavioural Regulation	**Factor 2 Imitation**	**Factor 3 Cognitive Flexibility**
Raisin task	.79*	-.19	.03
Whisper task	.69*	.15	-.05
Big Bear Little Bear task	.11	-.28	.70*
Tower task	.-.14	.28	.76*
Imitation of novel use of familiar objects	-.24	.67*	-.13
Imitation of intentional actions	.31	.70*	.15

NB: * factor loading > .40

2.2.3.3.4 Toddlers' ODD problems. The 'Oppositional Defiant Problems' subscale of the CBCL (CBCL version 1.5 to 5 years; Achenbach & Rescorla, 2000) was used as a measure of ODD symptoms in toddlers. This scale consists of 6 items, (1) defiant, (2) disobedient, (3) angry moods, (4) stubborn, (5) temper, (6) uncooperative. This scale was completed by at least one informant in 254 families (200 mothers, 122 fathers and 140 significant others who knew the child well). The internal consistency of this scale was confirmed with alpha coefficients of .79 for maternal, .85 for paternal and .80 for third informants' ratings. Mothers' reports were significantly associated with fathers' reports, r (168) = .37, $p < .001$, and with the third informant, r (172) = .48, $p < .001$, with fathers' and third informants' reports also significantly correlated, r (150) = .41, $p < .001$. Mplus 7 (Muthén & Muthén, 2012) was used to construct factor scores from the three informants' ratings. A confirmatory factor analysis using a Maximum Likelihood estimator with robust standard errors (MLR) to allow for deviations from normal distributions of the indicators was conducted. The resulting factors scores were analogous to standardised scores, with the mean and variance of the factor variables constrained to be 1 and 0 respectively. The resulting factor explained 43, 37 and 56 % of the variance in mothers', fathers' and third informants' ratings respectively.

2.2.3.4 Wave 6: Middle childhood assessment.

2.2.3.4.1 Symptoms of ADHD in middle childhood. Similarly to the questionnaires administered at toddler age, at Wave 6 the Child Behaviour Checklist (CBCL version 1.5 to 5 years; Achenbach & Rescorla, 2000) was administered to parents, whilst a teacher version was administered to teachers (Teacher Report Form, TRF; Achenbach & Rescorla, 2000). The items included in the TRF differed from the parent version and instead consisted of 13 items, which included: (1) 'can't concentrate, can't pay attention for long' (2) 'can't sit still,

restless, or hyperactive' (3) 'can't stand waiting; wants everything now' (4) 'demands must be met immediately' (5) 'daydreams or gets lost in his/her thoughts' (6) 'difficulty following directions' (7) 'disturbs other children' (8) 'gets into everything' (9) 'fails to carry out assigned tasks' (10) 'fidgets' (11) 'quickly shifts from one activity to another' (12) 'inattentive, easily distracted' (13) 'overactive'.

The CBCL/TRF was completed by at least one informant in 204 families (194 mothers, 124 fathers and 140 teachers). The internal consistency of this scale was confirmed with alpha coefficients of .80 for maternal, .72 for paternal and .91 for teacher's ratings. Mothers' reports were significantly associated with fathers', r (122) = .64, $p < .001$, and with the teacher's reports, r (138) = .54, $p < .001$, with fathers' and teacher's reports also significantly correlated, r (91) = .51, $p < .001$.

Primary caregivers completed Conners' 3AI-P index (Conners, 2008) in addition to the CBCL. This index contains the 10 items that best differentiate children with ADHD from healthy controls and are rated on a 4-point scale (see Table 2.5). Transposing rules need to be applied to the item responses after which a total raw score can be calculated. This score can be converted into a probability score (representing the probability that a child belongs to an ADHD group as opposed to the general population) or a T-score (which is used to assess how a child compares to children of the same age and gender). These scores are particularly useful for clinical practice; however the total raw score is more appropriate in research and was therefore used in this chapter. Conners' 3AI-P index was completed by 199 primary caregivers and the scale showed good internal consistency (α = .88). It also significantly correlated with the CBCL scales of primary caregivers (r (199) = .67, $p < .001$), fathers (r (121) = .53, $p < .001$) and the TRF scale of teachers (r (136) = .45, $p < .001$).

Table 2.5 Items included in Conners' 3AI-P ADHD index (Conners, 2008).

	Not at all	Just a little	Pretty often	Very often
1. Fidgeting	☐	☐	☐	☐
2. Does not seem to listen to what is being said	☐	☐	☐	☐
3. Doesn't pay attention to details; makes careless mistakes	☐	☐	☐	☐
4. Inattentive, easily distracted	☐	☐	☐	☐
5. Has trouble organising tasks or activities	☐	☐	☐	☐
6. Gives up easily on difficult tasks	☐	☐	☐	☐
7. Fidgets or squirms in seat	☐	☐	☐	☐
8. Restless or overactive	☐	☐	☐	☐
9. Is easily distracted by sights or sounds	☐	☐	☐	☐
10. Interrupts others (for example, butts into conversations or games)	☐	☐	☐	☐

Mplus 7 (Muthén & Muthén, 2012) was used to construct childhood age ADHD factor scores based on the three informants' ratings on the CBCL/TRF questionnaires and primary caregiver's rating on the Conners' 3AI-P. This resulted in latent factor scores being available for a total of 204 families (61.4% of the initial sample recruited in pregnancy) since Mplus 7 uses Full-Information Maximum Likelihood methods (FIML) which allow factor scores to be computed based on all available information (thus including cases where only 1 informant provided a rating). A confirmatory factor analysis, using a Maximum Likelihood estimator with robust standard errors (MLR) to allow for deviations from normal distributions of the indicators, was conducted, which included these 4 indicators and 1 latent factor (see Figure 2.9). The resulting factor scores were analogous to standardised scores, with the mean and variance of the factor variables constrained to be 1 and 0 respectively. The childhood

ADHD factor explained 78.5, 57.2 and 41.0% of the variance in mothers', fathers' and teachers' CBCL/TRF scores respectively and 57.3% of the variance in primary caregiver Conners' 3AI-P index. Standardised path coefficients are presented in Figure 2.9.

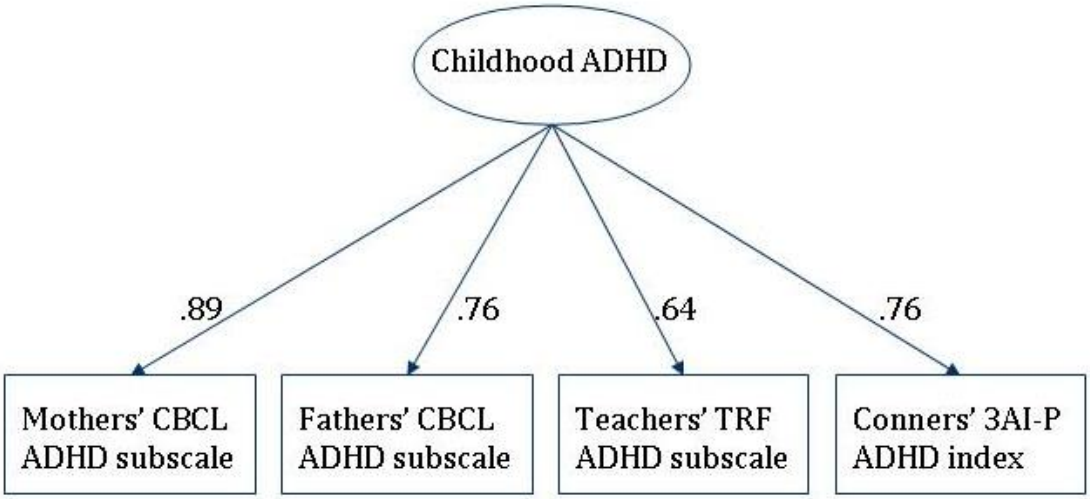


Figure 2.9 Structural model used to construct Childhood ADHD factor scores with standardised path coefficients.

2.2.3.4.2 Tester Ratings of Child Behaviour. A Tester's Ratings of Child Behaviour (TRCB) form was completed by child testers after each visit. This form contained two items that were considered relevant to symptoms of ADHD (see Table 2.6), which were therefore included in this thesis. Scores were averaged over the two visits. For a subsample of 20 participants, video-recorded child and family-interaction tasks were watched by independent raters, who then completed the TRCB form based on their observations. Not all tasks were video-recorded and limited independent rater's view of the visit compared with child testers. Pearson's correlations instead of intraclass correlations were therefore explored to establish inter-rater reliability/validity of the ratings. Correlations between raters' scores of .58 ($p <$ .001) and .73 ($p <$ .001) were observed for activity and attentiveness respectively.

Table 2.6 Questions on the TRCB that related to ADHD symptoms.

Activity This scale refers to how physically active the child was during the testing										
Very still/ little gross motor movements	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	Very active (wiggles a lot, a lot of arm/leg movements)
Attentiveness/Goal Directedness How long is the child interested and persistent in solving the presented task?										
Very short periods/ very short attention. No evidence of directed effort and absorption.	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	Very long periods/ long attention span. Very persistent and absorbed.

2.2.3.4.3 Amsterdam Neuropsychological Tasks (ANT; De Sonneville, 1999). The Amsterdam Neuropsychological Tasks are a computerised set of 38 tasks designed to measure executive functioning. These tasks are used for both clinical and research purposes and can be administered to preschool-aged children, school-aged children, adolescents and adults (De Sonneville, 1999). The tasks show satisfactory to good validity, sensitivity and reliability (De Sonneville, 2005). Five tasks were examined for the purpose of this thesis.

Firstly, a Baseline Speed reaction time task was used to assess alertness/attention during a task that requires minimal cognitive effort. During 32 trials the child was asked to press a mouse-key as quickly as possible, when a fixation cross in the centre of the computer screen changes into a white square. Outcome measures were the mean reaction time, the within-subject standard deviation of the reaction time and the number of premature responses (i.e. when the child presses the mouse-key before the square has appeared).

Secondly, a Set Shifting task was used as a measure of attentional flexibility. This task consists of three parts. A coloured circle moves randomly to the right or left of a horizontal bar in the centre of the computer screen. During part 1 the child is asked to make compatible response, by pressing the mouse-key on the same side as the direction of movement of the circle. A pre-potent response is established during this condition. During part 2 the child is required to make incompatible responses, by pressing the mouse-key on the

side opposite to the direction of the movement of the circle. The incompatible condition thus requires inhibition of pre-potent responses. During part 3, the colour of the moving circle varies randomly and the child is thus required to make compatible or incompatible responses, depending on the colour of the square. This condition requires attentional flexibility. Outcome measures were accuracy (number of errors), mean reaction time of the fixed task condition (averaged across part 1 and 2) and of part 3 and the number of premature responses.

Thirdly, a Pursuit task was included as a measure of eye-hand coordination, fine motor control and sustained attention. During this task the child is required to continuously track a target star that moves randomly on the screen for five minutes, by moving the computer mouse. Outcome measures were the mean distance of the mouse cursor to the moving target (accuracy of movement) and the associated standard deviation (fluctuation in accuracy).

The fourth task consisted of a Visuospatial Memory task, designed to measure working memory. During this task 9 circles positioned on a 3x3 matrix are displayed on the computer screen. After a beep signal an animation is run in which a finger points at a number of circles. During 24 trials the child is required to point out the same circles in the same order by clicking them with the mouse. Outcome measures were the number of correctly identified circles irrespective of order of identification and the number of circles identified in the correct order.

Finally, a Delay Frustration task was included as a measure of frustration tolerance. This consist of a simple task during which the child is required to select an image that matches a target image in either colour or shape, by clicking the correct image with the computer mouse. Once the correct image is clicked, the next trial commences (37 normal delay trials). However, the task is designed to randomly delay the onset of the next trial

during 8 short delay trials (lasting 2-9 secs) and 10 long delay trials that always last 16 seconds. The child is instructed prior to the start of the task with the following remark from the child tester: "We have noticed that the computer doesn't always work for this task. Sometimes the computer doesn't seem to notice that you clicked an image and it is possible that you might have to press again to continue the task. Ok?" Outcome measures are the number of mouse-clicks during the long delay trials and the average duration during which the mouse-button is held down during the long delay trials.

2.2.3.4.4 Middle childhood ODD problems. The 'Oppositional Defiant Problems' subscale of the CBCL (CBCL version 1.5 to 5 years; Achenbach & Rescorla, 2000) was used as a measure of ODD symptoms at age 7. The CBCL/TRF was completed by at least one informant in 204 families (194 mothers, 124 fathers and 140 teachers). The internal consistency of this scale was confirmed with alpha coefficients of .85 for maternal, .86 for paternal and .95 for teacher's ratings. Mothers' reports were significantly associated with fathers', r (120) = .56, $p < .001$, and with the teacher's reports, r (138) = .54, $p < .001$, with fathers' and teacher's reports also significantly correlated, r (91) = .51, $p < .001$. Mplus 7 (Muthén and Muthén, 2012) was used to construct childhood age ODD factor scores based on the three informants' ratings on the CBCL/TRF questionnaires and this resulted in latent factor scores being available for a total of 204 families (61.4% of the initial sample). A confirmatory factor analysis using a Maximum Likelihood estimator with robust standard errors (MLR) to allow for deviations from normal distributions of the indicators was conducted. The resulting factor scores were analogous to standardised scores, with the mean and variance of the factor variables constrained to be 1 and 0 respectively. The resulting factor explained 65, 54 and 50% of the variance in mothers', fathers' and teachers' ratings respectively.

2.2.4 Data Analysis

The settings for the measured activity data resulted in the number of movements being collected and summed for specified epochs of 15 seconds. The data were subsequently cleaned and divided into 30 second epochs. A mean activity score was calculated for each condition, which was used for all further analysis. Furthermore, in order to account for resting states (baseline), whilst examining children's reactions to the attentional and emotional challenges, a measure of reactivity was calculated, using the following equation: ((activity level $_{condition}$ – activity level $_{baseline}$)/ activity level $_{baseline}$) * 100. This was the percentage change in activity levels from baseline to attention and from baseline to the negative emotion challenge.

Missing data have resulted in a variation in participant numbers depending on the type of measure that was being examined throughout the thesis. For the current chapter, directly measured activity data for at least one condition could be extracted for 266 participants during the early infancy assessment. Subsequently, at the late toddlerhood assesment actigraph data for at least one condition could be extracted for 170 participants. Missing actigraph data were the result of equipment malfunction, extreme anomalies in the data, the actigraph being refused by the child or parent or the task not being completed. Table 2.7 shows the number of participants for which actigraph data was collected at 6 months (Wave 2) and 33 month of age (Wave 5).

Table 2.7 Number of participants for which Actigraph activity levels was available.

	Actigraph data 6 months		**Actigrahp data 33 months**	
	raw scores	controlled for baseline	raw scores	controlled for baseline
Informant-reported	265		-	
Baseline	265		148	
Attention	266	247	151	138
Restraint	261	242	107	100
Frustration	-		143	130
Peer Interaction	-		157	

The activity data were screened for violations in the assumptions of parametric tests. The assumptions of normality were not met and non-parametric tests were thus used to examine the activity data. In order to examine whether there were any differences in activity levels between conditions within the 6 and 33 month assessments Friedman's tests were used. Specific comparisons were made using Wilcoxon's tests, whilst gender differences were explored using Mann-Whitney U tests. Finally, to explore associations of activity levels with informant-reported activity levels at 6 months, cognitive task performance at 33 months of age and early manifestations of ADHD symptoms in toddlerhood, Spearman's rho correlations were examined.

Assumptions of normality, linearity, homoscedasticity, no multicollinearity, and independent errors were met for the informant-reported activity levels, possible ADHD symptoms and executive functioning tasks. Associations between these variables were thus explored using Pearson correlations. Finally, it must be noted that significance levels of $p < .05$ and $p < .01$ are reported throughout the thesis. It must be noted that in this chapter a total of five infancy precursor variables and 26 toddler and middle childhood outcome variables were correlated with eachother as well as with social risk and ODD symptoms, resulting in 130 observed correlations. A significance level of $p < .05$ and $p < .01$ would mean that by chance respectively 6.5 and 1.30 of these correlations would be significant. When a Bonferroni correction is applied, this would mean that only correlations with $p < .0004$ would be considered significant. This would be extremely conservative and limit the conclusions that can be drawn in this chapter. A less conservative significance-level of $p < .001$ was therefore adopted and reported along with the results using conventional significance-levels. Of course, when interpreting these significance values, it must be remembered that false positives might occur in 6.5 (conventional), 1.30 ($p < .001$) or 0.13 ($p < .001$) of the correlations.

2.3 Results

2.3.1 Activity levels in Infancy

It was found that informant-reported activity levels (as measured with the IBQ activity scale) were normally distributed (see Figure 2.10). They did not significantly correlate with the age of the infant at the six month assessment (r = .08, p = .20) or with the social risk index (r = .02, p = .78). Next, informant-reported activity levels were compared with measured activity levels at six months of age.

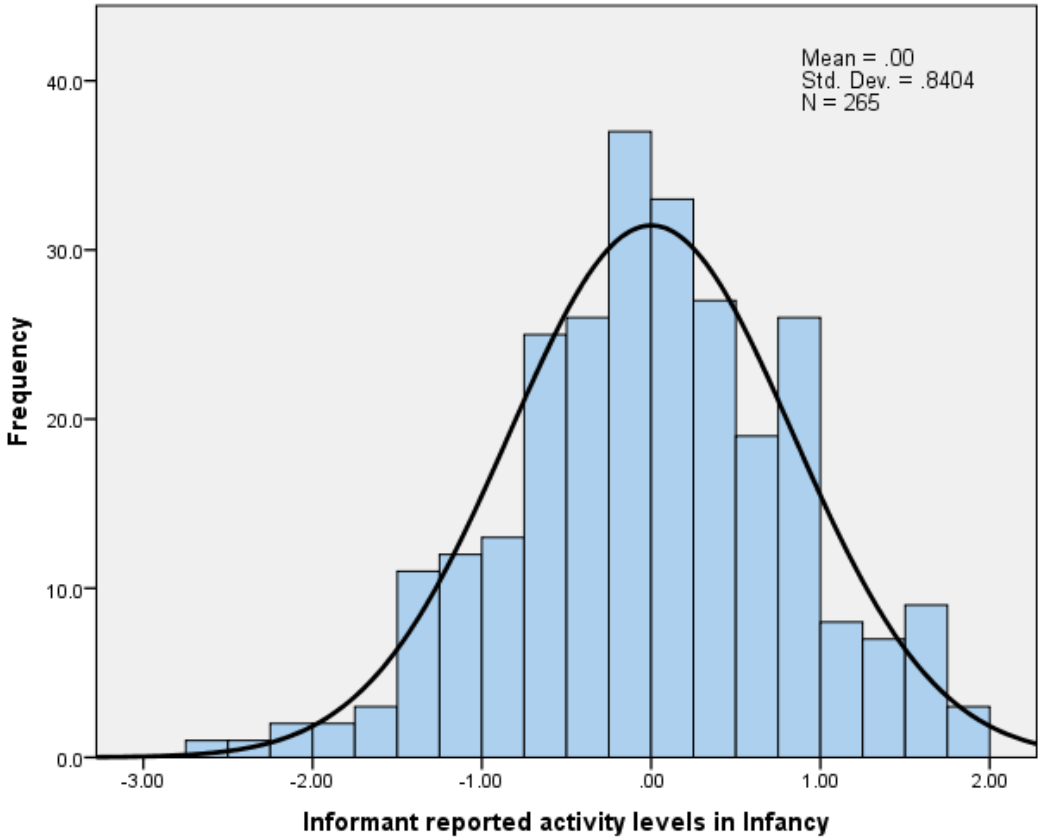
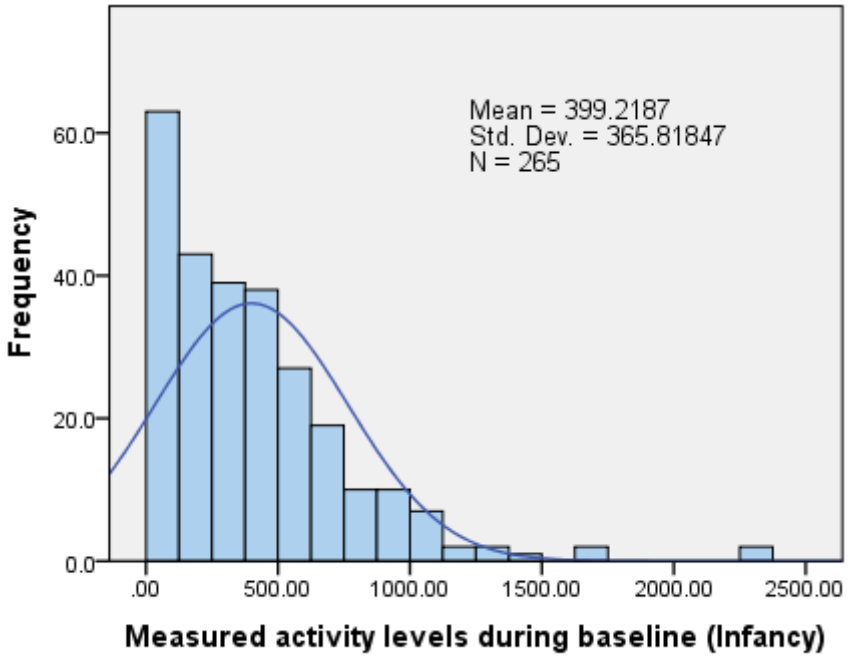


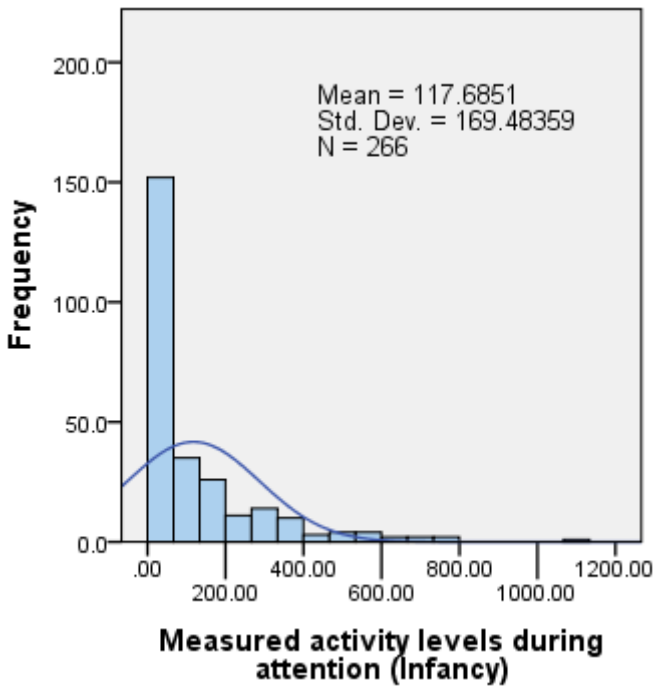
Figure 2.10 Distribution of informant-reported activity levels in infancy.

Activity levels at six months were measured during a baseline, attention and emotional challenge (restraint) condition. The distribution of baseline activity levels deviated from normality (slightly right-skewed, leptokurtic distribution), whereas the distribution of activity levels during attention and restraint were strongly skewed (see Figure 2.11).

A)



B)



C)

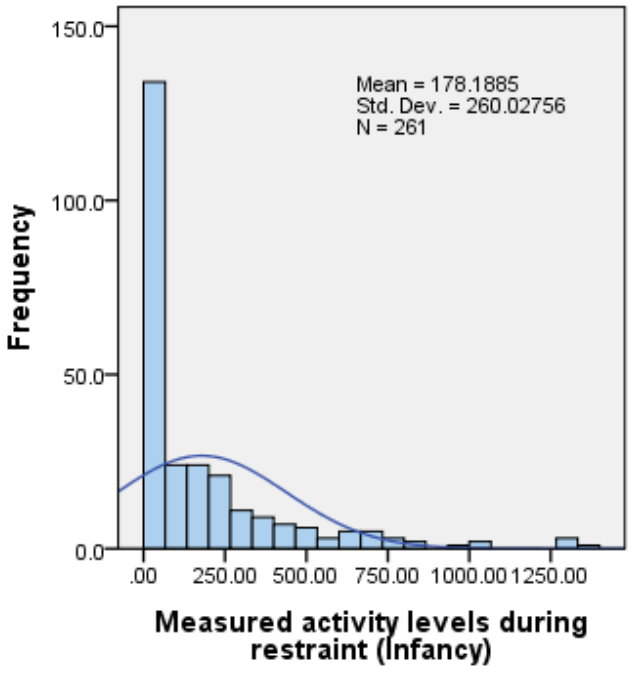


Figure 2.11. Distribution of measured activity levels in infancy, during baseline (A), attention (B) and restraint (C).

There was no significant correlation between the age of the infant at the six month assessment and activity levels during any of the conditions. Infants' measured activity levels

differed significantly depending on what condition they were placed in (χ^2 (2) = 112.38, p < .001). Activity levels were higher during baseline compared with attention (z = -10.78, p < .001) and restraint (z = -8.32, p < .001), whilst activity levels during restraint were higher than during attention (z = -2.71, p = .007); see Figure 2.12. This figure also shows that measured activity levels during baseline varied considerably compared with activity levels for the other two conditions. It must be noted however that infants' activity levels still correlated significantly between conditions, showing there was a level of consistency in infants' general levels of activity (see Table 2.8). A principal components analysis on measured activity levels yielded a single factor accounting for 43% of the variance (factor loadings: 0.73 for baseline, 0.59 for attention and 0.64 for restraint).

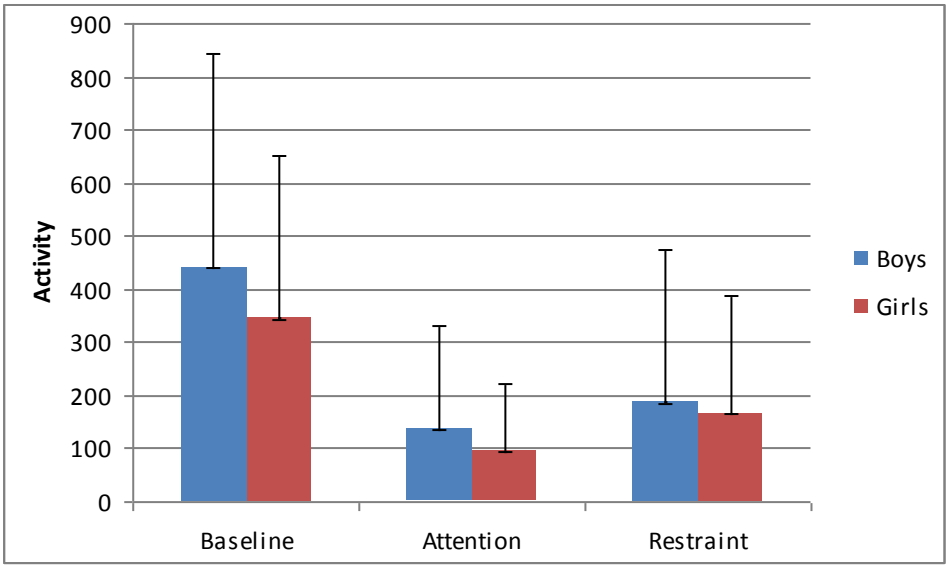


Figure 2.12 Mean activity levels and SD's (error bars) for boys and girls during baseline, attention and emotional challenge (restraint) in infancy (N= 267).

Informant-reported activity levels were significantly correlated with infants' measured activity levels during attention (but not when a stricter significance level was applied), but no correlations with the general activity level factor or with activity levels during the other conditions at six months of age were observed (see Table 2.4). Examination of activity levels

during attention and restraint, controlled for baseline levels of activity (i.e. reactivity), did not change these results.

Table 2.8 Spearman's rho correlations between informant-reported and measured activity levels.

	Informant reported activity levels	**Baseline**	**Attention**	**Restraint**
Measured Activity levels at 6 months				
Baseline	.05	-	-	-
Attention	.13*	.22***	-	-
Restraint	-.02	.25***	.15*	-
W2 activity factor	.10	.71***	.60***	.60***

NB: significance level †< .10 * < .05 ** < .01 *** < .001.

2.3.1 Measured Activity levels in Toddlerhood

Activity levels at 33 months were examined during a baseline, attention, and two emotionally challenging (restraint and frustration) conditions as well as during peer interaction following a third emotional challenge at the simulated birthday party. The distribution of baseline, attention, restraint and frustration activity levels deviated from strongly from normality, and resembled those observed in infancy (see Figure 2.11). Measured activity levels during peer interaction showed a normal distribution (see Figure 2.13).

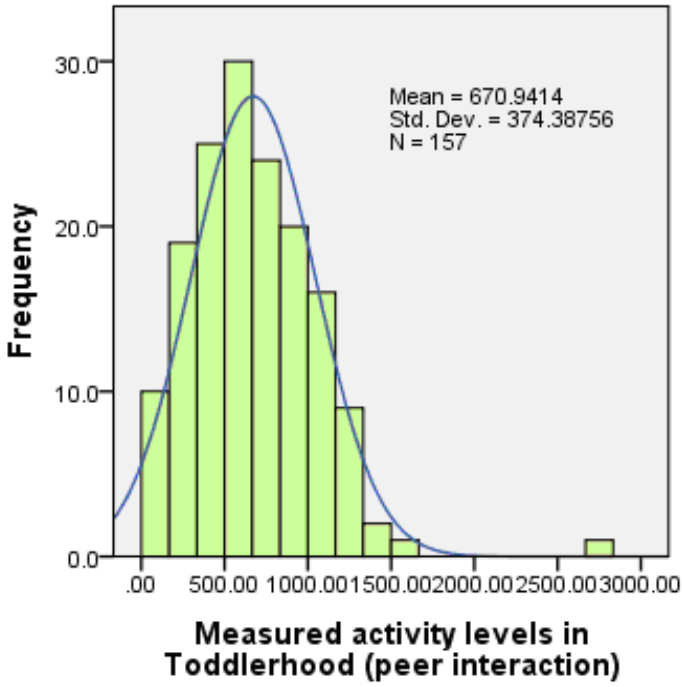


Figure 2.13 Distribution of measured activity levels in toddlerhood during peer interaction.

Again, there was no significant correlation between the age of the child at the 33 month assessment and measured activity levels during any of the conditions. Similarly, toddlers' activity levels differed significantly depending on what condition they were placed in, χ^2 (4) = 166.17, p < .001, see Figure 2.14. Unsurprisingly, activity levels were higher during the peer interaction session where the toddlers' movement was unrestricted, than during the individual testing session, in which the toddlers were seated in a chair (baseline: z = 7.65, p < .001; attention: z = 9.79, p < .001; restraint: z = 7.54, p < .001; frustration: z = 9.64, p < .001). A similar pattern to what was found in infancy could be identified within the cognitive testing session in toddlerhood, with higher activity levels during baseline compared with attention (z = -5.35, p < .001), restraint (z = -2.16, p = .03) and frustration (z = -4.21, p < .001). Moreover, activity levels were higher during restraint compared with attention (z = 3.70, p < .001) and frustration (z = -3.72, p < .001), but there was no significant difference between the attention and frustration condition (z = 0.67, p = .50). Again, it must be noted that toddlers' activity levels still correlated significantly between conditions, showing there

was a level of consistency in toddlers' general levels of activity at 33 months of age (see Table 2.9). This was particularly found for activity levels within the individual testing session, whilst activity levels during peer interaction were only significantly related to activity levels during the restraint condition. However, since a principal components analysis could not yield a single factor (instead yielding two factors that cross-loaded), activity levels will be explored in this thesis for each task individually.

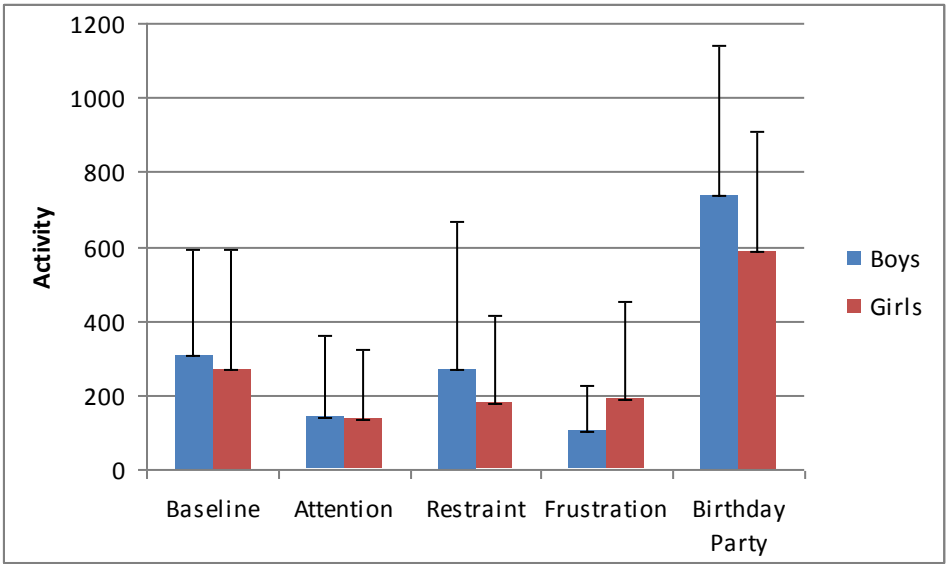


Figure 2.14 Mean activity levels and SD's (error bars) for boys and girls during baseline, attention and emotional challenge at 33 Months (*N*= 150).

Table 2.9 Spearman's rho correlations between toddlers' measured activity levels.

	Baseline	**Attention**	**Restraint**	**Frustration**
Measured Activity levels at 33 months				
Baseline	-	-	-	-
Attention	.28***	-	-	-
Restraint	.26**	.35***	-	-
Frustration	.21*	.36***	.22*	-
Peer Interaction	.11	.04	.25*	.06

NB: significance level †< .10 * < .05 ** < .01 *** <.001.

2.3.2 Gender Differences in Activity Levels

Informant reported activity levels (as measured with the IBQ activity scale) did not differ between boys and girls at six months of age (T (263) = 0.20, p = .84). However, at this age a trend was found for measured activity levels during the baseline condition, where boys were more active than girls (z = 1.84, p = .07); however no gender differences were found during the other conditions (attention: z = 1.31, p = .19; restraint: z = -0.09, p = .93), see Figure 2.9. Considering changes in activity levels compared with baseline did not alter these results, with no difference between boys and girls for either attention (z = 0.26, p = .79) or restraint *(*z = -0.90, p = .37). Comparing activity levels of boys and girls for the general activity factor that had been generated using a principal components analysis did show boys to be significantly more active overall (z = 2.03, p = .04).

At the thirty-three month assessment boys were significantly more active during the peer interaction compared with girls (z = 2.20, p = .03), but there were no differences between boys and girls during any of the other conditions (baseline: z = 1.14, p = .26; attention: z = 0.47, p = .64; restraint: z = 0.13, p = .89; frustration: z = -0.91, p = .36) and considering activity levels compared with baseline did not change these results (attention: z = 0.88, p = .38; restraint: z = -0.61, p = .54; frustration: z = -0.99, p = .33), see Figure 2.10.

2.3.3 ADHD Symptoms in Toddlerhood

The toddler ADHD factor scores derived from the confirmatory factor analysis were not related to children's age at the 33 month assessment, but a significant correlation with the social risk index was found (r (286) = .21, p < .001). No gender differences were found (t (283) = -1.27, p = .21). The factor score of toddler's ADHD symptoms showed a normal distribution (see Figure 2.15). To examine how many children would be in the clinical range, the original CBCL subscale scores were examined. It was found that according to the criteria

set out by Achenbach and Rescorla (2000), mothers indicated that 10/240 (4.2%) fell within the borderline and 3/240 (1.3%) fell within the clinical range. Fathers reported that 13/176 (7.4%) children fell within the borderline and 2/176 (1.1%) within the clinical range, whilst third informants rated 6/182 (3.3%) children as falling within the borderline and 1/182 (0.5%) as falling within the clinical range.

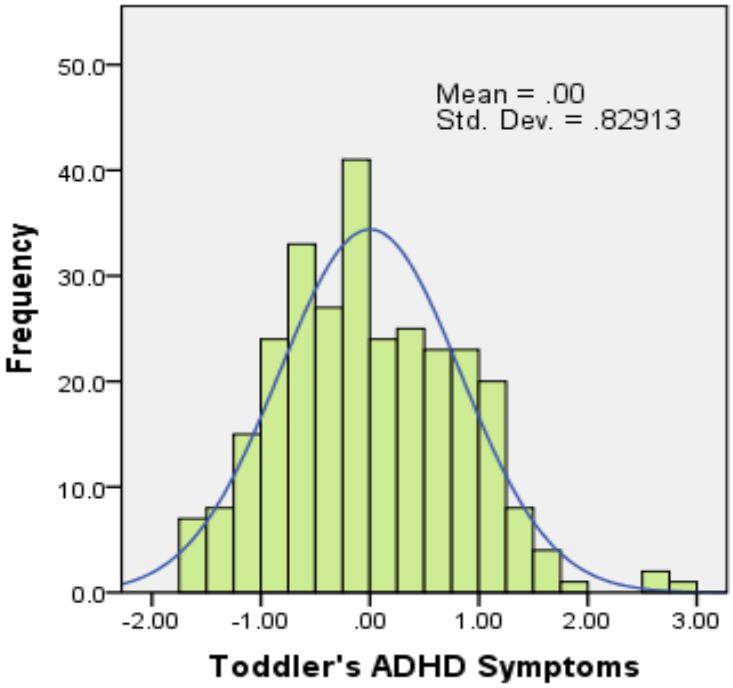


Figure 2.15 Distribution of toddlers' ADHD symptoms.

Spearman's rho correlations were examined to establish the relationship between ADHD symptoms in toddlerhood and measured activity levels at 33 months (see Table 2.10). Significant correlations with activity levels are found during the restraint condition and during peer interaction. These results did not change, when changes in activity levels compared with baseline were taken into account.

Table 2.10 Spearman's rho correlations between toddlers' ADHD symptoms and measured activity levels at 33 months.

	Toddlers' ADHD symptoms
Measured activity levels at 33 mth	
Baseline	-.11
Attention	.06
Restraint	.22*
Frustration	.04
Peer Interaction	.17*

NB: significance level † < .10, * < .05 ** < .01, *** < .001.

2.3.4 Correlates of Toddlers' ADHD Symptoms: Cognitive Task Performance

Toddlers' cognitive task performance at 33 months of age was measured using four cognitive tasks. The four tasks were completed by 212 children; however, a principal components analysis with mean imputation for missing values allowed factor scores for 231 children to be calculated. The distribution of the behavioural regulation and cognitive flexibility factor scores did not deviate from normality. Scores for the Raisin task could vary between 0 and 6 (M = 1.23, SD = 1.41, N = 225), for the Big Bear Little Bear task scores ranged from 0 to 4 (M = 1.21, SD = 1.61, N = 221), for the Tower task from 0 to 3 (M = 1.48, SD = 0.85, N = 222) and for the Whisper task from 0 to 30 (M = 13.29, SD = 8.27, N = 224). The distribution of the behavioural regulation and cognitive flexibility factor scores did not deviate from normality. Boys' behavioural regulation scores were marginally lower than girls' scores (t (229) = 1.84, p = .07), but no differences were found between boys and girls for cognitive flexibility scores (t (229) = 0.41, p = .69).

Table 2.6 shows that toddlers' ADHD symptoms are significantly related to their scores on the Big Bear/Little Bear task and marginally correlated with their scores on the Raisin task. Toddlers with higher scores on the ADHD subscale were thus found to perform more poorly on these tasks. The factor scores, derived from the principal component analysis described earlier in the method section, are also displayed. Table 2.11 shows that the

behavioural regulation factor is significantly associated with toddlers' ADHD symptoms, whereas the cognitive flexibility factor showed a marginal relationship.

Table 2.11 Pearson's correlations between ADHD symptoms, executive function tasks and factor scores.

	Toddlers'ADHD symptoms	**Raisin**	**Whisper**	**BBLB**	**Tower**	**BR**
Raisin task	-.12†	-	-	-	-	-
Whisper task	-.11	.22**	-	-	-	-
Big Bear/Little Bear task	-.16*	.09	.03	-	-	-
Tower task	-.02	-.07	-.01	.10	-	-
Behavioural regulation	-.14*	.79***	.70***	.11	-.14*	-
Cognitive flexibility	-.11†	.03	-.05	.71***	.76***	.000

NB: significance level †< .10, * < .05 ** < .01, *** < .001.

2.3.5 Toddler's ODD symptoms

Throughout this thesis, ODD symptoms are taken into account. It can be seen in Figure 2.16 that ODD symptoms were normally distributed within the CCDS sample. The toddler ODD factor scores derived from the confirmatory factor analysis were not related to children's age at the 33 month assessment, but a marginally significant correlation with the social risk index was found (r (254) = .12, p = .05). No gender differences were found (t (251) = -0.28, p = .78).

Toddlers' ODD symptoms were strongly correlated with toddlers' ADHD symptoms (r = .54, p < .001); however no relationship between toddler's ODD symptoms and toddler's behavioural regulation, cognitive flexibility or measured activity levels was found.

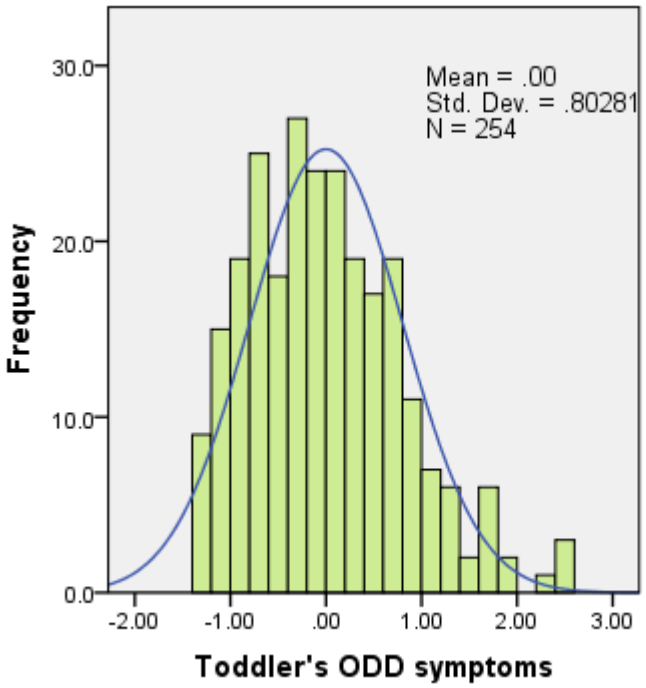


Figure 2.16 Distribution of toddlers' ODD symptoms.

2.3.6 ADHD Symptoms in Middle Childhood

ADHD symptoms in middle childhood were normally distributed. No significant gender differences were found for ADHD symptoms in middle childhood (t (200) = -1.58, p = .12), although more symptoms were found in boys (M = 0.08, SD = 0.96, N = 115) compared to girls (M = -0.13, SD = 0.85, N = 87). Inspection of the informants' reports individually revealed that scores did not significantly differ between boys and girls for mother and father reports of ADHD symptoms; however a significant gender difference was found for symptoms reported by teachers (t (124.91) = -3.62, p < .001), with boys (M = 5.28, SD = 2.44, N = 77) scoring significantly higher than girls (M = 2.44, SD = 3.32, N = 61).

All measures used to establish factor scores of ADHD symptoms at age 7 were significantly correlated (see Table 2.12). Moreover, tester's ratings of children's activity levels were significantly related to the children's ADHD symptoms, whilst testers' ratings of children's attention were negatively associated with ADHD symptoms.

Table 2.12 Correlations between all informants' ratings of ADHD symptoms at age 7.

	1	2	3	4	5	6
1. Mothers' CBCL	-	-	-	-	-	-
2. Fathers' CBCL	.64***	-	-	-	-	-
3. Teachers' TRF	.54***	.51***	-	-	-	-
4. Conners' 3AI-P	.67***	.53***	.45***	-	-	-
5. W6 ADHD Factor	.95***	.80***	.68***	.81***	-	-
6. TRCB activity	.21**	.16†	.09	.29***	.24**	-
7. TRCB attentiveness	-.37***	-.25**	-.45***	-.38***	-.43***	-.43***

NB: significance level † < .10, * < .05 ** < .01, *** < .001.

Furthermore, it was noted that Conners' raw scores could be converted into probability scores, which show the probability of an ADHD diagnosis or T-scores, which show how a child compares to his or her age and gender. The graphic representations of the scores found in this sample show that the majority of participants were unlikely to have a diagnosis of ADHD, whilst for a small number of children the likelihood is greater (see Figure 2.17). This pattern is similar for T-scores.

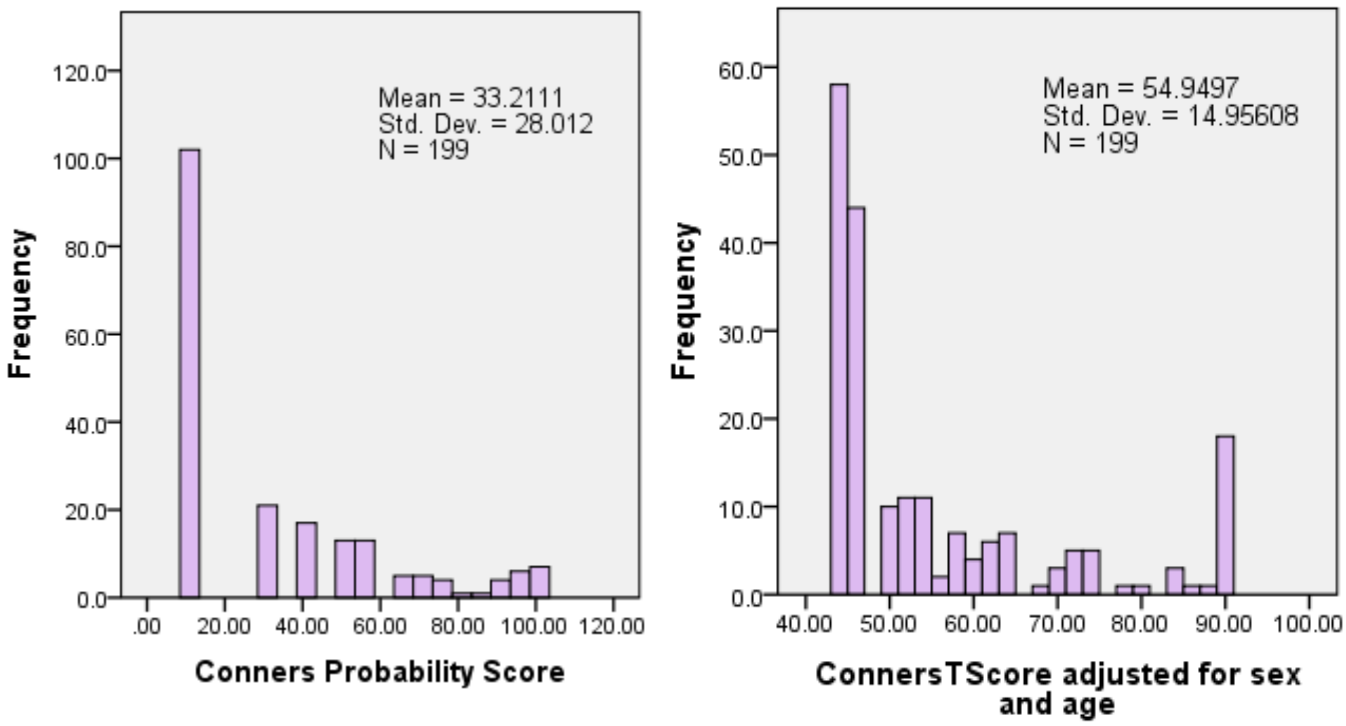


Figure 2.17 Conners' raw scores converted into probability scores (left) and T-scores (right).

2.3.7 Correlates of ADHD Symptoms in Middle Childhood: Cognitive Task Performance

Childrens' cognitive task performance at 7 years of age was measured using 5 executive function (ANT) tasks. The tasks were completed by 178 children. Table 2.13 shows the correlations of social risk with cognitive task performance in middle childhood. It was found that social risk was associated with errors during the set shifting task and poor performance on the working memory task. Table 2.13 also shows concurrent associations between childhood ADHD and ODD symptoms, child tester's ratings of activity and attention with cognitive task performance in middle childhood. Firstly, it was found that premature responses during the baseline speed task were associated with concurrent ADHD and ODD symptoms as well as with poorer attention scores as rated by child testers. Similarly, during the set shifting task, premature responses were also associated with concurrent ADHD and ODD symptoms as well as with increased activity and poorer attention scores as rated by child testers.

Secondly, errors during the set shifting task were associated with concurrent ADHD and ODD symptoms and increased activity and poorer attention scores as rated by child testers. Thirdly, the accuracy of movement (mean distance to target) as well as fluctuations in accuracy (*SD* of the distance to target) during the Pursuit task was significantly related to concurrent ADHD and ODD symptoms and increased activity and poorer attention scores as rated by child testers. Similarly, the number of identified targets and targets in the correct order were associated with concurrent ADHD and ODD symptoms and child tester ratings. Finally, it was found that the number of mouse-clicks and the duration of the mouse-clicks during the Delay Frustration task were related to increased activity and poorer attention scores as rated by child testers. ADHD symptoms were not significantly related to performance on this task.

Table 2.13 Associations between cognitive task performance in middle childhood, social risk, and concurrent ADHD and ODD symptoms.

	Social Risk	Childhood ADHD symptoms	TRCB activity	TRCB attention	Childhood ODD symptoms
Baseline Speed Task					
M reaction time	.03	.06	-.03	-.24**	.10
SD reaction time	.08	.12	.03	-.29***	.17*
Premature responses	.14†	.24**	.11	-.28***	.21**
Set Shifting Task					
Errors compatible	.13†	.24**	.11	-.25***	.21**
Errors incompatible	.20**	.17*	.09	-.15*	-.03
Errors mixed	.16*	.14†	.22**	-.36***	.08
Premature responses	.11	.28***	.17*	-.32***	.22**
M reaction time fixed	-.004	-.03	.03	-.11	.03
M reaction time mixed	.06	.05	.11	-.13†	-.03
Pursuit Task					
M distance to target	.15†	.41***	.19*	-.43***	.26***
SD distance to target	.07	.37***	.20**	-.42***	.16*
Working Memory Task					
N targets	-.10	-.32***	-.31***	.64***	-.26***
N targets in order	-.24**	-.34***	-.23**	.62***	-.23***
Delay Frustration Task					
N mouse-clicks	.05	.04	.15*	-.16*	-.04
M duration mouse-clicks	-.01	.03	.16*	-.15*	-.04

NB: significance level † < .10, * < .05 ** < .01, *** < .001.

2.3.8 ODD Symptoms in Middle Childhood

Throughout this thesis, ODD symptoms are taken into account. In middle childhood ODD symptoms were also normally distributed within the CCDS sample. The ODD factor scores were not related to children's age at the Wave 6 assessment, but a significant correlation with the social risk index was found (r (204) = .20, p < .001). No gender differences were found (t (200) = -0.93, p = .35).

Children's ODD symptoms were strongly correlated with children's ADHD symptoms (r = .65, p < .001). Relationships between children's ODD symptoms, and their concurrent cognitive performance were discussed in section 2.3.8.

2.4 Discussion

The main aim of this chapter was to introduce the CCDS sample and the measures that are used throughout this thesis. The CCDS sample was shown to be representative of the general population in all demographic factors, and attrition did not seem to be selective, with comparable demographic statistics for all waves. ADHD symptoms were normally distributed within the population, with only a small number of children meeting clinical cut-off criteria. Concurrent associations between measures used in infancy, toddlerhood and middle childhood were also explored.

Firstly, the precursor was introduced. Informant-reported activity levels in infancy were found to be normally distributed, whereas the distributions of measured activity levels were strongly skewed with many infants showing low measured levels of activity and fewer displaying high levels of activity. It was found that informant-reported and measured activity levels were related at 6 months during the attention condition, but not during other conditions. This was unexpected, and it is not clear what might explain this result. One might speculate that the informant-reported activity levels are measuring something slightly different, and when examining the items it is clear that the questions represent gross motor activities such as squirming, tossing, turning, kicking etc. The directly measured activity might pick up more subtle movements that would not be reported using this questionnaire. It must, of course, also be taken into account that the measured activity levels represent a short snap-shot of activity levels, whereas the informant-reported activity levels represent activity levels as observed by parents over a longer period of time.

It was not surprising that in general activity levels were higher during baseline, where infants were free to move around, compared with a condition in which they were attending to a novel toy and a condition in which they were restraint. Interestingly, measured activity

levels in infancy did correlate between conditions, such that those children that were more active during baseline also struggled to reduce their activity during attention and were more active during the restraint condition. This was in line with the hypothesis and this finding was replicated during toddlerhood.

Secondly, the first set of outcome variables, collected during toddlerhood, was introduced. ADHD symptoms were normally distributed within the CCDS sample. Some toddlers could be identified as falling within a clinical range according to CBCL criteria. Furthermore, as hypothesised, toddlers' ADHD symptoms were associated with reduced performance on various cognitive tasks, and the behavioural regulation factor in particular was significantly related to toddlers' ADHD symptoms. It was discussed in Chapter 1 that more basic deficits in inhibitory control and delay aversion in younger children were more strongly associated with ADHD symptoms than more complicated tasks involving interference control and vigilance (for which effect size increased with age) (Pauli-Pott & Becker, 2011). Given that the 'simpler' behavioural regulation tasks are likely to be mastered between 22 and 33 months of age (Garon et al., 2008) it is not surprising that in this study behavioural regulation was related to toddlers' ADHD symptoms, whereas general cognitive flexibility at 33 months of age was only marginally significantly related to toddler's ADHD symptoms. Behavioural regulation skills, tapped by the delay of gratification task and the inhibitory whisper task, might be more or less consolidated at this age, whereas other aspects of behavioural inhibition, such as interference control (the Big Bear Little Bear task) and more complex skills like planning (Tower of Cardiff task) were probably not fully developed yet. At 33 months, activity levels during restraint and peer interaction (following an emotionally challenging event – the birthday party featuring costumed characters), but not during other conditions, were significantly related to toddlers' symptoms of ADHD. It is possible that during challenging situations highly active children might struggle to regulate

their activity levels. Taken together, these findings suggest that regulatory deficits correlate particularly strongly with ADHD symptoms at toddler age.

Finally, the second set of outcome variables, collected during middle childhood, was introduced. Again, ADHD symptoms were normally distributed within the CCDS sample. Some children could be identified as falling within a clinical range according to Conners' probability scores. Furthermore, as hypothesised, children's ADHD symptoms were associated with reduced performance on various cognitive tasks. Children with more ADHD symptoms often responded prematurely (i.e. behavioural regulation), made more mistakes during the set shifting task (i.e. cognitive flexibility), and performed more poorly on the sustained attention and working memory task. Therefore, in line with the hypothesis also more complex executive functioning skills were correlated with ADHD symptoms in middle childhood. Furthermore, those with more ADHD symptoms were also rated by child testers as more active and less attentive during the home visits in middle childhood.

As expected, ADHD symptoms in toddlerhood as well as in middle childhood were significantly associated with social risk and concurrent ODD symptoms. Noticably, ODD symptoms did not correlate with behavioural regulation and cognitive flexibility during toddlerhood; however in middle childhood ODD symptoms were strongly correlated with cognitive outcomes. It was explained in Chapter 1 that it is important to differentiate between disorders, if one wants to define precursors that are specific to a particular disorder. The aim of this thesis is to identify precursors that are specific to ADHD symptoms, and these findings highlight the need to control for the presence of comorbid oppositional defiant disorder (ODD) problems, as well as social risk covariates.

Moreover, some gender differences were observed. During infancy, boys were significantly more active overall, although no significant differences were observed for specific conditions or for informant-reported activity levels. At toddler-age boys were

significantly more active than girls during peer interaction at the simulated birthday party at 33 months, but not during other conditions. A trend for boys to score lower on the behavioural regulation factor compared with girls was also observed. It was surprising that no gender differences were observed during other conditions or for informants' ratings of early activity levels and ADHD symptoms in toddlerhood and middle childhood (except for teachers' reports). This finding is comparable to that found in other community samples. Gender differences are evident in clinical samples; they are less frequently reported in community samples (Gaub & Carlson, 1997). It was also shown that few toddlers fell within a clinical range of ADHD symptoms. The symptoms of ADHD, like those of many behavioural disorders show continuous distributions with no distinct cut-off point that separates normality from abnormality (Rutter, Silberg, O'Connor, & Simonoff, 1999). This was confirmed in this sample, suggesting that these results might also be generalisable to clinical diagnoses of ADHD.

In the literature many studies have used older children (mostly around 4-6 years old) and broad age ranges, which makes this study particularly valuable, since a younger age was explored and there was little variability in the age at which children were assessed, enabling more accurately estimates of age-specific associations with ADHD symptoms. It allows for a more precise description of developmental trajectories to ADHD and for identifying potential time windows that might be suitable for an early valid assessment of specific basic deficits (Pauli-Pott & Becker, 2011). Moreover, the use of both laboratory observations and parental ratings is a preferred method, since it combines the advantages of both methods, whilst remedying the biases associated with the exclusive use of either approach (Kochanska et al., 1996).

Nevertheless, some limitations to this study need to be taken into account. A lack of precision regarding the nature and definition of inhibitory control is characteristic of

theoretical models of ADHD and has been highlighted by various authors (Nigg, 2001; von Stauffenberg & Campbell, 2007). It can be difficult to deduce what aspect of inhibitory control are addressed by the various available tasks, but it has been suggested that the two general types of inhibition include inhibition that is under executive control and inhibition that is under motivational control. However, the factor analysis that was performed appeared to separate the tasks to the extent in which they required behavioural regulation and cognitive flexibility and differentiated them from social learning ability (imitation), even though both imitation tasks also entailed suppression of a prepotent response to the affordances of the toys used. The behavioural regulation factor in this respect likely includes both types of inhibition described above. The two tasks that loaded heavily on this factor included the Whisper task, which requires a child to withhold a prepotent response (executive control), and the Raisin task, which likely taps the motivational aspects of inhibition (delay aversion). It is important that the exact nature and components of behavioural inhibition are clarified in future research to increase our understanding in the role that behavioural inhibition clearly plays in the development of ADHD.

There are also clinical limitations to this study, since none of the measures used in this study would be suitable for making a clinical diagnosis. This limitation however does not directly affect the results, since the focus of this thesis is on *symptoms* and/or *precursors* of ADHD. It could be argued however that the reliance on parental reports of children's symptoms of ADHD is a limitation. It was obviously not feasible for children of this age-category to reliably answer or understand questions about psychopathology themselves, whereas reliability for the parental measures that were used has been established repeatedly. Furthermore, parent report measures on the one hand provide a useful account, since they are able to summarise a history of the child's behaviour across multiple settings in a way that would not be possible with more objective observations, which capture a more limited sample

of children's behaviour (Hirshfeld-Becker et al., 2003). This also applies to the informants' reports of activity levels compared with objectively measured levels of activity. The current study however, has used observational methods in a variety of laboratory and home contexts, which increases its ecological validity. Parent report measures on the other hand might be influenced by distortions due to dispositional or emotional biases, parental expectations and a lack of knowledge about how their child compares to peers and subjective judgements can be difficult to standardise between informants (Hirshfeld-Becker et al., 2003). Teachers are considered better informants and combined reports would be most valuable, since they have been found sensitive to detecting clinical change and provide the best approximation to diagnostic status. Whilst collecting teacher reports was not feasible during toddlerhood, an effort was made to include teacher reports of ADHD symptoms in middle childhood.

Overall, it can be concluded that the CCDS sample is a highly representative community sample, in which ADHD symptoms are normally distributed. Some surprising findings were reported, such as no association between infants' informant-reported and measured activity levels, and a lack of gender differences. However, in line with expectations, concurrent associations between ADHD symptoms and cognitive performance in toddlerhood and middle childhood were observed. Finally, the importance of controlling for ODD symptoms was reiterated.

CHAPTER 3.

Are Precursors Similarly Associated with Familial Patterns as ADHD Symptoms in Toddlerhood and Middle Childhood?

3.1 Introduction

3.1.1 Aim of the Chapter

It was shown in Chapter 1 that the literature strongly supports a familial contribution to ADHD. The evidence made it clear that ADHD runs in families; however, the extent to which this influence can be explained by genetic factors as opposed to environmental factors remains unclear (Faraone et al., 1995). Nevertheless, familial symptoms of ADHD are considered a well-established risk factor of ADHD, and parental symptoms of ADHD will therefore be considered as a 'familial' risk factor (regardless whether their effect is genetic, environmental or a combination of both) for the purposes of this thesis. This chapter will test the second criterion of a precursor, namely the requirement that an established risk factor is associated with the precursor in the same way as with the outcome. Within the literature, the term precursor has often been applied to variables that actually should be defined as risk factors. The criterion tested in this chapter will help to differentiate precursors from risk factors and instead identify a precursor as an early form of the outcome.

Another term that is often cited in relation to familial patterns is the term 'endophenotype'. Johnson and colleagues (2015, p.230) defined an 'endophenotype' as a 'heritable attribute that mediates between genetic and behavioural levels of explanation', whereas a precursor was defined as a 'marker that indicates the approach of the disorder'. Others have described endophenotypes as heritable *quantitative* traits that index an

individual's liability to develop or manifest a given disease (Tannock, 2003) and thus act at earlier stages of the pathway from genes to behaviour. For example, it is argued that brain measures have a closer relationship with genes than behavioural ratings, but various inhibitory tasks have also been proposed as endophenotypes for ADHD (Martin, McDougall & Hay, 2008). These measures are also more objective and eliminate rater effects. Psychological theories of ADHD have proposed that neurocognitive (executive functioning) and motivational deficits give rise to the symptoms of ADHD (Sonuga-Barke, 2003), although most empirical studies have found modest effect sizes of group deficits and a substantial overlap between ADHD and non-ADHD samples with some ADHD children performing in the normal range (Nigg et al., 2005). Nonetheless, it has been proposed that impairments in executive function, response inhibition, delay aversion, temporal processing and working memory might function as neurocognitive intermediate phenotypes (Castellanos & Tannock, 2002). It is suggested that genetic factors should influence these neurocognitive deficits, which in turn should be associated with ADHD symptoms (Gottesman & Gould, 2003). The deficits should also be found at a higher rate in unaffected relatives than in the general population (Gottesman & Gould, 2003). This means that some of the outcome variables used in this thesis (i.e. cognitive task performance) might actually be identified as 'endophenotypes' according to these criteria.

In fact, some studies have examined the heritability and co-segregation within families for such cognitive endophenotypes. For example, attention set shifting and stop signal inhibition have been demonstrated to be familial and more frequent in non-affected family members than in controls (Coghill et al., 2005). Response inhibition, measured using the stop signal task, was shown to be familial (Goos, Crosbie, Payne, & Schacher, 2009) and to share genetic risk with ADHD traits (Crosbie et al., 2013). Another study, using a battery of delay-aversion tasks, found that children with ADHD performed worse than their

unaffected sibling, who in turn scored worse than typical controls (Bitsakou, Psychogiou, Thompson, & Sonuga-Barke, 2009). Similarly, several studies using a neuropsychological battery of executive functioning tasks have provided evidence of impairments in unaffected relatives (Doyle, Biederman, Seidman, Reske-Nielsen, & Faraone, 2005; Slaats-Willemse, Swaab-Barneveld, De Sonneville, van der Meulen, & Buitelaar, 2003; Slaats-Willemse, Swaab-Barneveld, De Sonneville, & Buitelaar, 2005). A recent study furthermore found a link between familial (parental) risk and ADHD, which was significantly mediated by inhibitory control and delay aversion deficits (Pauli-Pott et al., 2013). Finally, there are also a few studies that have investigated the influence of the DRD4 7-repeat allele on cognitive functioning in ADHD, but whilst some found poorer performance (Langley et al., 2004; Loo et al., 2008; Mill et al., 2006), others found the opposite result (Bellgrove et al., 2005; Swanson et al., 2000). Taken together, these findings demonstrate that 'executive' inhibitory deficits as well as 'motivational' delay aversion deficits might be considered and have been defined as endophenotypes within the literature. In this chapter familial associations with cognitive performance will be examined, and the results might provide further support for the characterisation of these behavioural measures as 'endophenotypes' (though not as 'precursors').

Throughout this thesis the importance of differentiating terminology is highlighted. The terms 'precursor' and 'endophenotype' (like 'precursor' and 'risk factor') have also been used interchangeably in the literature. However, whilst cognitive deficits in toddlerhood might be defined correctly as 'endophenotypes', according to the criteria set out in this thesis, they cannot be considered as 'precursors'. The most important issue is that they occur simultaneous with the onset of ADHD symptoms, whereas a precursor should precede symptom onset. Secondly, whilst it must be noted that our definition of a precursor partially overlaps the idea of an endophenotype, the criteria that were set out in Chapter 1 for an early

behaviour to classify as a precursor, are more stringent. For a precursor not only association with established 'familial' risk factors and ADHD symptoms are required, but a precursor also needs to 'resemble' the later outcome, relate to other risk factors in a similar way and show continuity over time (Hay et al., 2014). However, it is possible that the precursor tested in this thesis (i.e. high activity levels in infancy) might also meet Gottesman and Gould's (2003) criteria for 'endophenotypes'.

3.1.2 Hypotheses

In line with the literature, it is expected that ADHD symptoms in toddlerhood and middle childhood are significantly associated with mothers' and fathers' symptoms of ADHD. Correlates of ADHD symptoms in toddlerhood and middle childhood are also expected to be associated with parental symptoms of ADHD.

The proposed precursor of high activity levels in infancy is hypothesised to be related to parental symptoms of ADHD in the same manner as the outcome variables (see Figure 3.1). Thus, informant-reported activity levels, as well as measured activity levels during baseline, attention and restraint conditions are expected to be positively associated with familial symptoms of ADHD. This hypothesis is in line with a study that reported that infants with a familial history of ADHD showed an increase in negative vocalisations during an arm restraint task at 6 months of age (Sullivan et al., 2015).

Whilst not directly relevant to the aim of testing precursor behaviours in this thesis, it was noted that endophenotypes might be a valuable tool in the investigation of the familial basis of ADHD. They represent traits that might be more closely linked to underlying genetic factors and represent more objective measures. It is expected that the cognitive tasks examined in toddlerhood and middle childhood are not only associated with concurrent ADHD symptoms (see Chapter 2), but are also significantly associated with parental

symptoms of ADHD. Whilst these variables are considered outcome variables in this thesis, such associations would also support the definition of these variables as 'endophenotypes'. Furthermore, significant associations between activity levels in infancy and familial symptoms of ADHD would not only support the definition of these behaviours as 'precursors', but means these variables could also be considered 'endophenotypes'.

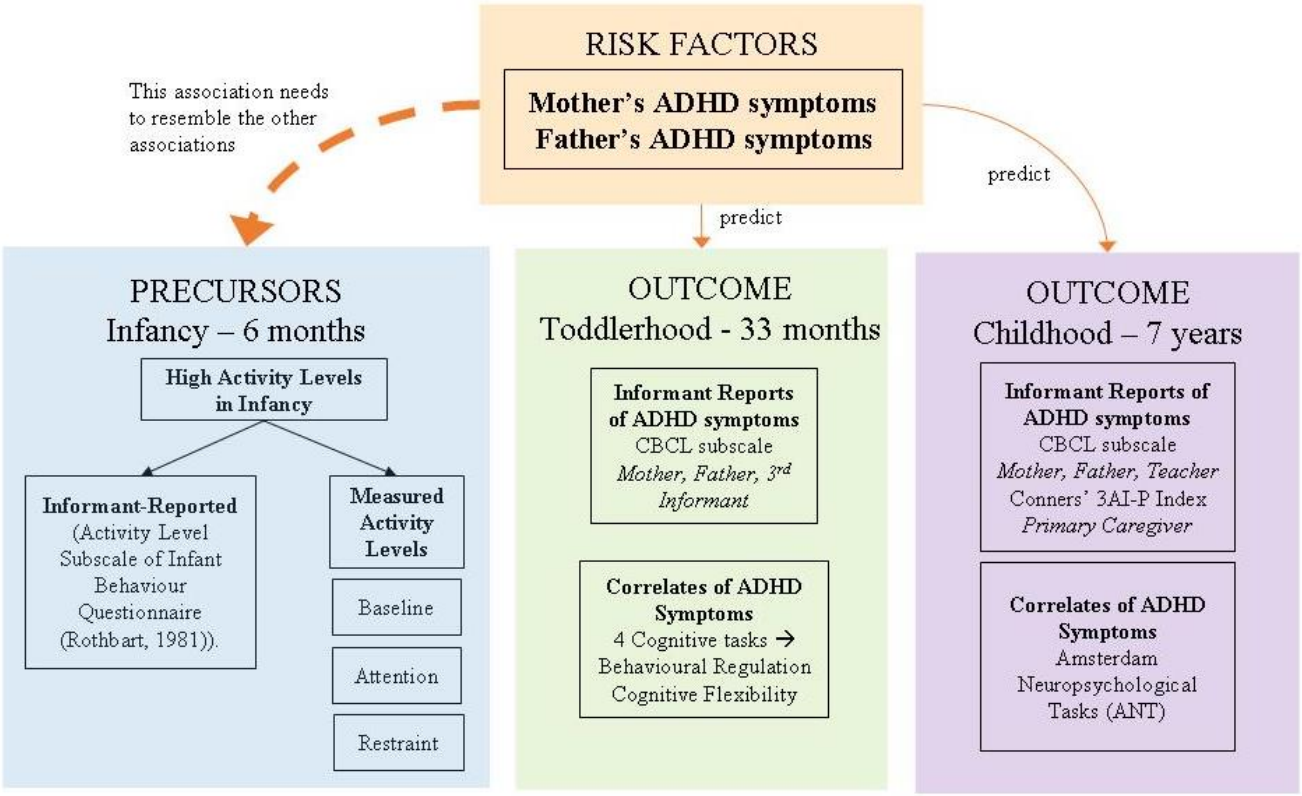


Figure 3.1 Hypothesised relationships between familial risk factors, precursor and outcome variables.

3.2 Method

3.2.1 Participants

This chapter includes the precursor and outcome variables from the first, second, fifth and sixth wave of data collection, which were introduced in Chapter 2. During the prenatal wave of data collection mothers and fathers were asked to complete information on their own

retrospective symptoms of ADHD. This information was available for 332 mothers and 288 fathers.

3.2.2 Procedure

The procedures for the antenatal visit, the six month home assessment, the thirty-three month lab assessment and the home visit at 7 years of age were described extensively in chapter 2 and will therefore not be repeated here. For the purpose of this chapter, responses from mothers and fathers on the 'What I Was Like When I Was Young' Questionnaire that was completed during the first wave of data-collection, were used in addition to the tasks described earlier.

3.2.3 Measures

3.2.3.1 Parental ADHD symptoms. In order to measure parental ADHD symptoms, both fathers and mothers completed the 'What I Was Like When I Was Young' Questionnaire. This questionnaire contained 28 questions, which included 5 items that measured parental DSM-IV ADHD symptoms retrospectively. The questions are given in Table 3.1 and these items could be rated as 'not true (0)', 'somewhat true (1)' or 'certainly true (2)'. If parents had missed out items, the scale score was prorated in order to maximise the sample size. For parents who reported whether they had been diagnosed with ADHD as a child, but who had not completed the questionnaire, a regression analysis was conducted to compute a predicted score. The internal consistency of this scale was acceptable for fathers (α = .66) and good for mothers (α = .70).

Table 3.1 Questions used in the 'What I Was Like When I Was Young' Questionnaire

(1) I was restless and could not stay still for long.
(2) I was constantly fidgeting or squirming.
(3) I was easily distracted and found it difficult to concentrate.
(4) I thought things out before acting on them.
(5) I saw tasks through to the end. My attention was good.

3.2.4 Data Analysis

The screening of violations in assumptions of parametric tests of the precursor and outcome variables was described earlier (see Chapter 2). Non-parametric tests will be used in this chapter for measured activity levels in infancy.

Firstly, association between mothers' and fathers' ADHD symptoms and ADHD symptoms and correlates of ADHD in toddlerhood and middle childhood were examined. Regression analyses were performed to assess the individual contribution of maternal and paternal ADHD symptoms to toddlers' and children's symptoms of ADHD and cognitive task performance, whilst controlling for social risk factors and comorbid ODD symptoms. Analyses were performed firstly using only maternal symptoms, and then repeated using a smaller subsample, where data for the father's history of ADHD symptoms were also available. Secondly, associations between mothers' and fathers' ADHD symptoms and the infancy precursor were investigated. Again, regression analyses were performed (if appropriate) to account for social risk and comorbid ODD symptoms.

It must be noted that in this chapter two familial risk variables were correlated with a social risk variable, a total of five infancy precursor variables and 26 toddler and middle childhood outcome variables, resulting in 64 observed correlations. A significance level of $p < .05$ and $p < .01$ would mean that by chance respectively 3.2 and 0.64 of these correlations would be significant. When a Bonferroni correction is applied, this would mean that only

correlations with $p < .0007$ would be considered significant. This would be extremely conservative and limit the conclusions that can be drawn in this chapter. A less conservative significance-level of $p < .001$ was therefore adopted and reported along with the results using conventional significance-levels. Of course, when interpreting these significance values, it must be remembered that false positives might occur in 3.2 (conventional), 0.64 ($p < .001$) or 0.06 ($p < .001$) of the correlations.

3.3 Results

3.3.1 Associations Between Parental and Toddler's ADHD Symptoms

Mothers' ($M = 3.53$, $SD = 2.27$) and fathers' ($M = 4.33$, $SD = 2.19$) ADHD scores ranged from 0 to 10. Table 3.2 shows that maternal and paternal ADHD symptoms are both significantly related to ADHD symptoms in toddlers, even when a more stringent significance-level is observed. ADHD symptoms in parents are also correlated with each other, suggesting that having one parent with ADHD symptoms increases the likelihood of having a second parent with these symptoms. It must be noted that social risk and ODD symptoms were also significantly associated with ADHD symptoms in mothers, fathers and toddlers.

In order to explore the unique contribution of parental symptoms of ADHD to ADHD symptoms in toddlers, two regression analyses were undertaken (see Table 3.3 and 3.4). Firstly, the influence of mothers' ADHD symptoms was explored, using a sample of 286 participants. In the first step, social risk was accounted for, whilst mothers' ADHD symptoms were entered in the second step. Table 3.3 shows that social risk significantly predicts toddlers' ADHD symptoms, and this relationship remains significant after mothers' ADHD symptoms were added to the model. The addition of mothers' ADHD symptoms to the model

explained additional variance, and mothers' ADHD symptoms show an independent significant effect on toddlers' symptoms of ADHD.

Table 3.2 Pearson's correlations between child ADHD symptoms, social risk, parental ADHD symptoms, cognitive tasks and factor scores.

	Toddler's ADHD symptoms	**Mother's ADHD symptoms**	**Father's ADHD symptoms**
Mother's ADHD symptoms	.20***	-	-
Father's ADHD symptoms	.24***	.17**	-
Raisin task	-.12†	-.08	-.15*
Whisper task	-.11	-.14*	-.08
Big Bear/Little Bear task	-.16*	-.10	-.06
Tower task	-.02	.03	-.03
Behavioural regulation	-.14*	-.16*	-.12†
Cognitive flexibility	-.11†	-.05	-.06
Social Risk Index	.21***	.33***	-.20***
Toddler's ODD symptoms	.54***	.17**	.15*

NB: significance level † < .10 * < .05 ** < .01 *** <.001

Table 3.3 Relationship between mothers' and children's ADHD symptoms.

Predictor	**B coef**	**(95% CI)**	**Beta**	***P***
Social Risk Index[1]	0.12	(0.05 to 0.19)	0.21	<.001**
Social Risk Index	0.09	(0.02 to 0.16)	0.16	.01*
Mother's ADHD symptoms[2]	0.05	(0.01 to 0.10)	0.15	.02*

[1] Dependent variable: Toddlers' ADHD symptoms. N= 286, $R^2 = .04$, $p < .001$
[2] Dependent variable: Toddlers' ADHD symptoms. N= 286, $R^2 = .06$, $p < .001$

Secondly, fathers' ADHD symptoms were added to the analysis, which meant that the sample size was reduced to 254 participants. Table 3.4 shows that the addition of fathers' ADHD symptoms does not affect the relationship between social risk and toddlers' ADHD symptoms, which remained significant. Adding fathers' ADHD symptoms to the model did explain additional variance, with mothers' ADHD symptoms showing an independent

marginal effect and fathers' ADHD symptoms showing a significant effect on toddlers' symptoms of ADHD.

Table 3.4 Relationship between parental and children's ADHD symptoms.

Predictor	**B coef**	**(95% CI)**	**Beta**	***P***
Social Risk Index[1]	0.15	(0.07 to 0.23)	0.23	< .001**
Social Risk Index	0.11	(0.02 to 0.19)	0.16	.01*
Mother's ADHD symptoms	0.04	(-0.004 to 0.09)	0.11	.07†
Father's ADHD symptoms[2]	0.07	(0.03 to 0.12)	0.19	.002**

[1] Dependent variable: Toddlers' ADHD symptoms. N= 254, $R^2 = .05$, $p < .001$
[2] Dependent variable: Toddlers' ADHD symptoms. N= 254, $R^2 = .10$, $p < .001$

A final analysis was performed to determine whether parental ADHD symptoms predicted toddlers' symptoms when ODD symptoms at Wave 5 were taken into account. ODD symptoms explained additional variance ($R^2 = .31$, $p < .001$; $ß = 0.51$, $p < .001$, $N = 228$), nonetheless fathers' ADHD symptoms continued to predict toddlers' symptoms significantly ($R^2 = .33$, $p = .02$; $ß = -0.13$, $p = .02$), whilst the effect of mothers' ADHD was no longer significant ($ß = 0.09$, $p = .11$).

3.3.2 Parental ADHD Symptoms and Toddler's Cognitive Task Performance

Table 3.2 shows that children's ADHD symptoms are marginally related to poorer performance on the raisin task and significantly correlated with poorer performance on the Big Bear/Little Bear task. Fathers' symptoms of ADHD were associated with toddlers' poorer performance on the Raisin task, whilst mothers' symptoms of ADHD were related to children's poorer scores on the Whisper task. The factor scores, derived from the principal components analysis described in Chapter 2 are also displayed. Table 3.2 shows that the behavioural regulation factor is significantly associated with mothers' ADHD symptoms and marginally with fathers' ADHD symptoms. The cognitive flexibility factor did not show any relationship with parental symptoms of ADHD. It must alos be noted that when a more

stringent significance-level is applied, no significant correlations between parental ADHD symptoms and toddler's cognitive performance are found.

Two regression analyses were performed (see Tables 3.5 and 3.6), which revealed that when social risk factors are taken into account, mothers' ADHD symptoms remain a significant predictor of children's behavioural regulation (see Tables 3.5 and 3.6), whilst fathers' ADHD symptoms only show a marginally significant effect (see Table 3.6).

Table 3.5 Relationship between maternal ADHD symptoms and behavioural regulation.

Predictor	**B coef**	**(95% CI)**	**Beta**	***P***
Social Risk Index[1]	0.05	(-0.05 to 0.12)	0.07	.30
Social Risk Index	0.09	(-0.01 to 0.19)	0.12	.07†
Mother's ADHD symptoms[2]	-0.09	(-0.14 to -0.03)	-0.20	.004*

[1] Dependent variable: Behavioural Regulation. N= 231, R^2 = .01, p = .30
[2] Dependent variable: Behavioural Regulation. N= 231, R^2 = .04, p = .01

Table 3.6 Relationship between parental ADHD symptoms and behavioural regulation.

Predictor	**B coef**	**(95% CI)**	**Beta**	***P***
Social Risk Index[1]	0.03	(-0.06 to 0.13)	0.04	.58
Social Risk Index	0.09	(-0.002 to 0.19)	0.11	.14
Mother's ADHD symptoms	-0.08	(-0.15 to -0.02)	-0.18	.01*
Father's ADHD symptoms[2]	-0.05	(-0.12 to 0.01)	-0.12	.09†

[1] Dependent variable: Behavioural Regulation. N= 211, R^2 = .002, p = .58
[2] Dependent variable: Behavioural Regulation. N= 211, R^2 = .05, p = .02

A final analysis was performed to determine whether parental ADHD symptoms predicted toddlers' behavioural regulation when ODD symptoms at Wave 5 were taken into account. ODD symptoms did not significantly explain additional variance (R^2 = .02, p = .07; $ß$ = -.13, p = .07, N = 195), and mothers' ADHD symptoms continued to predict toddlers' behavioural regulation significantly (R^2 = .06, p = .02; $ß$ = -0.17, p = .02), whilst the effect of fathers' ADHD symptoms was no longer significant ($ß$ = -0.11, p = .13).

3.3.3 Associations Between Parental and ADHD Symptoms in Middle Childhood

Associations between parental ADHD symptoms and childhood symptoms of ADHD are shown in Table 3.7. Mothers' and fathers' ADHD symptoms significantly predicted symptoms of ADHD in middle childhood, even when more stringent significance-levels were applied. Fathers' ADHD symptoms also significantly predicted tester's ratings of their child's attentiveness, whilst a marginal effect of mothers' symptoms of ADHD was found.

Table 3.7 Correlations between social, familial and perinatal risk factors and informants' ratings of ADHD symptoms at age 7.

	Childhood ADHD	TRCB activity	TRCB attentiveness
Social Risk Index	.33***	.04	-.15*
Mother's ADHD symptoms	.31***	.04	-.13†
Father's ADHD symptoms	.29***	.12	-.16*

NB: significance level † < .10, * < .05, ** < .01, ***<.001.

A two-step regression analysis was performed for childhood ADHD symptoms. After controlling for social risk (R^2 = .09, p < .001), parental ADHD symptoms significantly explained additional variance (R^2 = .21, p < .001, N = 181), with both mothers' ($ß$ = 0.27, p < .001) and fathers' ADHD symptoms ($ß$ = 0.22, p = .002) showing a significant independent effect on middle childhood symptoms of ADHD. A final three step regression analysis was performed to account for concurrent ODD problems at age 7. Parental symptoms of ADHD explained additional variance (R^2 = .52, $R^2change$ = .03, p < .01, N = 181) and mothers' ADHD symptoms remained a significant predictor ($ß$ = 0.17, p < .01), whilst a marginal effect of fathers' ADHD symptoms remained ($ß$ = 0.09, p < .10).

3.3.4 Parental ADHD Symptoms and Cognitive Task Performance in Middle Childhood

It can be seen in Table 3.8 that mothers' and fathers' ADHD symptoms were not as strongly associated with cognitive task performance compared with ADHD symptoms in the

children themselves (see Chapter 2, section 2.3.8). Nevertheless, some associations were observed, particularly for fathers' symptoms of ADHD. These were related to poor performance on the set shifting task (cognitive flexibility), the sustained attention and the working memory task. Mothers' symptoms of ADHD were related to poor performance on the working memory task, but no associations were observed for other tasks. Few of these correlations would remain if a more stringent significance level is observed.

Table 3.8 Parental ADHD symptoms and cognitive task performance in middle childhood.

	Social Risk	**Mothers ADHD symptoms**	**Fathers' ADHD symptoms**
Baseline Speed Task			
M reaction time	.03	-.02	.08
SD reaction time	.08	-.03	.08
Premature responses	.14†	.07	.14†
Set Shifting Task			
Errors compatible	.13†	.04	.21**
Errors incompatible	.20**	-.12†	.26***
Errors mixed	.16*	.05	.18*
Premature responses	.11	.02	.11
M reaction time fixed	-.004	-.01	.06
M reaction time mixed	.06	.10	.09
Pursuit Task			
M distance to target	.15†	.11	.17*
SD distance to target	.07	.07	.15†
Working Memory Task			
N targets	-.10	-.14†	-.18*
N targets in order	-.24***	-.23***	-.20*
Delay Frustration Task			
N mouse-clicks	.05	.09	.02
M duration mouse-clicks	-.01	.09	.04

NB: significance level * < .05 ** < .01 ***<.001, † < .10.

3.3.5 Parents' ADHD Symptoms and Infants' Activity Levels

Table 3.9 shows that mothers' and fathers' ADHD symptoms were unrelated to their infants' informant-reported activity levels at 6 months of age. Fathers' symptoms of ADHD were significantly related to a reduction in activity levels at 6 months during baseline and increased activity levels during restraint (but only when baseline activity levels were

controlled for). Mothers' symptoms were not related to measured activity levels in infancy. Social risk was unrelated to measured or informant-reported activity levels. None of the observed correlations are significant, if a more stringent significance-level is applied.

Table 3.9 Spearman's rho correlations between parental ADHD symptoms and activity levels at the 6 month and the 33 months assessment (with Pearson's correlations for the IBQ activity scale).

	Social Risk Index	**Mother's ADHD symptoms**	**Father's ADHD symptoms**
Informant reported activity levels at 6 months	.02	.04	.07
Measured Activity levels at 6 months			
Baseline	-.003	-.11†	-.18**
Attention	-.02	.06	-.03
Restraint	.02	.02	.05 (.16*)
W2 activity factor	-.06	-.10	-.08

NB: significance level * < .05 ** < .01 *** < .001, † < .10; values in brackets represent correlations with activity levels when baseline levels are taken into account.

3.4 Discussion

In order to test whether the proposed precursor in infancy met the second criterion of association with well-established risk factors of ADHD, this chapter looked at the relationship between parental symptoms of ADHD and infants' activity levels. Firstly, it was established that toddlers' and children's symptoms of ADHD were associated with mothers' and fathers' symptoms of ADHD (even when social risk and ODD symptoms were taken into account). Some cognitive correlates of ADHD symptoms in toddlerhood and middle childhood were also associated with familial symptoms of ADHD. However, these patterns were not replicated for the precursor. Informant-reported activity levels were not associated with parental ADHD symptoms. Measured activity levels were negatively associated with fathers' ADHD symptoms, whilst a positive association between infants' high activity levels and fathers' ADHD symptoms was observed during the restraint condition only when baseline activity levels were controlled for. No association between measured activity levels and mothers' symptoms of ADHD were found.

These results indicate that informant-reported activity levels do not meet the second criterion of a precursor. They are not associated with the well-established familial risk factor of ADHD. A lack of clinically significant ADHD symptoms in this population cannot explain this finding, given that significant associations are observed between parents' and children's ADHD symptoms. Measured activity levels did not relate to mothers' symptoms of ADHD. Fathers' symptoms could be related to higher activity levels during the restraint condition, which means that the criterion is partially supported for this precursor. However, caution is needed, given that mothers' symptoms were not related to activity levels during this condition. It is not clear why during the baseline condition fathers' symptoms were related to a reduction in activity level in infants. This association was unexpected and it is difficult to draw any conclusions as to what might explain this negative relationship.

The lack of association between infants' activity levels and familial symptoms of ADHD not only means that the second criterion for a precursor is not met, it also implicates that these variables cannot be considered 'endophenotypes'. It was explained that some variables that cannot be considered precursors might qualify as endophenotypes. In this chapter it was shown that mothers' ADHD symptoms related significantly to children's cognitive task performance, in particular with the behavioural regulation factor score, which was also marginally related to fathers' ADHD symptoms. When social risk and ODD symptoms were controlled for, mothers' ADHD symptoms remained a significant predictor of children's behavioural regulation, with fathers' ADHD symptoms maintaining a marginally significant effect. Given that behavioural regulation was also significantly associated with concurrent symptoms of ADHD (see Chapter 2, section 2.3.5), it might possibly be considered as an 'endophenotype' for genetically informative studies.

It is also interesting to note that whilst social risk is associated with children's scores on the ADHD subscale of the CBCL, no relationship between behavioural regulation and

social risk was found. Neurocognitive endophenotypes are argued to be more closely associated with structural brain circuitries, and are therefore less likely to be influenced by social risk than the more behavioural aspects of an ADHD diagnosis. This might explain why maternal and paternal ADHD, but not social risk factors, are predictive of impairments in behavioural regulation. These findings support its use as an endophenotype further.

In middle childhood, fathers' symptoms of ADHD predicted poor performance on the set shifting task (cognitive flexibility), the sustained attention task and the working memory task. Mothers' symptoms were related to poor performance on the working memory task only. Poor performance on these tasks (as well as premature responses) was also related to concurrent ADHD symptoms (see Chapter 2, section 2.3.8), meaning that this study supports their conceptualisation as 'endophenotypes'.

It is an interesting finding that parents' ADHD symptoms were related to each other. This might be an indication of assortative mating, where an individual chooses a partner who is similar to themselves in a certain characteristic or trait. The influence of assortative mating might of course lead to an increase in the genetic vulnerability of children to develop ADHD, but it might also enhance the environmental effect of having a parent with ADHD.

As was discussed above, the effect of parental ADHD symptoms might not only be due to an increased genetic vulnerability, but it could also be due to an environmental effect of parenting style. Whilst this study highlights the familial nature of ADHD, it must be noted that the measures of ADHD symptoms in parents provide an inadequate method to control for genetic effects. Whilst social risk factors were controlled for, the current study did not examine the influence of parenting styles and practices. As a result no inferences can be made about whether, in this sample, the influences of parental symptoms were due to a genetic or an environmental effect. In future it might be interesting to test these causal hypotheses in the context of a genetically informed design. However, for the purposes of gaining confidence in

our definition of early behaviours as precursors, the analyses undertaken in this chapter are sufficient.

A potential limitation of this study is that information about parental ADHD symptoms was obtained retrospectively. A distiction between remitted and persistent symptoms of ADHD in parents would have allowed for differentiation between more genetic influences of remitted ADHD and the additive environmental effect of persistent ADHD in parents. Despite these limitations, it can be concluded that the findings were in line with the literature and support a familial contribution to ADHD symptoms. The second criterion for a precursor was not met (summarised in Figure 3.2). Informant-reported and measured activity levels were not consistently associated with mothers' and fathers' ADHD symptoms. Behavioural regulation deficits in toddlerhood as well as poor performance on executive functioning tasks in middle childhood were associated with parental as well as children's symptoms of ADHD, supporting the use of these task as endophenotypes.

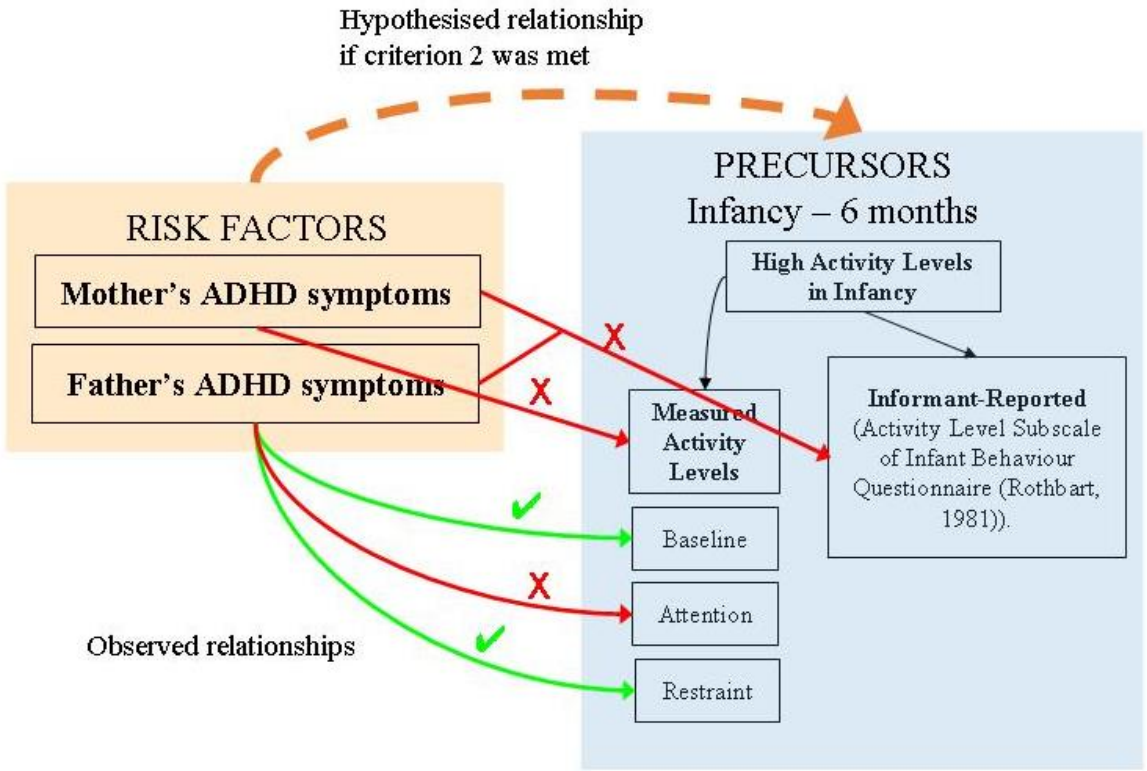


Figure 3.2 Hypothesised and observed relationship between familial risk and the precursor.

CHAPTER 4.

Do Perinatal Risk Factors Show Similar Associations with Precursors and ADHD Symptoms?

4.1 Introduction

4.1.1 Aim of the Chapter

In addition to familial risk associated with ADHD, a second important source of risk was identified in Chapter 1. Intrauterine and perinatal circumstances can have a detrimental effect on early brain development and have repeatedly been associated with ADHD (Barkley, 2006). However, inconsistent findings within this literature meant that only a limited number of perinatal risk factors were suited to our aim of validating high activity levels in infancy as a precursor of ADHD symptoms.

Whilst any conclusions regarding causality would be premature, three types of perinatal variables are regarded as well-established risk factors (see section 1.2 for a discussion of the difference between causal factors and risk factors), meaning that these factors have consistently been shown to raise the *probability* of developing ADHD symptoms. Firstly, exposure to prenatal smoking was shown to increase the risk of developing ADHD symptoms, suggesting a dose-response-like association (Biederman, Monuteaux, Faraone, & Mick, 2008; Kotimaa et al., 2003; Linnet et al., 2003; Thapar et al., 2003). Secondly, prenatal stress was identified as a risk factor, since mother-reported stress and/orcortisol-exposure during pregnancy has consistently been shown to increase the risk of ADHD symptoms in offspring. Finally, birth weight was identified as a well-established risk factor. It is unclear exactly how these risk factors affect the development of hyperactivity, impulsivity and attention problems; however, all factors might be in line with the

programming hypothesis, i.e., the claim that foetal adaptation to a non-optimal environment permanently increases offspring's susceptibility to a variety of disorders later in life (Barker, 1998, 2004). Other theories explain the increased risk through specific effects of nicotine (Curatolo, Polascia, D'Agati, Moavero, & Pasini, 2008) and cortisol exposure on foetal brain development (de Weerth & Buitelaar, 2005; Rice et al., 2009). Whilst these theories makes it plausible that these risk factors play a causal role, for our purpose of assessing whether activity levels in infancy are associated with these risk factors. In a similar way, later symptoms of ADHD in toddlerhood and middle childhood are not necessarilly needed to demonstrate that the observed associations represent causal effects.

4.1.2 Hypotheses

In line with the literature, it is expected that ADHD symptoms in toddlerhood and middle childhood are significantly associated with increased exposure to smoking, stress exposure during pregnancy and reduced birth weight. Correlates of ADHD symptoms in toddlerhood and middle childhood are expected to relate to these risk factors in the same way.

The proposed precursor of high activity levels in infancy is hypothesised to be related to the perinatal risk factors in the same manner as the outcome variables (see Figure 4.1). Informant-reported activity levels, as well as measured activity levels during baseline, attention and restraint conditions are expected to be positively associated with exposure to smoking and stress during pregnancy; whilst a negative relationship with birth weight is expected.

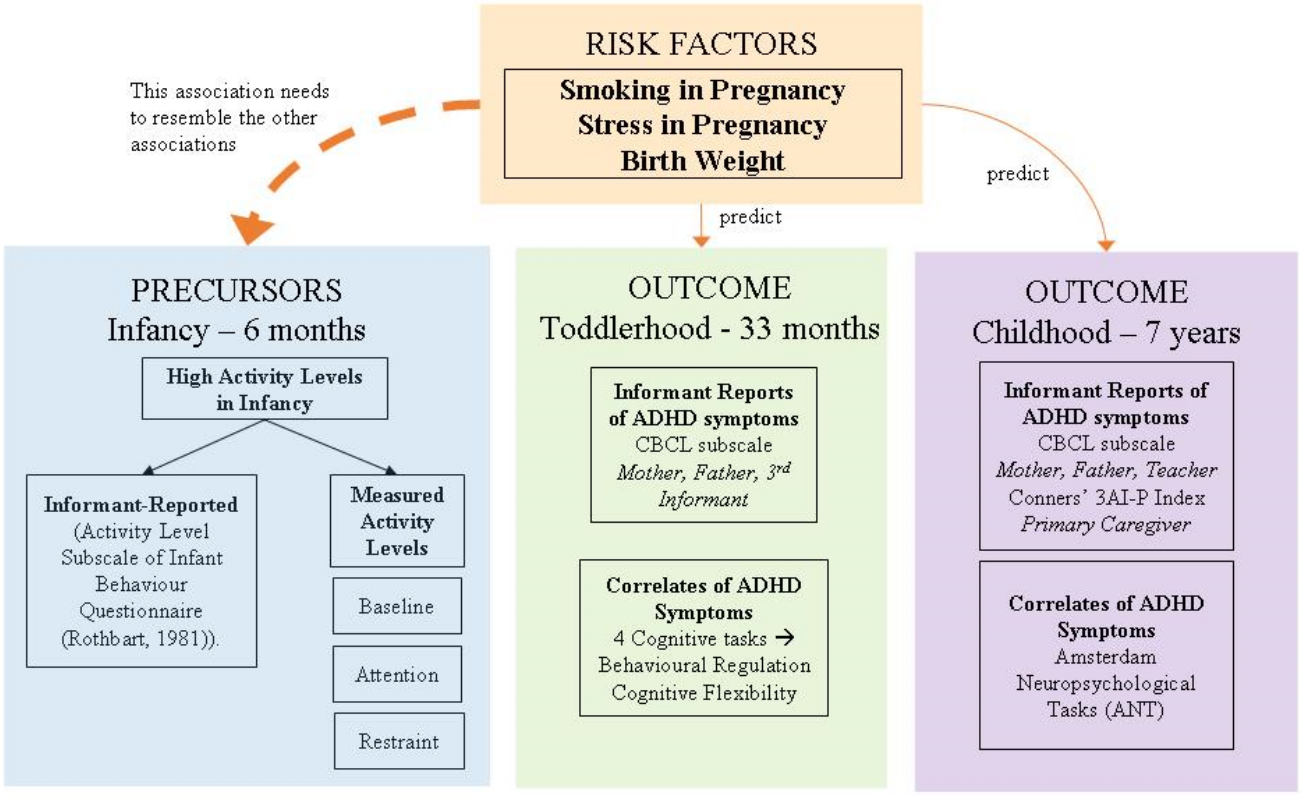


Figure 4.1 Hypothesised relationships between perinatal risk factors, precursor and outcome variables.

4.2 Method

4.2.1 Participants

Because of missing data on particular variables, the number of participants throughout this thesis varies depending on the type of data that is included in the analyses. This chapter includes variables from the first, second, fifth and sixth wave of data collection. During the prenatal wave of data collection as well as at the first home visit (Wave 2) mothers were asked to complete a number of pregnancy-related questions. This information was available for 332 mothers at Wave 1 and 305 mothers at Wave 2.

4.2.2 Procedure

The procedures for the antenatal visit, the six month home assessment, the thirty-three month lab assessment and the home visit at 7 years of age were described extensively in chapter 2. For the purpose of this chapter some additional variables were used in addition to the tasks described earlier.

Firstly, information from questionnaires and interview data collected during the antenatal visit was used. Mothers were asked questions, which covered socio-economic risk factors, familial and personal medical history, measures of parental psychopathology and their pregnancy. Pregnancy-related questions covered areas such as their consumption of toxins during different stages of their pregnancy (smoking, alcohol and drugs), their psychological (stress, psychopathology) and physical health (illnesses, complications, medication taken, etc.). These data were collected prospectively during pregnancy in order to minimise the risk of recall bias.

During the six-month assessment, a tape-recorded interview was conducted with the mother, concerning questions surrounding the last part of the pregnancy, the labour and the health and development of the baby during the first six months of life. Information on birth weight was also collected at this stage. Only the information regarding smoking and stress during pregnancy and birth weight was used in this chapter (however, see Appendix II for information on intercorrelations between perinatal circumstances and additional analyses).

4.2.3 Measures

4.2.3.1 Prenatal stress. Mothers were asked about prenatal stress during each trimester, which was measured using an 11-point Likert scale adapted from Rice et al. (2009) (see Figure 4.2). Missing data were imputed using predicted scores based on diagnoses for depression during pregnancy. Diagnoses were made in consultation with a psychiatrist on the

basis of the maternal interview during pregnancy, which included the affect disorder section of the Schedules for Clinical Assessment in Neuropsychiatry (Wing et al., 1990).

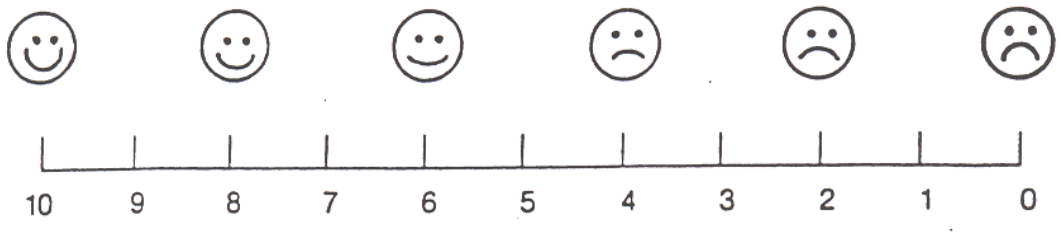


Figure 4.2 Likert scale used to determine stress levels during each trimester.

4.2.3.2 Smoking during pregnancy. The pregnant women were asked at Wave 1 to report on substances that they were using during their pregnancy. They were asked to report the number of cigarettes smoked per day for the three semesters of pregnancy.

4.2.3.3 Measurement of birth weight and gestational age. The children in this sample had an average birth weight of 3.37 kg (*SD* = 0.48, range 1.84 to 4.76) and an average gestational age of 40.06 weeks (*SD* = 1.63, range 32 to 43 weeks), which is comparable with those found in the general population. It was found that birth weight and gestational age were correlated strongly (r = .48, p < .001); however Figure 4.3 shows that much variability in birth weight still exists for each gestational age. There are children born prematurely (gestational age below 37 weeks) who show a normal birth weight, whilst some children born within the normal range could be classified as low birth weight (< 2500 grams). Standardised scores for birth weight (adjusted for gestational age and gender) were therefore used in this study in order to establish the true relationship between birth weight and subsequent behavioural problems.

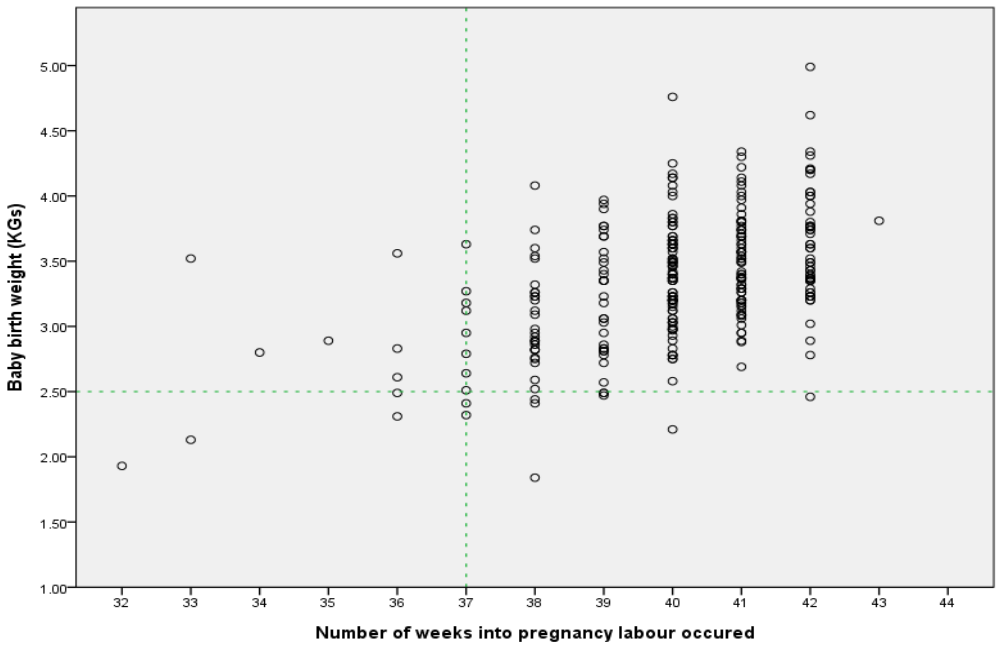


Figure 4.3 Relationship between birth weight and gestational age.

4.2.3.4 Parental Symptoms of ADHD. In order to maximise the sample size, measures of maternal and paternal ADHD symptoms were combined to create a composite variable, which represented familial risk of ADHD symptoms across caregivers. This variable was constructed by averaging maternal and paternal scores on the ADHD subscale, which had been completed as part of the 'What I Was Like When I Was Young' questionnaire at Wave 1 (see Chapter 3, section 3.2.3.1). If only maternal ADHD symptoms were available, this score was included.

4.2.4 Data Analysis

The screening of violations in assumptions of parametric tests of the precursor and outcome variables was described earlier (see Chapter 2). Non-parametric tests will be used in this chapter for measured activity levels in infancy.

Association between perinatal risk factors and ADHD symptoms and correlates of ADHD in toddlerhood and middle childhood were examined first. Regression analyses were

performed to assess the individual contribution of perinatal risk factors to toddlers' and children's symptoms of ADHD and cognitive task performance, whilst controlling for social risk factors, familial risk factors and comorbid ODD symptoms. Analyses were performed firstly using only maternal symptoms, and then repeated using a smaller subsample, where data for the father's history of ADHD symptoms were also available. Secondly, Pearson's and Spearman's rho correlations between perinatal risk factors, and reported and measured activity levels in infancy were examined. Again, regression analyses were performed (if appropriate) to account for social risk and comorbid ODD symptoms.

It must be noted that in this chapter 7 perinatal variables were correlated with a total of 5 infancy precursor variables and 27 toddler and middle childhood outcome variables, resulting in 224 observed correlations. A significance level of $p < .05$ or $p < .01$ would mean that by chance respectively 11.2 or 2.24 of these correlations would be significant. When a Bonferroni correction is applied, this would mean that only correlations with $p < .0002$ would be considered significant. This would be extremely conservative and limit the conclusions that can be drawn in this chapter. A less conservative *p*-value of $p < .001$ was therefore adopted and reported along with the results using conventional *p*-values without correction. Of course, when interpreting these significance values, it must be remembered that false positives might occur in 11.2 (conventional), 2.24 ($p < .01$) or 0.22 ($p < .001$) of the correlations.

4.3 Results

Depression during pregnancy was found in 53 mothers (16%), whilst 79 mothers smoked during pregnancy (23.8%) (see Table 4.1). The stress scores (with missing values

imputed using predicted scores) and the number of cigarettes smoked declined over the course of pregnancy.

Table 4.1 Descriptive statistics of perinatal risk factors.

Variable		**Descriptive statistics**
Stress in pregnancy	*Mean, SD (range)*	
N = 332	*First trimester*	4.80, 2.56 (0-10)
	Second trimester	3.44, 2.12 (0-10)
	Third trimester	2.98, 2.16 (0-10)
Smoking in pregnancy	*Yes*	79 (23.8%)
N = 316	*No*	237 (71.4%)
Number of cigarettes*	*Mean, SD (range)*	
N = 79	*First trimester*	9.49, 6.01 (0-30)
	Second trimester	6.01, 6.23 (0-30)
	Third trimester	4.57, 5.36 (0-20)
Birth Weight	*Mean, SD (range)*	3.37 kg,0.48 (1.84-4.76)
Gestational Age	*Mean, SD (range)*	40.06 weeks, 1.63 (32-43)

*average number of cigarettes for smokers (*N* = 79), subsequent analyses included number of cigarettes for all mothers who reported their smoking behaviour, including non-smokers (*N* = 316; *M* trim1= 2.33 (*SD* =5.18); *M* trim2 = 1.47 (*SD* =4.02); *M* trim3= 1.11 (*SD* =3.28)).

4.3.1 Associations between Perinatal Risk Factors and Toddler's ADHD symptoms and correlates

Table 4.2 shows that toddlers' ADHD symptoms were significantly associated with smoking throughout pregnancy and increased levels of stress during mid and late pregnancy. Birth weight was not associated with toddlers' ADHD symptoms. It must be noted that these risk factors were also significantly related to toddler's ODD symptoms. When a more stringent significance level is observed, only the correlation between toddlers' ADHD symptoms and cigarettes in mid-pregnancy and stress in late-pregnancy can be considered significant.

In order to further explore the independent contribution of each risk factor to the development of ADHD, a regression analysis was undertaken (see Table 4.3). Social risk was entered at the first step. Social risk significantly predicted toddlers' ADHD symptoms; however this effect did not remain when other risk factors were added to the model. In the second step, parental symptoms of ADHD were entered into the model and explained

additional variance. A third step included toddlers' ODD symptoms, which were strongly associated with toddlers' ADHD symptoms. In a final step obstetric data were added, including smoking (pregnancy average) and stress in mid and late pregnancy (averaged). These risk factors did not explain any additional variance, and did not show any independent effect on toddlers' ADHD symptoms. Since birth weight was not significantly associated with ADHD symptoms, it was not included in the analysis.

Table 4.2 Pearson's correlations between risk factors and toddlers' ADHD symptoms.

	Toddlers' ADHD symptoms	**Toddlers' ODD symptoms**
Cigarettes early pregnancy	.13*	.13*
Cigarettes mid pregnancy	.19***	.16*
Cigarettes late pregnancy	.12*	.10
Stress early pregnancy	.03	.13*
Stress mid pregnancy	.12*	.16**
Stress late pregnancy	.19***	.24***
Birth weight [a]	-.09	-.10

NB: significance level † < .10 ,* < .05 ** < .01 *** < .001.
[a] Birth weight was adjusted for gestational age

Table 4.3 Relationship between risk factors and toddlers' ADHD symptoms.

Predictor	**B coef**	**(95% CI)**	**Beta**	***P***
Social Risk Index[1]	0.13	(0.06 to 0.20)	0.21	.001**
Social Risk Index	0.08	(0.01 to 0.16)	0.14	.03*
Parental ADHD[2]	0.12	(0.06 to 0.18)	0.25	.001**
Social Risk Index	0.06	(-0.002 to 0.13)	0.10	.06†
Parental ADHD	0.08	(-0.03 to 0.13)	0.16	.004**
Toddlers' ODD Symptoms[3]	0.53	(0.41 to 0.64)	0.49	.001**
Social Risk Index	0.06	(-0.10 to 0.08)	0.10	.12
Parental ADHD	0.08	(-0.05 to 0.06)	0.16	.01*
Toddlers' ODD Symptoms	0.52	(0.02 to 0.11)	0.49	.001**
Mean # cigarettes pregnancy	0.002	(-0.02 to 0.06)	0.01	.90
Stress mid/late pregnancy[4]	0.01	(-0.03 to 0.05)	0.02	.76

[1] Dependent variable: Toddlers' ADHD symptoms. N= 254, R^2 = .04, p = .001
[2] Dependent variable: Toddlers' ADHD symptoms. N= 245, R^2 = .10, p < .001
[3] Dependent variable: Toddlers' ADHD symptoms. N= 254, R^2 = .33, p < .001
[4] Dependent variable: Toddler's ADHD symptoms. N= 254, R^2 = .33, p = .94

Finally, in Table 4 the correlations between the perinatal risk factors and toddlers' cognitive correlates of ADHD symptoms are shown. This table shows that behavioural regulation and cognitive flexibility scores at 33 months were not related to perinatal risk factors.

Table 4.4 Correlations between perinatal risk factors and toddlers' cognitive performance.

	Raisin	Whisper	BBLB	Tower	Behavioural Regulation	Cognitive Flexibility
Cigarettes early pregnancy	.03	-.01	-.07	.07	.02	.01
Cigarettes mid pregnancy	.01	.06	-.09	.002	.04	-.06
Cigarettes late pregnancy	.03	.01	-.08	-.003	.03	-.05
Stress early pregnancy	.06	-.03	.004	.002	.02	.01
Stress mid pregnancy	-.01	-.02	-.07	-.03	-.03	-.04
Stress late pregnancy	-.05	-.02	-.10	.03	-.07	-.05
Birth weight[1]	-.04	.09	.02	.01	.05	.03

NB: significance level † < .10 * < .05 ** < .01, *** <.001.
[1] birth weight was adjusted for gestational age

4.3.2 Associations Between Perinatal Risk Factors and ADHD Symptoms in Middle Childhood

Next, associations between the perinatal risk factors and childhood symptoms of ADHD were explored (see Table 4.5). Smoking in mid-pregnancy, stress in mid- and late pregnancy and birth weight significantly predicted symptoms of ADHD in middle childhood. Tester's ratings of activity were not predicted by perinatal risk factors; however, ratings of attentiveness were significantly predicted by smoking in mid-pregnancy and stress in late pregnancy; whilst marginal correlations with smoking in early and late pregnancy and stress in mid-pregnancy were found. When a more stringent significance-level is observed, only the correlation between ADHD symptoms and stress in late-pregnancy can be considered significant.

When social risk, parental ADHD symptoms and children's ODD symptoms were taken into account, only a marginally significant independent effect of stress in mid- and late pregnancy was found (see Table 4.6). Smoking in pregnancy and birth weight were no longer associated with ADHD symptoms in middle childhood.

Table 4.5 Correlations between perinatal risk factors and informants' ratings of ADHD symptoms at age 7.

	Childhood ADHD symptoms	TRCB activity	TRCB attentiveness	Childhood ODD symptoms
Cigarettes early pregnancy	.14†	.05	-.14†	.07
Cigarettes mid pregnancy	.16*	.05	-.14*	.14†
Cigarettes late pregnancy	.08	.05	-.13†	.05
Stress early pregnancy	-.06	.07	.02	-.02
Stress mid pregnancy	-.24**	-.07	.14†	.15*
Stress late pregnancy	-.31***	.07	.19*	.20**
Birth weight[1]	-.14*	-.01	.10	-.08

NB: significance level † < .10, * < .05, ** < .01, *** < .001.
[1] birth weight was adjusted for gestational age

Table 4.6 Relationship between risk factors and childhood ADHD symptoms.

Predictor	B coef	(95% CI)	Beta	*P*
Social Risk Index[1]	0.21	(0.11 to 0.30)	0.30	<.001***
Social Risk Index	0.13	(0.03 to 0.23)	0.19	.01*
Parental ADHD[2]	0.14	(0.07 to 0.22)	0.27	<.001***
Social Risk Index	0.07	(-0.01 to 0.15)	0.11	.07†
Parental ADHD	0.08	(0.01 to 0.14)	0.14	.02*
ODD symptoms middle childhood[3]	0.63	(0.51 to 0.74)	0.60	<.001***
Social Risk Index	0.09	(-0.001 to 0.17)	0.12	.05†
Parental ADHD	0.07	(0.002 to 0.13)	0.12	.04*
ODD symptoms middle childhood	0.61	(0.49 to 0.72)	0.58	<.001***
Cigs mid-pregnancy	-0.02	(-0.04 to 0.01)	-0.06	.30
Stress mid/late pregnancy	-0.06	(-0.002 to 0.12)	.11	.06†
Birth weight[4]	-.06	(-0.16 to 0.05)	-.06	.30

[1] Dependent variable: Childhood ADHD symptoms. N= 189, R^2 = .09, p < .001
[2] Dependent variable: Childhood ADHD symptoms. N= 189, R^2 = .15, p < .001
[3] Dependent variable: Childhood ADHD symptoms. N= 189, R^2 = .48, p < .001
[4] Dependent variable: Childhood ADHD symptoms. N= 189, R^2 = .50, p = .12

4.3.3 Perinatal Risk Factors and Performance on Executive Function Tasks in Middle Childhood

It can be seen in Table 4.7 that smoking during the first trimester predicted premature responses during the baseline speed task significantly. Smoking during pregnancy was also negatively related to performance on the working memory task. Stress during the second trimester predicted longer and more variable reaction times during the baseline speed task,

increased errors and longer reaction times on the set shifting task and reduced performance on the working memory task. Stress during the third trimester was associated with increased premature responses during the baseline speed task and increased errors and reaction times during the set-shifting task. Finally, lower birth weight predicted poorer performances on the sustained attention and working memory task. It must be noted that when a more stringent *p*-value is observed, none of these correlations can be considered significant.

Table 4.7 Perinatal risk factors and executive function task performance in middle childhood.

	Smoke 1st trim.	**Smoke 2nd trim.**	**Smoke 3rd trim.**	**Stress 1st trim.**	**Stress 2nd trim.**	**Stress 3rd trim.**	**Birth Weight**
Baseline Speed Task							
M reaction time	-.07	-.02	-.07	-.01	.16*	.03	.13†
SD reaction time	.01	-.02	-.05	-.04	.18*	.06	.14†
Premature responses	.19**	.09	.10	-.07	.14†	.17*	-.08
Set Shifting Task							
Errors compatible	.10	.04	.05	-.05	.15*	.20*	-.10
Errors incompatible	.06	.03	.02	-.03	.06	-.06	-.03
Errors mixed	.05	-.001	-.09	.09	.09	.04	.02
Premature responses	.09	.05	.01	-.10	-.02	.07	-.09
M reaction time fixed	.004	.01	.002	.01	.13†	.11	-.06
M reaction time mixed	-.04	-.08	-.05	.13†	.17*	.18*	.01
Pursuit Task							
M distance to target	-.02	.02	-.05	.02	.10	.04	-.21**
SD distance to target	-.09	-.04	-.07	.004	.11	.03	-.21**
Working Memory Task							
N targets	-.12	-.08	-.03	.01	-.08	-.07	.18*
N targets in order	-.20**	-.17*	-.12	.05	-.18*	-.10	.13†
Delay Frustration Task							
N mouse-clicks	-.02	.04	.04	.06	.03	.05	.07
M duration mouse-clicks	-.03	.03	-.01	.06	.03	.07	.09

NB: significance level † < .10, * < .05, ** < .01, *** <.001.

4.3.4 Perinatal Risk Factors and Infants' Activity Levels

Table 4.8 shows that the number of cigarettes smoked and stress levels during late gestation are significantly associated with informant-reported activity levels at 6 months of age. A significant negative relationship between the number of cigarettes smoked in early pregnancy and measured activity levels during baseline was found. Measured activity levels during

attention and restraint were not related to perinatal risk factors. It must also be noted that when a more stringent significance-level is observed, none of the correlations with activity levels in infancy can be considered significant.

In order to further explore the independent contribution of these risk factors to informant-reported activity levels at 6 months of age, several regression analyses were undertaken, particularly in order to control for social risk (step 1) and parental ADHD symptoms (step 2). It was found that adding stress in late pregnancy and the number of cigarettes smoked in late pregnancy explained additional variance, and remained significant predictors after controlling for social and familial risk factors (see Table 4.9).

Table 4.8 Spearman's rho correlations between perinatal risk factors and activity levels at the 6 month assessment (with Pearson's correlations for the IBQ activity scale).

	Informant-reported activity levels	**Baseline**	**Attention**	**Restraint**	**Activity factor**
Cigarettes early pregnancy	-.04	-.13*	.01	-.07	-.11†
Cigarettes mid pregnancy	.03	-.11†	.07	.02	-.06
Cigarettes late pregnancy	.14*	-.11†	.07	.01	-.04
Stress early pregnancy	.11†	.08	.08	.001	.11†
Stress mid pregnancy	-.001	.02	-.01	.10	.07
Stress late pregnancy	.17**	-.09	-.04	-.01	-.05
Birth weight[a]	-.03	.06	-.02	.03	.05

NB: significance level † < .10, * < .05, ** < .01, *** < .001; [a] Birth weight was adjusted for gestational age

Table 4.9 Relationship between prenatal risk factors and informant-reported activity levels.

Predictor	B coef	(95% CI)	Beta	*P*
Social Risk Index[1]	0.01	(-0.07 to 0.09)	0.02	.75
Social Risk Index	0.00	(-0.09 to 0.09)	-0.001	.99
Parental ADHD[2]	0.03	(-0.03 to 0.09)	0.06	.35
Social Risk Index	-0.04	(-0.13 to 0.05)	-0.06	.40
Parental ADHD	-0.01	(-0.07 to 0.06)	-0.01	.88
Cigarettes late pregnancy	0.05	(0.01 to 0.10)	0.16	.02*
Stress late pregnancy[3]	0.07	(0.02 to 0.12)	0.18	.005**

[1] Dependent variable: Informant-reported activity levels. N= 257, $R^2 < .001$, p = .75
[2] Dependent variable: Informant-reported activity levels. N= 257, $R^2 = .004$, p = .35
[3] Dependent variable: Informant-reported activity levels. N= 257, $R^2 = .05$, p = .002

4.4 Discussion

Similar to the analyses performed in Chapter 3, this chapter looked at the relationship between perinatal risk factors and infants' activity levels, in order to test whether the proposed precursor in infancy met the second criterion of association with well-established risk factors of ADHD. Firstly, it was established that toddlers' symptoms of ADHD were associated with smoking throughout pregnancy and stress in mid- and late pregnancy, and that children's symptoms of ADHD were associated with the number of cigarettes in mid-pregancy, stress in mid- and late pregnancy and birth weight (but not when controlled for social risk, parental ADHD symptoms and ODD symptoms). In addition, associations between cognitive performance in middle childhood (but not in toddlerhood) and perinatal risk factors were observed. Some of these patterns were replicated for the precursor. Informant-reported activity levels were significantly associated with the number of cigarettes smoked and levels of stress in late pregnancy. Measured activity levels during baseline were negatively associated with the number of cigarettes smoking in early pregnancy. No associations between measured activity levels and other perinatal risk factors were found.

This means that the second criterion is partially met for informant-reported activity levels in infancy. The criterion was not met for measured activity levels in infancy, and it is not clear why during the baseline condition smoking in early pregnancy was related to a reduction in activity level in infants. However, with regards to informant-reported activity levels it is interesting to note that similar associations are observed with stress during late pregnancy, which was also more strongly related to symptoms of ADHD than stress earlier in pregnancy. Associations in infancy with smoking in pregnancy did not perfectly mirror associations with ADHD symptoms (which were strongest during mid-pregnancy); however it is noteworthy that the associations in infancy with stress and smoking in late pregnancy

remained significant, even when social and familial risk was taken into account. ODD symptoms were not controlled for here, since ODD symptoms were not measured during infancy. This is a limitation and it must be noted that when ODD symptoms during toddlerhood was controlled for in a similar regression analysis, these effects of smoking and stress on informant-reported activity levels disappeared.

It must also be emphasised that whilst some similarity in the correlation matrices was observed, most of these correlations cannot be considered significant when a more stringent significance-level is applied. Of course, whilst not wanting to be too conservative, it must be remembered that false positives might have occurred in 11.2 (conventional significance level) or 0.22 ($p < .001$) of the correlations. Nevertheless, even without making a value judgement on the exact significance of the findings, it can be concluded that the correlations observed for perinatal risk factors with informant-reported activity levels and ADHD symptoms in toddlers and children follow a similar pattern.

It is interesting that stress in mid and late pregnancy but not stress in early pregnancy predicted ADHD symptoms, although this association did not remain after controlling for ODD symptoms. Previously O'Connor and colleagues (2002) found that anxiety in late pregnancy predicted hyperactivity and inattention and it has been hypothesised that cortisol affects the neurodevelopment of the serotonergic system during late gestation (Rice et al., 2009). The findings contrast with others, suggesting that stress influences ADHD mainly during the first half of pregnancy (Rodriguez & Bohlin, 2005; van den Bergh & Marcoen, 2004; van den Bergh et al., 2005). However, these studies did not control for ODD symptoms. Whilst our results suggest that mid- and late pregnancy might be a particularly vulnerable period in development, it is important to interpret these findings with caution. It is likely that some of these effects can be explained by comorbid ODD symptoms, especially since links between stress and/or psychopathology in pregnancy and disruptive (aggression,

ODD, CD) outcomes have been reported repeatedly (Waters, Hay, Simmonds, & van Goozen, 2014). Of course, the definition of stress and/or ADHD symptoms might also have differed between studies. Whilst the ADHD symptom factor scores used in this study are likely to tap into the same construct, it is not a diagnostic measure and results must therefore be interpreted with caution.

Whilst smoking during pregnancy has been related to ADHD symptoms in children repeatedly and significant correlations with informant-reported activity levels, as well as symptoms of ADHD were found in this sample as well, these effects did not hold up when other factors were controlled for. It is possible that our study lacked statistical power, since only a small percentage of mothers smoked during pregnancy. However, it is also possible thats the link between smoking during pregnancy and ADHD symptoms is accounted for by confounding (genetic) variables, which confer susceptibility to both nicotine dependence and ADHD (Thapar et al., 2009). It is worth noting that maternal ADHD symptoms were significantly related to the number of cigarettes smoked in pregnancy.

Whilst it was hypothesised that low birth weight would be related to precursors as well as ADHD symptoms, an effect of birth weight was only found in middle childhood and precursors could not be associated with this risk factor. The associations with cognitive performance in middle childhood might help to explain this finding. Lower birth weight predicted poorer performance on sustained attnention and working memory, but not on other tasks. One might speculate that the well-established risk of birth-weight in relation to ADHD is specifically associated with later developing (more complex) cognitive deficits. This would also explain the lack of association with toddlers' symptoms of ADHD and toddler's cognitive performance. Obviously more research is needed to test this theory.

Some further limitations must be addressed here. Whilst this study has taken familial influences into account by measuring parental ADHD symptoms, it must be noted that this

proxy measure is an inadequate method of controlling for genetic effects. Maternal characteristics influence many important prenatal risk factors and impact on the infant's development in utero (Rice et al., 2008). In future it would be interesting to undertake these analyses in the context of a genetically informative design.

In conclusion, the results from this study indicate that the second criterion for identifying early behaviours as a precursor was partially met for informant-reported activity, but that similar associations between perinatal risk factors and precursor measured activity levels in infancy were not supported (see Figure 4.4). It was also found that associations between perinatal risk factors and ADHD symptoms were strongly confounded by the presence of ODD symptoms. This highlights the importance of controlling for comorbid symptomatology.

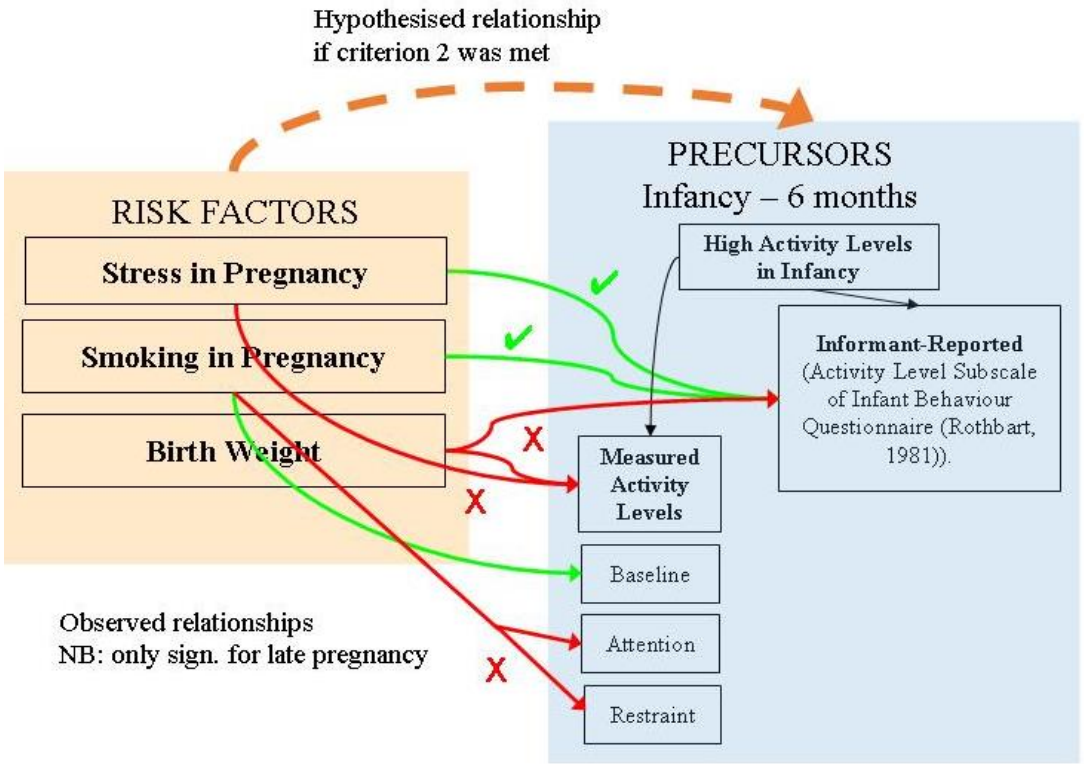


Figure 4.4 Hypothesised and observed relationship between familial risk and the precursor.

CHAPTER 5.

Stability of Individual Differences in Precursors over Time

5.1 Introduction

5.1.1 Aim of the Chapter

Thus far, adherence to the first two criteria of precursors has been assessed. In Chapter 1 high activity levels in infancy were argued to resemble later symptoms of ADHD sufficiently. Chapters 3 showed that infants' informant-reported and measured activity levels were not significantly associated with parental ADHD symptoms, and therefore did not meet the requirement of association with well-established risk factors. In Chapter 4, perinatal risk factors could be linked to informant-reported but not measured activity levels, meaning that the second criterion was only partially met. The final criterion, and perhaps the most important criterion, requires that precursors show continuity over time. The first aim of this chapter is therefore to investigate the continuity of precursor behaviour over time, up to middle childhood. It will be examined whether informant-reported and measured activity levels in infancy predict measured activity levels in toddlerhood, symptoms of ADHD in toddlers and children, and executive functioning correlates of ADHD symptoms in toddlers and children (see also Chapter 1, Figure 1.5).

Secondly, this chapter will test the precursor in two additional ways. It will be tested whether the precursor adds predictive power, beyond the effects of the risk factors that are associated with both the precursor and the later outcome (Hay et al., 2014). The second aim of this chapter is thus to test whether the precursors, when added to a regression model in a second step, after risk factors are accounted for, explain any additional variance. It is also of interest whether risk factors are associated with the continuity of precursors to later

outcomes. In other words, it is examined whether risk factors are associated with a move to higher scores (i.e. with a consolidation into disorder). Therefore rather than testing the direct association between risk factors and precursor (as was done in Chapter 3 and 4), the third aim of this chapter is to test whether risk factors predict the continuity from precursor behaviour to final outcome.

Moreover, it has been argued that the associations between precursors and risk factors need to resemble the associations between the later outcome and risk factors. Symptoms of ADHD in toddlerhood (full sample) as well as middle childhood (subsample) as measured with the Child Behaviour Check List (Achenbach & Rescorla, 2000) have been used as outcome variables. In Chapter 1 ADHD symptoms were shown to emerge in toddlerhood, and evidence was quoted, which showed that ADHD symptoms can successfully be measuresed in toddlers and can be distinguished from normative behaviours. Nonetheless, some might question the validity of the measurement of ADHD symptoms at toddler age. Moreover, attention skills are acquired during the preschool to early school years and developmental change might therefore still be a factor at 33 months of age, whereas by age 7 relatively stable attention skills are found (Rietveld et al., 2004). It was suggested that caution was still needed, and that the measurement of ADHD symptoms is likely to be less accurate in preschool than in school-age children. The final aim of this chapter is therefore to establish the continuity of ADHD symptoms from toddler age to middle childhood. Additionally, the continuity of executive functioning deficits will be examined by establishing whether performance on the tasks used in toddlerhood predicts performance in middle childhood. These analyses serve to support the validity of measuring ADHD symptoms and executive functioning correlates in toddlerhood.

5.1.2 Hypotheses

It is expected that individual differences in infants' activity levels will show continuity over time. Specifically, it is hypothesised that informant-reported as well measured activity levels will predict measured activity levels in toddlerhood, ADHD symptoms in toddlerhood and middle childhood, as well as executive functioning correlates of ADHD symptoms in toddlerhood and middle childhood. Positive correlations are expected with measure activity levels and ADHD symptoms, whereas a negative association with executive functioning performance is hypothesised. Given the smaller time-gap as well as the larger sample size in toddlerhood, it is hypothesised that associations with toddler outcomes will be larger.

Secondly, activity levels in infancy are hypothesised to predict ADHD symptoms in a regression analysis, after associations with well-established risk factors are controlled for. This analysis will be conducted for the whole sample in toddlerhood and for a subsample in middle childhood. The predictive power up to toddlerhood is expected to be larger than to middle childhood. Thirdly, it is expected that well-established risk factors are associated with a measure of the continuity from the precursor to the outcome (i.e. standardised change scores). Standardised change scores will be calculated for outcomes in toddlerhood and middle childhood separately. It is expected that consolidation from precursor into disorder (i.e. a move to higher standardised scores) is positively associated with well-established risk factors.

Finally, it is hypothesised that ADHD symptoms in toddlerhood will predict ADHD symptoms in middle childhood, and that performance on inhibitory control tasks in toddlerhood will predict executive functioning performance in middle childhood.

5.2 Method

5.2.1 Participants

Because of missing data on particular variables, the number of participants throughout this thesis varies, depending on the type of data that is included in the analyses. This chapter includes variables from the first, second, fifth and sixth wave of data collection. A detailed description of the participants used in this chapter can be found in Chapter 2, section 2.2.1.

5.2.2 Procedure and Measures

The procedure and measures for the antenatal visit, the six month home assessment, the thirty-three month lab assessment and the home visit at 7 years of age were described extensively in chapter 2 and will therefore not be repeated here.

5.2.3 Data-analysis

The screening of violations in assumptions of parametric tests of the precursor and outcome variables was described earlier (see Chapter 2). Non-parametric tests were used in this chapter for measured activity levels in infancy. Spearman's rho correlations between informant-reported and measured activity levels and activity levels in toddlerhood were examined first. Associations with ADHD symptoms and executive functioning performance were also examined.

Next, to establish whether precursors add predictive power, beyond the effects of the risk factors, two-step regression analyses were performed, where all significant risk factors were included in the first step and the precursor was included in a second step. Next, standardised change scores were calculated for the change from activity levels in infancy to ADHD symptoms in toddlerhood and middle childhood. Since informant-reported activity

and ADHD symptoms were already standardised factor scores, a simple subtraction (outcome – precursor) was applied. Measured activity levels were first transformed into standardised scores, before change scores were calculated.

Finally, correlations between the outcome measures in toddlerhood and the outcome measures in middle childhood were explored. ODD symptoms and risk factors were controlled for in subsequent regression analyses. It must be noted that in this chapter a total of 308 correlations were examined. A significance level of $p < .05$ or $p < .01$ would mean that by chance respectively 15.4 or 3.08 of these correlations would be significant. When a Bonferroni correction is applied, this would mean that only correlations with $p < .0002$ would be considered significant. This would be extremely conservative and limit the conclusions that can be drawn in this chapter. A less conservative *p*-value of $p < .001$ was therefore adopted and reported along with the results using conventional *p*-values without correction. Of course, when interpreting these significance values, it must be remembered that false positives might occur in 15.4 (conventional), 3.08 ($p < .01$) or 0.31 ($p < .001$) of the correlations.

5.3 Results

5.3.1 Stability from Infants' to Toddlers' Activity Levels

The continuity between informant-reported and measured activity levels measured at 6 months and activity levels at 33 months of age was explored. Informant-reported activity levels did not significantly predict toddlers' activity levels. Figure 5.1 shows infants' measured activity levels compared with toddlers' measured activity levels. A marginally significant Spearman's rho correlation was found for the restraint condition ($\rho = 0.19$, $p = .07$), but activity levels at 6 and 33 months did not correlate during the other conditions. A

significant decrease in activity levels across time was found for baseline (z = -3.29, p = .001), but no significant differences were found when comparing the other conditions over time (attention: z = 0.99, p = .32; restraint: z = 0.02, p = .98; frustration: z = -1.08, p = .28).

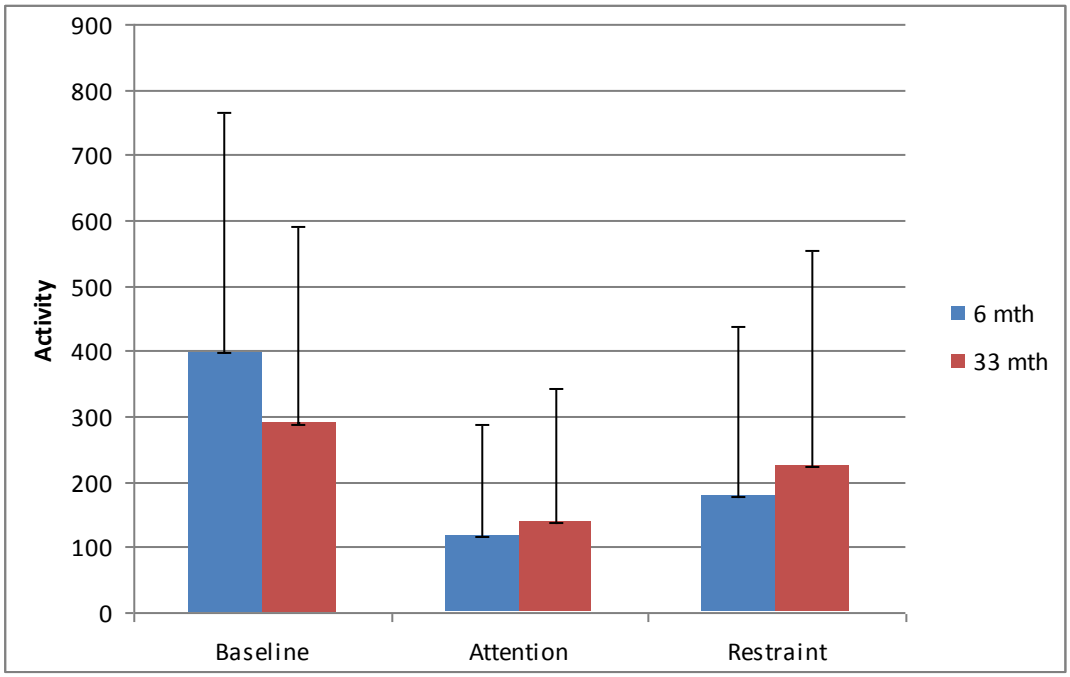


Figure 5.1 Mean activity levels and SD's (error bars) at 6 and 33 months during baseline, attention and restraint.

5.3.2 Stability from Infants' Activity Levels to ADHD Symptoms

Table 5.1 shows that ADHD symptoms in toddlers and children were significantly related to informant-reported activity levels, but were not related to measured activity levels. When resting state (baseline) was taken into account similar results were found with the percentage change in activity levels from baseline to attention and from baseline to restraint not correlating with toddlers' ADHD symptoms. When toddlers' ODD symptoms were taken into account, informant-reported activity levels at six months continued to significantly predict toddlers symptoms of ADHD (R^2 = .29, $R^2change$ = .02, p < .01; ß = 0.15, p < .01; N = 222). When ODD symptoms at age 7 were taken into account, only a marginally significant

association of childhood ADHD symptoms with informant-reported activity levels at six months remained (R^2 = .45, $R^2change$ = .01, p = .08; ß = 0.10, p = .07; N = 168).

Table 5.1 Spearman's rho correlations between informant-reported and measured activity levels at 6 months and toddlers' ADHD symptoms (with Pearson's correlation for informant-reported activity scale).

	Toddlers' ADHD symptoms	**Childhood ADHD symptoms**
Informant-reported activity levels at 6 mth	.21***	.17*
Measured activity levels at 6 mth		
Baseline	-.04	-.03
Attention	-.03	.09
Restraint	.04	-.01
Activity Factor	-.02	.04

NB: significance level † < .10, * < .05 ** < .01, *** < .001.

5.3.3 Stability from Infants' Activity Levels to Executive Functioning Performance in Toddlerhood and Middle Childhood

Firstly, the relationship between toddlers' scores on the inhibitory control tasks and infants' activity levels were explored, see Table 5.2. Toddlers' cognitive flexibility scores at 33 months of age were marginally associated with informant-reported activity levels at 6 months of age, with poorer scores being associated with higher activity levels. There were no significant associations with measured activity levels at 6 months.

Table 5.2 Spearman's rho correlations between inhibitory control tasks and informant-reported and Measured activity levels at 6 and 33 months.

	Raisin	Whisper	BBLB	Tower	Behavioural Regulation	Cognitive Flexibility
Informant-reported activity levels at 6 months	.05	.04	-.12†	-.03	.01	-.12†
Measured activity levels at 6 months						
Baseline	-.01	.08	.12	-.11	.05	-.04
Attention	.05	.13†	-.05	-.07	.10	-.08
Restraint	-.12†	-.07	-.12	-.02	-.10	-.10
W2 activity factor	-.06	.03	-.01	-.14†	-.03	-.11

NB: significance level †< .10, * < .05, ** < .01, ***< .001.

Secondly, the relationship between performance on the executive functioning task and infants' activity levels was explored (see Table 5.3). Informant-reported activity levels were significantly associated with the mean and SD of the reaction time during the baseline speed task, as well as with the number of mouse clicks during the delay frustration task. Significant associations were also observed for activity levels during attention and errors and reaction time during the set shifting task. The activity factor was related to a longer time spend clicking the mouse during the delay frustration task. If stricter significance levels are applied, none of these associations reach significance.

Table 5.3 Associations between cognitive task performance at 33 months and cognitive task performance in middle childhood.

	Informant-reported activity levels	**Baseline**	**Attention**	**Restraint**	**Activity Factor**
Baseline Speed Task					
M reaction time	-.20*	.07	-.07	-.06	-.05
SD reaction time	-.18*	-.02	-.01	-.10	-.06
Premature responses	-.05	-.06	-.07	-.02	-.09
Set Shifting Task					
Errors compatible	-.01	-.14†	.09	.03	-.06
Errors incompatible	-.06	-.03	.09	-.91	.004
Errors mixed	.02	.13	.24**	-.07	.12
Premature responses	-.01	-.02	.09	.04	.05
M reaction time fixed	-.06	.03	-.19*	-.01	-.14
M reaction time mixed	-.08	.06	-.01	.07	-.02
Pursuit Task					
M distance to target	-.13	.12	.12	.08	.12
SD distance to target	-.14	.09	.10	.04	.07
Working Memory Task					
N targets	.11	-.13†	-.03	-.01	-.06
N targets in order	.11	-.07	-.01	-02	-.004
Delay Frustration Task					
N mouse-clicks	.20*	.07	.05	-.03	.09
M duration mouse-clicks	.15†	.09	.10	.03	.15*

NB: significance level † < .10, * < .05 ** < .01, *** < .001.

5.3.4 Predictive Power of Precursors, Beyond Effects of Risk Factors

Several regression analyses were performed in order to examine whether infants' activity levels explained additional variance in toddler and childhood symptoms of ADHD,

beyond that explained by the risk factors (see Figure 5.2). Only informant-reported activity levels were explored, since measured activity levels were not associated with the outcome. The first step of the regression analyses included the risk factors, which had previously been associated with childhood symptoms of ADHD. Analyses were repeated to include ODD symptoms. It can be seen in Figure 5.2 that informant reported activity levels significantly explained additional variance in toddlers' symptoms, beyond that associated with risk factors, even when ODD symptoms were taken into account. Informant-reported activity levels explained some additional variance in childhood ADHD symptoms, after risk factors were accounted for. However, this effect was only marginally significant, and disappeared when ODD symptoms were additionally controlled for.

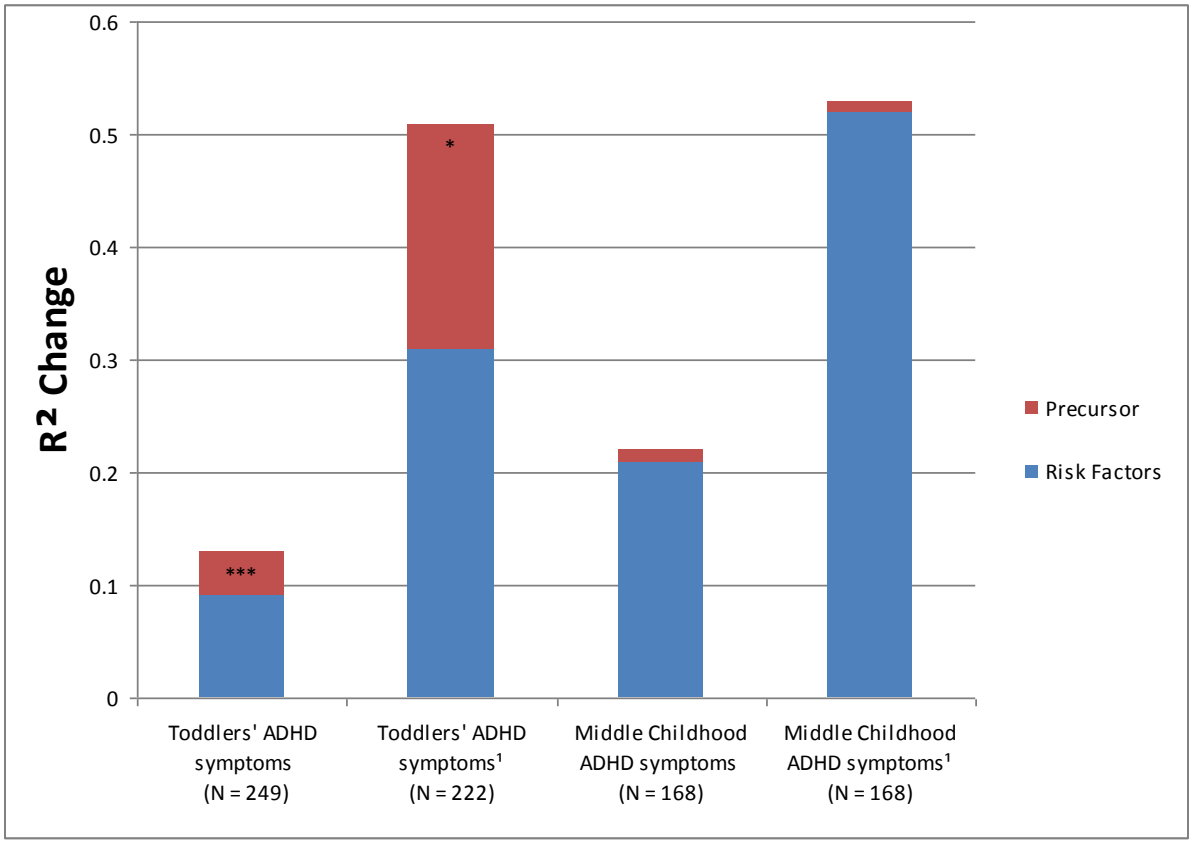


Figure 5.2 Amount of variance in toddler and childhood symptoms of ADHD explained by risk factors and additional variance (R^2change) explained by informant-reported activity levels. (Risk factors included social risk, parental ADHD symptoms, stress in mid- and late pregnancy and ODD symptoms[1].

NB: significance level *<.05, ** < .01 *** < .001;[1]only included in marked analyses.

5.3.5. Risk Factors and the Continuity From Precursor to Outcome

Table 5.4 shows the relationship between the well-established risk factors and standardised change scores (measuring the continuity from precursors to later outcomes). A positive correlation means that the risk factor was associated with a move to higher standardised scores from infancy to toddlerhood/middle childhood. Such a move from informant-reported activity levels to ADHD symptoms was associated with social risk, mothers' ADHD symptoms, an increased number of cigarettes in early pregnancy and stress in mid- and late pregnancy. From baseline to ADHD symptoms, an increase in scores was related to social risk, mothers' and fathers' ADHD symptoms, increased smoking throughout pregnancy, and stress in mid- and late-pregnancy and low birth weight. From attention to ADHD symptoms, it was associated with social risk, mothers' and fathers' ADHD symptoms, stress in mid- and late pregnancy and low birth weight. From restraint, associations with social risk, mothers' ADHD symptoms, stress in mid- and late pregnancy and birth weight were found. Finally, a move from higher overall activity levels to ADHD symptoms was significantly related to social risk, ADHD symptoms in both parents, smoking in early and mid-pregnancy, stress in mid- and late pregnancy and birth weight.

5.3.6 Stability in ADHD Symptoms from Toddlerhood to Middle Childhood

Toddlers' ADHD symptoms significantly predicted symptoms of ADHD (r = .48, p < .001) and the tester's ratings of attentiveness (r = -.26, p < .001) in middle childhood; they were marginally related to tester's ratings of activity (r = .13, p = .07). Toddlers' ADHD symptoms were also significantly predictive of ODD symptoms in middle childhood (r = .22, p < .01). Concurrent ODD problems at age 7 were therefore taken into account in a two-step regression analysis. Toddlers' ADHD symptoms continued to significantly predict childhood symptoms of ADHD (R^2 = .51, R^2*change* = .12, p < .001; ß = 0.35, p < .001; N = 191).

Table 5.4 Associations between standardised change scores and well-established risk factors.

Standardised Change Scores	Informant-reported activity levels	Baseline	Attention	Restraint	Activity Factor
Continuity to Toddlerhood					
Social Risk Index	.14*	.14*	.15*	.10	.13*
Mothers' ADHD Symptoms	.11†	.23***	.10	.16*	.19**
Fathers' ADHD Symptoms	.12†	.28***	.18**	.11	.21**
Cigarettes early preg	.13*	.16*	.10	.07	.13*
Cigarettes mid preg	.10	.17**	.12†	.09	.15*
Cigarettes late preg	-.01	.14*	.05	.05	.10
Stress[1] early pregnancy	-.05	-.01	-.01	.00	-.03
Stress[1] mid pregnancy	.09	.14*	.12†	.14*	.15*
Stress[1] late pregnancy	-.05	-.06	-.06	-.07	-.08
Birth weight[2]					
Continuity to Middle Childhood					
Social Risk Index	.20**	.21**	.26***	.20**	.22**
Mothers' ADHD Symptoms	.19*	.32**	.24**	.27***	.32***
Fathers' ADHD Symptoms	.16†	.25**	.13†	.12	.18†
Cigarettes early preg	.05	.22**	.11	.11	.17*
Cigarettes mid preg	.04	.22**	.13†	.10	.17*
Cigarettes late preg	-.02	.14†	.00	.03	.08
Stress[1] early pregnancy	.04	-.03	-02	-.02	-.05
Stress[1] mid pregnancy	.21**	.12	.25***	.05	.11
Stress[1] late pregnancy	.18*	.16*	.17*	.16*	.16*
Birth weight[2]	-.08	-.17*	-.16*	-.22**	-.20**

NB: significance level † <.10, *<.05, ** < .01, *** < .001.

5.3.7 Stability of Cognitive Task Performance

To examine whether individual differences in behavioural regulation and cognitive flexibility were stable over time, correlations with performance on the ANT tasks were explored. Table 5.5 shows that behavioural regulation at 33 months of age was predictive of the number of premature responses during the baseline speed and set shifting task. It also significantly predicted the number of targets identified during the working memory task. Whilst cognitive flexibility at 33 months did not significantly predict task performance in middle childhood, observed correlations were in the expected direction for the set shifting task. Cognitive flexibility was marginally related to sustained attention during the pursuit task

and a shorter duration of mouse-clicks during the delay frustration task. Again, it must be noted that when a stricter significance level is applied, most of these effects disappear.

Table 5.5 Associations between cognitive task performance at 33 months and cognitive task performance in middle childhood.

	Raisin	**Whisper**	**BB/LB**	**Tower**	**Behavioural Regulation**	**Cognitive Flexibility**
Baseline Speed Task						
M reaction time	-.09	-.02	.03	.05	-.07	.05
SD reaction time	-.14	-.07	.04	-.03	-.13	-.001
Premature responses	-.23**	-.05	-.07	.08	-.17*	.01
Set Shifting Task						
Errors compatible	-.15†	.03	-.07	-.06	-.05	-.08
Errors incompatible	-.04	.07	.08	-.01	.06	.06
Errors mixed	.02	-.003	-.03	-.15†	.02	-.13
Premature responses	-.26**	-.03	-.03	-.12	-.18*	-.12
M reaction time fixed	.08	.03	.04	.11	.07	.12
M reaction time mixed	.13	.04	.03	-.20*	.13	-.11
Pursuit Task						
M distance to target	-.15	.001	-.05	-.18†	-.09	-.18†
SD distance to target	-.16†	-.04	-.03	-.19*	-.11	-.16†
Working Memory Task						
N targets	.26***	.11	.20*	-.09	.24**	.06
N targets in order	.19*	.10	.16†	.03	.16†	.12
Delay Frustration Task						
N mouse-clicks	.04	.04	.03	-.17†	.07	-.09
M duration mouse-clicks	.03	-.01	.02	-.22*	.03	-.14†

NB: significance level † < .10, * < .05 ** < .01, *** < .001.

5.4 Discussion

The main aim of this chapter was to examine the stability of individual differences in the precursor over time (see Figure 5.4 for a visual summary of the results). Infants' activity levels did not predict activity levels in toddlers significantly. Informant-reported activity levels did predict ADHD symptoms in toddlerhood and middle childhood significantly, and in toddlerhood this prediction remained when ODD symptoms were taken into account. Infants' activity levels did not predict toddlers' performance on inhibitory control tasks

significanty and observed relationships with childhood executive functioning were not significant, if a stricter significance level was observed.

The lack of stability in measured activity levels was unexpected. This finding might possibly be explained by differences in context (home visit in infancy vs. laboratory visit in toddlerhood) or the short time period during which activity was measured (ranging between 30 seconds for the restraint task and 5 minutes during peer interaction). Whilst it is interesting to note that associations between infants' activity levels and toddlers and children's executive functioning were in the expected direction, the lack of significance of these findings limits any conclusion that might be drawn from these findings.

To further test the stability of informant-reported activity levels, it was examined if this precursor explained additional variance in toddler and childhood symptoms of ADHD, beyond that explained by the risk factors. When the precursor was added to a regression model that predicted ADHD symptoms, the predictive power of informant-reported activity levels up to toddler age was confirmed. Additional variance in toddlers' symptoms was explained beyond that associated with risk factors, including ODD symptoms. The additional variance in symptoms in middle childhood explained by the precursor was only marginally significant. Taken together these findings suggest that there is continuity in informants' reports of activity from 6 months to 7 years of age. Continuity in measured activity levels was not supported, meaning that the requirements for this criterion of a precursor were met for informant-reported, but not for measured activity levels.

Furthermore, it was examined whether well-established risk factors were associated with standardised change scores. A move towards higher standardised scores can be interpreted as a consolidation into the disorder, and associations between such continuity from the precursor to the outcome and well-established risk factors would further support the validity of the precursor as an early manifestation of the disorder. Results indicated that

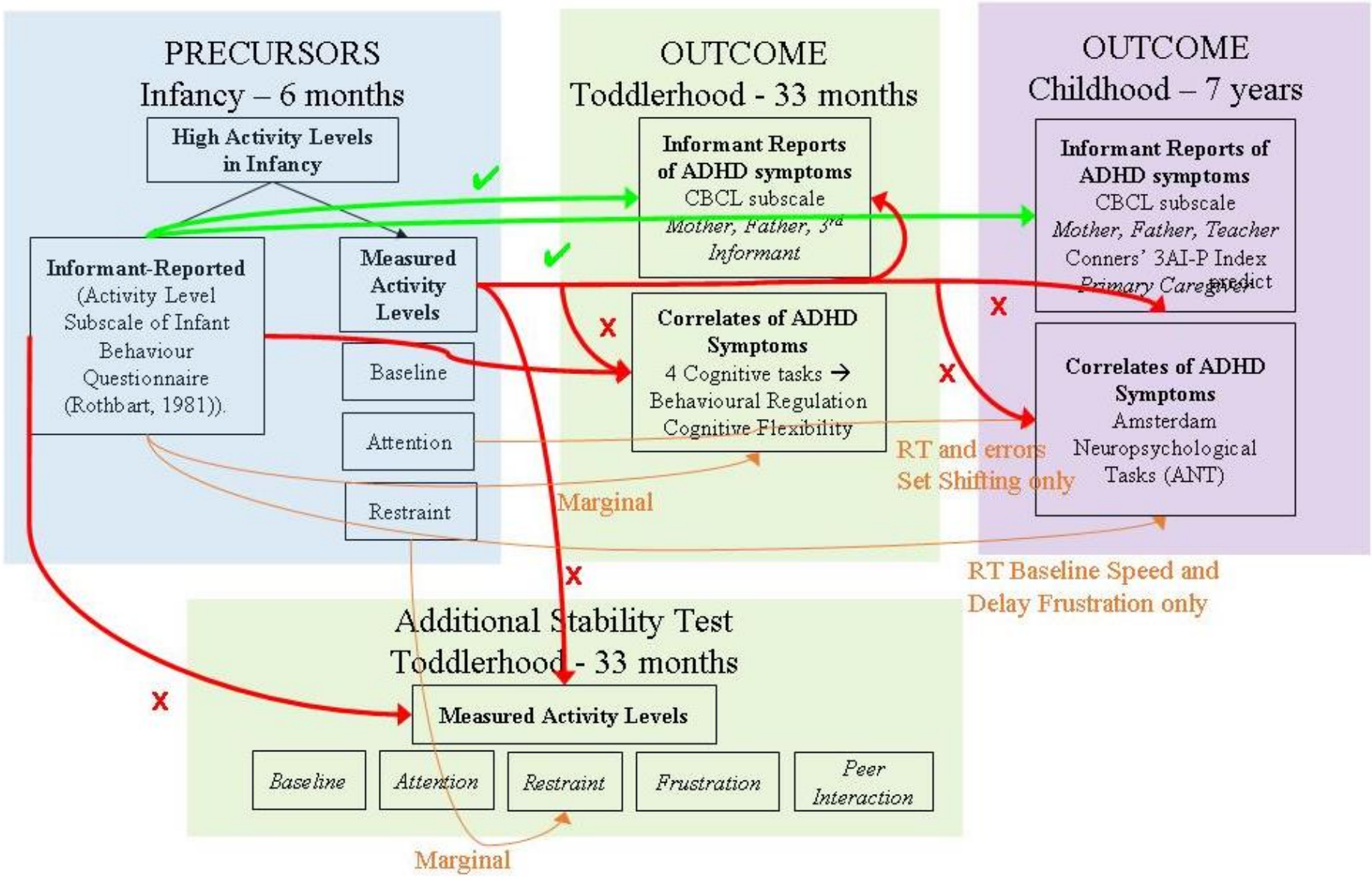


Figure 5.4 Observed relationships between precursor and outcome variables.

standardised change scores of informant-reported activity levels were associated with social risk, mothers' ADHD symptoms, smoking in early pregnancy and stress in mid- and late pregnancy. These findings therefore support the validity of informant-reported activity levels as a precursor of ADHD symptoms, although all effects disappeared when stricter significance levels are applied. Standardised change scores of measured activity levels could also be associated with risk factors. This was especially true for baseline and overall activity levels, whereas activity levels during attention and restraint were related to fewer risk factors (but notably with parental ADHD symptoms and stress in mid/late pregnancy). Again, most effects disappeared when stricter significance levels are applied.

A second aim of this chapter was to validate the outcome measures used in toddlerhood, by examining their stability up to middle childhood. Firstly, the stability in ADHD symptoms was confirmed, and prediction to middle childhood was significant even when a stricter significance level was applied and ODD symptoms were controlled for. These findings support the validity of the measure of ADHD symptoms in toddlerhood and suggest that symptoms can already be detected at this early stage of development.

Individual differences in behavioural regulation were predictive of the number of premature responses during the baseline speed and set shifting task, and of the number of targets identified during the working memory task. This finding therefore suggests some continuity over time in children's ability to regulate their behaviour. Responding prematurely is indicative of a difficulty inhibiting prepotent responses. The relationship with poor performance on the working memory task is more difficult to explain, since working memory is generally considered part of the executive functions. Perhaps to perform effectively on this task, it is essential that participants focus their attention and inhibit interference from other stimuli in the environment. Nevertheless, it must be remember that the stability over time of behavioural regulation did not pass a stricter significance level.

Cognitive flexibility did not significantly predict task performance in middle childhood, but was marginally related to sustained attention during the pursuit task and a shorter duration of mouse-clicks during the delay frustration task. Whilst a lack of power (small sample size) might account for these non-significant findings[1], it must also be noted that more specific correlations between the cognitive tasks at 33 months and the ANT tasks at age 7 were observed. Poor performance on the Tower of Cardiff task was significantly associated with slower reaction times during the mixed trial of the set shifting task, poorer sustained attention during the pursuit task and a shorter duration of mouse-clicks during the delay frustration task, whilst poor performance on the Big Bear Little Bear task was significantly associated with fewer targets identified during the working memory task. Caution must of course be taken, since these non-significant results cannot be taken as evidence of stability in cognitive flexibility.

It can be concluded that the findings reported in this chapter not only provide some additional support for the validity of the measures used throughout this thesis, but will also help us to determine whether the proposed precursors meet all the criteria set out in the introduction. Stability up to 7 years of age was supported for informants' reports of infants' activity levels, but not for measured activity levels. Associations of risk factors with continuity from precursor to outcome were noted for both informant-reported and measured activity levels, providing some additional support for the precursor, namely that consolidation from the precursor to the outcome is associated with risk factors of ADHD that are well-established.

[1] Observed correlations with performance on the set-shifting task (a measure of attentional flexibility) were in the expected direction, with cognitive flexibility positively predicting improved performance on this task.

CHAPTER 6.

General Discussion.

6.1 A Summary of the Findings

The principal aim of this thesis was to identify precursors to symptoms of ADHD in infancy in the context of a longitudinal study of first-born children (the CCDS). To determine whether an early behaviour could be identified as a precursor, three criteria were used: 'resemblance between the precursor and later developmental outcome', 'association with well-established risk factors for the later outcome', and 'continuity over time' (Hay et al., 2014). The adherence to these criteria was explored in three empirical chapters. Two additional tests were performed. The first required that the precursor added predictive power beyond the effects of the risk factors that are associated with both the precursor and the later outcome (Hay et al., 2014). The second assessed whether consolidation from precursor into disorder was associated with well-established risk factors. These were addressed in the final empirical chapter. The findings relating to each criterion will now be discussed.

6.1.1 Resemblance between Precursor and Later Developmental Outcome

The aim of the first chapter was to establish what ADHD symptoms as an outcome 'look like' in the population at large. ADHD was characterised as a developmental disorder featuring high activity levels, impulsive and inattentive behaviours, which are proposed to be the result of multiple pathways. Informant-reported as well as measured activity levels during various tasks were therefore explored. Two main pathways towards symptoms of ADHD were emphasised: the first resulted from deficits in executive/cognitive (cool) functions,

whilst the second was affected by motivational/affective (hot) functions. High activity levels during presentation of novel toy that elicited *attention* might relate to the first pathway, whereas high activity levels during an emotionally challenging *restraint* task might relate especially to the second pathway. These tasks were also argued to reflect the other core symptom domains of inattention and impulsivity. Since these precursors were based on the features of ADHD and the psychological theories, it can be concluded that the first criterion of 'resemblance with later outcome' was met. That said, the subjective nature of this judgement was highlighted and must be acknowleged here.

6.1.2 Association with Well-Established Risk Factors for the Later Outcome

6.1.2.1 Associations with familial risk. The aim of the third chapter was to establish whether parental ADHD symptoms were related to infants' activity levels in the same way as the outcome. This chapter therefore addressed the second criterion of precursors. It was important to establish in what way familial risk was associated with the later outcome, therefore the associations with ADHD symptoms and executive functioning correlates were examined. ADHD symptoms in toddlers and age 7 were significantly related to both mothers' and fathers' retrospective symptoms of ADHD. When social risk and ODD symptoms were controlled for, only mothers' symptoms remained significant whilst fathers' ADHD symptoms showed a marginal effect. Toddlers' behavioural regulation was significantly related to mothers' ADHD symptoms and marginally associated with fathers' ADHD symptoms, and these effects remained when social risk and ODD problems were taken into account. Cognitive flexibility at 33 months was not significantly related to parental symptoms of ADHD. Fathers' ADHD symptoms were also related to testers' ratings of attentiveness and performance during several cognitive tasks (set shifting, working memory and sustained attention) in middle childhood. In order to meet the criterion, the associations between

familial risk and precursor behaviour should resemble these associations with ADHD symptoms in childhood.

Mothers' and fathers' ADHD symptoms were unrelated to informant-reported activity levels at 6 months of age; therefore this precursor was not associated with risk in the same way as the later outcome. Measured activity levels at 6 months of age were not related to mothers' symptoms of ADHD; however fathers' symptoms were associated with increased activity levels during restraint and reduced activity during baseline. This finding therefore partially supports the definition of this behaviour as a precursor.

6.1.2.2 Associations with perinatal risk. The aim of the fourth chapter was to establish whether perinatal risk factors were related to precursor behaviours, and this chapter therefore addressed the second criterion of precursors in a similar way as chapter 3. Again, it was necessary to establish the relationship between perinatal risk and children's symptoms of ADHD. Toddlers' symptoms of ADHD were associated with smoking throughout pregnancy and stress in mid- and late pregnancy[1], and symptoms of ADHD in middle childhood were associated with the number of cigarettes in mid-pregancy, stress in mid- and late pregnancy and birth weight[2]. When social risk, parental ADHD symptoms and ODD symptoms were controlled for only a marginal effect of stress in mid- and late pregnancy on ADHD symptoms in middle childhood (but not in toddlerhood) remained. Relationships between executive functioning performance in middle childhood (but not in toddlerhood) and perinatal risk factors were also observed, but did not remain when a stricter significance level was applied. Again, in order to meet the criterion, the associations between perinatal risk and precursor behaviour should resemble these associations with ADHD symptoms in childhood and toddlerhood.

[1] When stricter significance levels were applied, only the association of toddlers' ADHD symptoms with smoking in mid-pregnancy and stress in late pregnancy was considered significant.
[2] When stricter significance levels were applied only the association between children's ADHD symptoms and stress in late pregnancy was considered significant.

It was found that informant-reported activity levels were significantly associated with the number of cigarettes smoked and levels of stress in late pregnancy. Measured activity levels during baseline were negatively associated with the number of cigarettes smoking in early pregnancy. No associations between measured activity levels and other perinatal risk factors were found.

6.1.2.3 Associations with gender. Prevalence of ADHD is higher for boys than girls and it was therefore surprising that no gender differences were found for toddler and childhood ADHD symptoms. Some gender differences were observed in infants' activity levels, with boys being significantly more active overall at 6 months (marginally during baseline). It might be argued that these gender differences are consistent with increased risk for boys reported in the literature, and that these findings therefore provide additional support for these precursors. However, a lack of gender differences is more often reported in community samples (Willoughby et al., 2012) and the non-significant differences in symptoms suggest that gender does not constitute a risk factor in this sample.

6.1.3 Stability of Individual Differences over Time

The aim of the final chapter was to establish whether individual differences in precursor behaviours showed continuity over time and thus whether the proposed precursors met the third criterion. Stability was assessed for the full sample into toddlerhood and up to 7 years of age in a subsample of 200 participants. To determine whether the criterion of 'continuity over time' was met, relationships were explored between informant-reported and measured activity levels at 6 months of age and measured activity levels at 33 months of age, ADHD symptoms in toddlers and children, and cognitive performance in toddlers and children.

The precursors did not significantly predict measured activity levels in toddlers. Informant-reported activity levels, but not measured activity levels predicted ADHD symptoms in toddlerhood and middle childhood significantly. In toddlerhood this prediction remained when ODD symptoms were taken into account. Infants' activity levels did not predict toddlers' performance on inhibitory control tasks significanty and the small number of observed relationships with childhood executive functioning would not be considered significant, if a stricter significance level was applied.

The outcome measures were found to be more stable, and especially the stability in ADHD symptoms from toddlerhood to middle childhood was confirmed. Individual differences in behavioural regulation also showed some continuity up to age 7, whilst levels of cognitive flexibility were not significantly associated with later outcomes. These findings support the validity of the measure of ADHD symptoms in toddlerhood and suggest that symptoms can already be detected at this early stage of development.

6.1.4 Predictive Power of Precursor, Beyond Contribution of Risk Factors

The aim of the final empirical chapter was to apply the more stringent test for a precursor, which requires that the precursor adds predictive power, beyond the effects of the risk factors that are associated with both the precursor and the later outcome (Hay et al., 2014). It was expected that when precursors were added to a regression model in a second step, after risk factors are accounted for, additional variance would be explained by the precursor. When toddlers' ADHD symptoms were predicted, informant-reported activity levels in infancy significantly explained additional variance, even when ODD problems were controlled for. In middle childhood, the additional variance explained by informant-reported activity levels was not significant. These results suggest that the more stringent test was met

for informant-reported activity levels, whilst measured activity levels did not meet this requirement (not tested, since no relationship with ADHD symptoms was found).

6.1.5 Association between Well-Established Risk Factors and Continuity from Precursor to Later Outcome

As a final test, associations between well-established risk factors and the consolidation from precursor into disorder (measured using standardised change scores) were examined. A move from informant-reported activity levels to higher standardised ADHD symptom scores was associated with social risk, mothers' ADHD symptoms, smoking in early pregnancy and stress in mid- and late pregnancy. An increase from standardised measured activity levels to standardised ADHD symptoms was also associated with risk factors. Especially, for baseline and total activity levels association were found with all risk factors. For activity during attention relationships with social risk mothers' and fathers' ADHD symptoms, stress in mid- and late pregnancy and low birth weight were found, whilst the same, excluding fathers' ADHD symptoms, was found for activity levels during restraint. These findings support the validity of activity levels during infancy as a precursor of ADHD symptoms. As a precursor activity levels are conceptualised as an early sign or manifestation of the disorder. Therefore, associations of well-established risk factors for ADHD with a move from such a precursor state towards higher standardised scores for the outcome make logical sense.

6.2 Limitations and Future Directions

Some limitations need to be addressed after summarising the findings. Firstly, it might be argued that the measurement of ADHD symptoms at toddler age might not be a sufficient measure of the disorder. However, it was hoped that the inclusion of a subsample at age 7 might overcome this problem. The strong correlation between toddler and childhood symptoms is in line with the literature and suggests that symptoms were already detected in toddlerhood. Reliance on parental reports of children's symptoms of ADHD might also be conceived as a limitation; parent report measures can be distorted due to dispositional or emotional biases, parental expectations or a lack of knowledge about how their child compares to peers (Hirshfeld-Becker et al., 2003). However the reliability of the parental measures in this thesis has been established repeatedly. Additionally, multiple informants were used to establish combined factor scores, which included parental, but also a third informant's perspective. At age 7, an effort was made to include teachers' reports in the composite ADHD symptom scores.

Furthermore, despite a moderate sample size, the fact that participants were drawn from a 'general' population likely limited the prevalence of ADHD symptoms in the sample. In future, it might be interesting to explore these precursors in a clinical or 'at risk' (for example younger siblings of children with ADHD) sample. Moreover, missing data for several tasks and measures led to a further reduction in sample size. This may have reduced statistical power.

Another potential limitation of this study is that information about parental ADHD symptoms was obtained retrospectively. It might have been more informative to examine both historic and concurrent parental symptoms. This might have allowed separation between genetic and environmental effects of parental symptoms of ADHD. The current analyses also

provide an inadequate method to control for genetic effects and in future it would be interesting to undertake these analyses in the context of a genetically informative design. However, it is argued that the measure was sufficient for the purposes of gaining confidence in our definition of these early behaviours as precursors.

Moreover, it was noted that across time points there were differences in settings (home vs. laboratory environment), methods and reporters of symptoms. This may have limited statistical power to detect continuity in activity levels in particular. It must also be remembered that these measures of activity levels are only snapshots of children's general activity levels, and findings could therefore easily be obscured by various sources of variance and error.

Some clinical limitations to this thesis must also be noted, given that none of the measures used in this study would be suitable for making a clinical diagnosis. This limitation however does not directly affect the results, since the focus of this thesis was on identifying precursors of ADHD symptoms rather than identifying clinical cases. Moreover, the symptoms of ADHD show continuous distributions with no distinct cut-off point that separates normality from abnormality (Rutter et al., 1999), and it is therefore likely that the findings reported in this thesis are generalisable to clinical diagnoses of ADHD.

6.3 Implications of the Findings

The identification of precursors, which can be observed and measured before the disorder can be reliably diagnosed, could facilitate further prospective studies of etiological mechanisms and could also inform the development of targeted prevention or intervention programmes. So far most treatments (i.e. pharmacological, parent training, contingency management) do not address the underlying neural and neurocognitive determinants of ADHD, but rather have been shown to (temporarily) suppress behavioural difficulties (Halperin & Healey, 2011).

Targeting early precursors might help to inform preventative interventions in early childhood that take into account individual predispositions.

The findings reported in this thesis suggest that informant-reported, but not measured activity levels at 6 months of age might be targeted as a precursor. Table 6.1 summarises the adherence of the precursors to the criteria and tests. Informant-reported activity levels were not association with familial risk, but passed all other tests. Measured activity levels were not associated with risk factors and did not show stability over time. The negative results for measured activity levels might have been caused by a reduced sample size for activity levels in toddlerhood (mostly due to refusion of the device at this age), a lack of ADHD symptomatology in this community sample and changes in settings over time. The duration of the activity sample might also not have been sufficient. However, it is interesting that a move from standardised measured activity levels towards higher standardised ADHD symptom scores could be associated with risk factors. This does suggest that these measures capture some early variance in activity levels, and I would suggest that further testing of measured activity levels in infancy is needed. This study presents a method for testing this further.

Table 6.1 Adherence to criteria and additional tests of a precursor.

	1st Criterion	2nd Criterion		3rd Criterion	Test 1	Test 2
		Familial Risk	Perinatal Risk			
Informant-reported activity levels	✔	X	✔	✔	✔	✔
Measured activity levels						
Baseline	✔	✔ Father	✔ Smoking Trim1	x	x	✔
Attention	✔	X	x	x	x	✔
Restraint	✔	✔ Father	x	x	x	✔
Activity Factor	✔	X	x	x	x	✔

NB: ✔requirement met, ✔association in opposite direction, **X** requirement not met.
1st criterion: resemblance between precursor and outcome; 2nd criterion: similar association with well-established risk factors for outcome; 3rd criterion: stability over time of individual differences; test 1: predictive power beyond risk factors; test 2: association between well-established risk factors and continuity from precursor to outcome.

Whilst not the main aim, the findings reported in this thesis contribute to our understanding of how risk factors might affect the development of ADHD symptoms. Toddlers' and childhood symptoms of ADHD were independently predicted by parental symptoms and stress in mid- and late pregnancy (although not all these associations remained when ODD symptoms were also taken into account). Whilst these findings replicate previous studies, associations with precursors are less frequently reported. The associations of risk factors with precursors may also clarify the mechanisms by which these risk factors exert their influence on the development of symptoms.

6.4 Final Conclusions

This thesis has followed a method that has enabled us to identify precursors to ADHD symptoms in infancy. In doing so, it fills a gap in the wider ADHD literature, which is characterised by an inconsistent use of the term 'precursor'. This is concerning, given the potential benefits of knowing about *valid* precursors for early identification and intervention. Informant-reported activity levels were supported by all criteria and additional tests, except one (association with familial ADHD symptoms), whereas measured activity levels were not supported as a precursor to ADHD symptoms. Whilst these results may have been limited by various sources of error, and a lack of power to detect precursors in this normal community sample, the formulation of clear criteria and the provided example of an application of these criteria will enable other researchers to follow the same methodology. It is time that the study of ADHD is placed firmly within a developmental framework and the systematic search for precursors is encouraged here as a good starting point, which in turn might lead to a better understanding of the aetiological mechanisms underlying ADHD, and ultimately to improved prevention and treatment.

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Appendix I

Psychological Theories of ADHD

Whilst no clear biological cause has thus far been established, the literature on ADHD nonetheless has traditionally adopted a theoretical approach that studies psychopathology as the consequence of some kind of psychological dysfunction or deficit. ADHD has been explained by deficits in cognitive and behavioural characteristics of attentional processes. The brains of hyperactive children have been studied extensively to examine these deficits further and brain circuits linking the prefrontal cortex, striatum and cerebellum have been found not to function normally in children with ADHD (Castellanos & Acosta, 2002). This type of research is typified by an approach that combines physical reductionism and reconstructionism. Physical reductionism is achieved when the components of cognition and behaviour are reduced to their physical substrate (i.e. the brain), whilst reconstructionism accounts for how interactions amongst the elementary units of the nervous system give rise to the phenomena of cognition and behaviour (Pennington, 2002).

However more recently researchers have started to look at misbehaviour in a more functional manner, since children's behaviours can provide the means to certain desired goals (Sonuga-Barke, 1994). Thus rather than viewing the behaviour as simply the consequence of some sort of dysfunction or deficit, it is the motivational attitudes of hyperactive children that are regarded as atypical. These motivational attitudes are said to be influenced over time by both environmental and biological factors and develop into a stable pattern of behaviour, known as ADHD. However, given the complexity of the disrupted behaviours found in ADHD, it is not surprising that the various pathways leading up to this disruption are also likely to be complex (Pennington, 2002). A good psychological theory of ADHD should be able to account for the psychological and physiological mechanisms that underlie the

disorder, whilst not ignoring the developmental processes that enable the establishment of these mechanisms. The various psychological accounts of ADHD up to date will now be described and the merits and weaknesses of the various approaches will be discussed. Those theories that have identified specific deficits will be considered first after which more motivational accounts of the disorder are dealt with.

Theories of Inhibitory Deficits in ADHD

As explained in the previous section, it has been found that children with ADHD display behaviour which is hyperactive, impulsive and inattentive. The problems in self-regulatory capabilities and executive attention are often explained by a deficit in inhibitory control and this lack of inhibition is often considered to be at the core of ADHD. Several tasks were discussed that exemplify this deficit, such as the stop-signal task, the go/no-go task, anti-saccade tasks, the continuous performance task, the Stroop task and the flanker task (section 1.2). Furthermore, the brain anatomy of children with ADHD has been related to some of these behavioural measures. Since impaired inhibitory control is one of the most consistent findings in ADHD, several theorists have tried to explain the origin of this deficit.

Logan's 'race' model (1981). According to Logan's race model (1981), stimuli in the environment trigger signals for both the activation and inhibition of responding. A race between these two processes determines which behaviour will result. The stop signal paradigm lies at the heart of this theory and the results from this task have provided substantial evidence that inhibitory deficits are central to the disorder. In this task children with ADHD are slower at initiating response inhibition and show an inability to disengage or shift responding (Barkley, 2006). According to Logan's race-model, this could be due either to a strong pre-potent impulse or to failing inhibitory processes, which are two independent processes.

The Quay-Gray model. The poor response inhibition found in children with ADHD might also be explained using Jeffrey Gray's (1987) model of brain function. This model explains behaviour in terms of the activity of either the Behavioural Inhibition System (BIS), which serves to inhibit behaviour and is sensitive to punishment signals or the Behavioural Activation System (BAS), which controls the initiation of behaviour and is sensitive to reward signals. According to Gray, psychopathology emerges from interactions of these two systems. It is argued that children with ADHD suffer from an underactive Behavioural Inhibition System (BIS), which affects their inhibitory control (Quay, 1997). By contrast, children with ADHD and conduct disorder (CD) might also be argued to suffer from an overactive BAS, which dominates the BIS, so that response inhibition is impaired indirectly through interference from a strong tendency to respond (Quay, 1997). In this theory behavioural inhibition is conceptualised as an interruption of behaviour that is due to an anxious, motivated or negative reaction to unexpected events. This approach therefore ignores strategic interruptions of behaviour which are part of executive control (Nigg, 2005). The Quay-Gray model however, does not account sufficiently for executive deficits.

The hybrid model of executive functions (Barkley, 1997). Children with ADHD demonstrate impairments on a wide variety of tests that measure frontal lobe functioning (see Barkley, Grodzinsky, & DuPaul 1992 or Pennington, & Ozonoff, 1996). Therefore Barkley (1997) developed a neuropsychological model of self-regulation, which focuses on the executive function system. He proposed that behavioural inhibition provides the foundation and is critical to the development, privatisation and performance of four executive functions (explained below). This behavioural inhibition creates a delay between an event and the response to that event and consists of three interrelated processes: inhibiting a planned or prepotent response, stopping an ongoing response and protecting the delay-period and the self-directed responses that occur within this period from disruption (also known as

interference control). The self-directed actions within the delay period that is created by inhibitory control make up 'self-control' or 'self-regulation' and are further defined as the executive functions. Four executive functions exist according to Barkley, including (1) non-verbal working memory (covert sensory-motor action towards the self), (2) the internalisation of speech (verbal working memory), (3) the self-regulation of affect, motivation and arousal and (4) planning or reconstitution. The information that is generated through these executive functions during the delay in response is able to control motor actions and behaviour. In other words, the executive functions enable deliberate, reasoned, intentional and future oriented behaviour and motor control.

According to Barkley's model, the combined type of ADHD can thus be characterised by deficits in executive functions, which are mainly caused by impaired behavioural inhibition. These executive deficits lead to difficulties in the control or self-regulation of goal-directed motor behaviour. The findings of poor performance on tasks presented earlier support Barkley's theory. The stop-signal task, go/no-go task, CPT and anti-saccade task were designed to create a prepotent response that needs to be inhibited, whilst the Stroop task and flanker task tap the interference control aspect of behavioural inhibition.

However, significant differences between groups do not prove the existence of a single core deficit as proposed. The effect sizes in general are only moderate with substantial distributional overlap between ADHD and comparison samples (Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005). The same appears true for the broader domain of executive function, with a meta-analysis of 83 studies that administered executive function measures and compared ADHD and comparison groups finding effect sizes that fell within the medium range (d = .46 - .69) (Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). In addition, a meta-analysis of neuropsychological test performance compared the effect sizes of deficits in

intellectual ability (Full Scale Intelligence Quotient; FSIQ), non-executive[1] and executive functioning[2] and found that children with ADHD performed worse than comparison children on all measures, but that in general more impairment was found on measures of executive functioning than on non-executive measures, in line with Barkley's theory (Frazier, Demaree, & Youngstrom, 2004). However, when individual tasks were compared, smaller effects on several executive measures were found compared with FSIQ effects, suggesting not all executive functions are equally impaired and that further impairments in non-executive functions need to be accounted for. There is also some evidence that links executive function deficits to the inattention dimension of ADHD rather than the hyperactivity/impulsivity dimension (Castellanos, Sonuga-Barke, Milham, & Tannock, 2006; Nigg et al., 2005).

Nevertheless, the executive functions have repeatedly been shown to be mediated by the prefrontal regions of the brain and related networks in the basal ganglia, striatum and cerebellum (Barkley, 2006). Prefrontal lesions have further been found to produce symptoms of ADHD, such as behavioural hyperactivity, distractibility, impulsivity and deficits on executive functioning tasks (Willcutt et al., 2005). A meta-analysis of the structural imaging findings concluded that children with ADHD show volumetric reductions set against comparison subjects in the cerebellum (particularly the posterior inferior vermis), the splenium of the corpus callosum, total and right cerebral volume, the right caudate, prefrontal and other frontal lobe regions of interest and deep frontal white matter (Valera, Faraone, Murray, & Seidman, 2007). Therefore, some of the brain-imaging findings are in line with deficits in executive functions.

It has been concluded that executive function deficits are 'neither necessary nor sufficient to cause all cases of ADHD' (Willcutt et al., 2005; p.1336). However, whilst

[1] Measures of non-executive functions included the Rey Complex Figure task, PPVT receptive language ability task and Wechsler's vocabulary, block design and similarities subtests.

[2] Measures of executive functions included the Wechsler's digit span subtest, CPT, stop signal task, trail making test, Wisconsin card sorting test, Stroop task, matching familiar figures test and the word fluency test.

Barkley's theory might not be able to account for all cases of ADHD, the evidence on balance does support the involvement of executive function problems in at least a subset of children with ADHD.

The Cognitive Energetic Model of ADHD

An alternative 'deficit-based' theory suggests that the core symptoms of ADHD might be explained by a cognitive-energetic model (Sergeant, Oosterlaan, & van der Meere, 1999). According to this theory ADHD might reflect non-optimal activation states, which cause impaired motor processing resulting in difficulties for both the execution and inhibition of responses. It is essentially a model of information processing, which argues that efficient information processing is determined by both process (computational) and state factors (effort, arousal and activation) (Sergeant, 2000). A computational mechanism of attention forms a first level, which includes several stages: encoding, search, decision and motor organisation. The second level of the model involves three state factors or energetic pools (the effort, arousal and activation pool). The effort pool affects the other state factors, by either inhibiting or exciting these pools (Sergeant, 2005). A third level, the management or evaluation mechanism, conceptually close to 'executive functioning' includes functions such as planning, monitoring, detection of errors and correction of errors (Sergeant, 2000). The three levels are interactive and include both bottom-up and top-down processes. This interplay between the computational mechanisms of attention, the state factors and management/executive function determines the overall efficiency of information processing.

According to the cognitive-energetic model, ADHD affects all three levels of the model: cognitive deficits[1], energetic deficits and management system deficits. The network involved in this model does not only include prefrontal areas of the brain, but also

[1] Motor organisation is particularly affected, with encoding and searching remaining intact (Sergeant, 2005).

encompasses the basal ganglia and cerebellum (Sergeant, 2005). The model argues that the inhibitory deficits found in ADHD are dependent on the state of the subject and the allocation of energy for the tasks at hand (Sergeant, 2000). Therefore, in contrast with Barkley's theory, the cognitive-energetic theory suggests that disinhibition is a secondary rather than primary feature of the disorder. Findings from several tasks support the hypothesis that the inhibitory dysfunctions seen in children with ADHD are caused by energetic failures. It has been demonstrated using CPTs that when event rate (speed of stimulus presentation) is manipulated, the response stage of the cognitive-energetic model is affected (Sergeant, 2000). Event rates influence the energetic state of the subject with fast conditions promoting over-arousal or over-activation (leading to fast-inaccurate responses) and slow conditions bringing about under-arousal or under-activation (slow-inaccurate responses). Inadequate activation of the inhibitory mechanisms is thus argued to cause the poor performance seen in children with ADHD (Sergeant, 2000). Performance of children with ADHD on a go/no-go task provides further support of this theory, with these children making more errors of commission during the fast and slow conditions, but not in the medium condition, suggesting that deficits in response inhibition are modulated by their struggle to adjust their state (van der Meere, Stemerdink, & Gunning, 1995). A tapping task further demonstrated that children with ADHD overestimate short time intervals (3 sec) and underestimate longer time intervals (17 sec), which is consistent with the influence of event rates (Sergeant, 2005). During the stop-task hypo-frontality at the right caudate and right mesial frontal lobe has been found in children with ADHD, suggesting a different energetic condition of the brain-state of these children (Sergeant, 2000). A meta-analysis of the Stroop task found a general slowing in colour naming as well as reading speed, consistent with a 'non-optimal activation state' (van Mourik et al., 2005). This theory is further supported by the enhanced performance of

children with ADHD that take stimulants. Methylphenidate is able to influence the activation level of children, which in turn affects performance (Oosterlaan et al., 1998).

Halperin and colleagues (2008) recently investigated differences between adolescent ADHD persisters, remitters and comparisons in order to dissociate potential causal versus secondary deficits. Their work suggests that less consciously controlled automatic processes might cause the disorder initially, but that recovery is associated with improvement in prefrontal executive functioning, which is able to compensate for the more enduring sub-cortical deficits. It was found that persisters performed more poorly on working memory in particular as well as the continuous performance task (CPT; hits, false alarms, RT and response bias [lnβ]) and waist activity, whilst both persisters and remitters showed impairments on other aspects of the CPT (RTSD and perceptual sensitivity [*d'*]) and ankle activity in contrast with a comparison group. It is argued that *d'* reflects arousal mechanisms, lnβ reflects activation and RTSD reflects state regulation. The finding that all three variables were impaired in those with a history of ADHD suggests that poor arousal, activation and state regulation mechanisms may play a role in ADHD (Halperin et al., 2008). The fidgety, arousal and state regulatory symptoms of remitters are of particular interest, since it is argued that these reflect core deficits, in line with the cognitive-energetic model, whilst the impairments in working memory and activation are likely to be epiphenomenal secondary deficits. Whilst this study highlights the importance of the prefrontally mediated executive functioning processes, it does question Barkley's (1997) assumption that executive deficits play a causal role in ADHD. The cognitive-energetic model therefore posits a plausible alternative to the more common theories of ADHD, which emphasise inhibitory control and executive functions.

The Dynamic Developmental Theory of ADHD

Sagvolden, Aase, Johansen and Russell (2005) proposed a dynamic developmental theory of ADHD, which is based on the interaction between a hypo-functioning dopamine system and dysregulated frontostriatal circuits. Individual differences in dopamine functioning (explained by genetic factors, drug use and/or environmental pollutants) are argued to interact with parenting styles, societal styles and medication to produce the stable behavioural outcomes associated with ADHD.

Dopamine is an important neuromodulator, which exerts strong regulatory effects on prefrontal functioning and plays a particularly important role in reinforcement and extinction (Johansen, Aase, Meyer, & Sagvolden, 2002). A hypofunctioning mesolimbic dopamine system produces a shorter and steeper delay-of-reinforcement gradient and abnormally low tonic dopamine activity. The effect of a reinforcer will be greatest, when the time interval between the response and the reinforcer is very short and the delay-of-reinforcement gradient represents this time interval. Reinforcement processes do not only affect single responses, but the relationships between responses are also conditioned in this manner (inter-response times; IRTs). A shorter and steeper delay gradient in children with ADHD means that responses with longer delays between response and reinforcer will not be reinforced (reinforcement should thus be immediate) and only short IRTs will be reinforced (Sagvolden et al., 2005). This explains delay aversion, poorly sustained attention if reinforcers are less frequent as well as motor impulsiveness (conceptualised as the preferential selection of short sequences of behaviour or IRTs). A low tonic dopamine activity furthermore means that a floor effect will make the phasic decrease in dopamine release, associated with extinction, less noticeable. When extinction does not take place, this will result in an accumulation of responses without the pruning effect of each reinforcer and thus increased behavioural variability (overactivity). You would not expect this overactivity to be present at the beginning of a new situation, since

it is acquired as a function of the number of reinforcers delivered (Sagvolden Aase, Zeiner, & Berger, 1998). The failure to inhibit responding (disinhibition) as well as the lack of hyperactivity in novel situations found in children with ADHD might thus be explained by this inadequate extinction process (Sagvolden et al., 2005). It is further proposed that a hypofunctioning mesolimbic system will interact with other hypofunctioning systems, such as the mesocortical dopamine system (involved in planning, short-term memory, attention and behavioural organisation) and the nigrostriatal dopamine system (involved in the timing of responses, force regulation, motor control and habit learning).

In line with a shorter and steeper delay gradient, it was found that during a game-like test with coins and trinkets as reinforcements children with ADHD gradually developed hyperactivity, which consisted of bursts of activity with short IRTs, both during the reinforcement and the extinction schedule (Sagvolden et al., 1998). The presence of responses during extinction is an indication of deficient sustained attention, since stimulus control was not established. In contrast, the comparison group did not show these impulsive bursts of activity and stopped responding during the extinction phase. A further study showed that when reinforcement was frequent, no differences between ADHD children and a comparison group were found; however during infrequent reinforcement children with ADHD showed deficient sustained attention and increased spatial variability (Aase & Sagvolden, 2006). Variability in responding is more often found in ADHD and might be explained as the result of increased induction of responses by scheduled and unscheduled reinforcers and faulty extinction processes (Aase & Sagvolden, 2006).

The dynamic developmental theory of ADHD is consistent with findings of delay aversion and a ‘motivation problem’ in ADHD. A short and steep delay gradient could explain why children with ADHD prefer immediate (small) rewards over delayed preferred rewards. Moreover children with ADHD are not always cognitively impulsive, since the use

of potent and frequent reinforcers enables them to temporarily plan ahead and organise themselves (Johansen et al., 2002). Furthermore, psychostimulants that affect dopamine availability, such as methylphenidate and amphetamines, are argued to lengthen the delay-of-reinforcement gradient and increase tonic dopamine levels and are found to be an effective treatment for ADHD.

The Delay aversion Hypothesis

An alternative account of ADHD reflecting a delay aversion has been proposed by Sonuga-Barke (1994). This hypothesis is based on the observation that children with ADHD often display hypersensitivity to delay and have difficulties waiting and this model is therefore in line with some of the mechanism proposed by Sagvolden and colleagues (2005). Perceptions of length of time are dependent on the attentional style that individuals adopt; temporal stimulation increases the perceived length of time (clocks, timers, boring/frustrating tasks) whilst non-temporal stimulation reduces the perceived length of time. When a delay-aversion is present, children might adopt elaborate self distraction techniques to avoid waiting. It has been suggested that delay aversion becomes problematic when children are set tasks by parents or teachers that involve temporal stimulation. Thus rather than a deficit in cognitive abilities and inhibition, ADHD is argued to reflect a motivational style and the inattentive, hyperactive and impulsive symptoms result from a delay aversion. It is not that hyperactive children are not capable of performing a set task optimally, but rather that they do not want to. Strategies include stimulus seeking behaviour (by acting on the people or objects in the environment) and stimulus producing behaviour (by producing proprioreceptive stimulation through fidgeting and wriggling) (Sonuga-Barke, 1994). When children are in control of their environment, they can choose to minimize delay by acting impulsively; however when children are not in control and are expected to behave in certain ways or face

sanctions, they will often choose to distract themselves from passing the time either by daydreaming (inattention) or fidgeting (hyperactivity) (Sonuga-Barke, 2002).

The delay aversion can furthermore have an impact on children's cognitive development and the acquisition of organisational skills. The inability of a child to engage sufficiently in delay-rich environments (possibly because of reward circuit abnormalities) may elicit punitive or negative responses from parents (child-x-environment correlation). Delay-rich environments in this way become associated with negative connotations and this punitive social environment, which in part is created by the child's behaviour, moderates the link between early behaviour and the establishment of a more generalised delay aversion (child-x-environment interaction). These developmental processes thus enable a child's underlying predisposition to develop into impairing impulsivity that further limits the child's learning opportunities, so that cognitive and self-organisational deficits become part of a fundamentally motivational disorder (Sonuga-Barke, 2005).

The delay-aversion hypothesis presents delay aversive processes as a single overarching construct; however a recent principal components analysis identified two components within this construct, including a negative effect of delay on performance and secondly a positive effect of delay. This second component represented a commitment to wait for a desired outcome or persist in a task, even when this was not required (Sonuga-Barke, Bitsakou, & Thompson, 2010). This study therefore suggest that the construct might not only represent an aversion to delay, but also reflects an inability to use delays positively.

In line with theory, it was found that delay periods produce an increase in activity and inattention in children with ADHD set against a comparison group (Antrop, Buyse, Roeyers, & van Oost, 2002). The delay aversion hypothesis moreover is a plausible theory, which is in line with the work of Sagvolden et al. (2005). Whilst evidence suggests a delay aversion in some children with ADHD, a similar problem emerges as was observed in the executive

dysfunction literature. In fact, when a 90th percentile normal population cut-off was used in a study of preschool ADHD children, 29 percent displayed both delay aversion and executive dysfunction, 27 percent delay aversion only, 15 percent executive dysfunction only and 29 percent neither problem (Nigg et al., 2005). Delay aversion alone is thus unlikely to explain the symptoms of all children with ADHD, however the evidence does suggest the involvement of motivational processes in at least a subset of children with ADHD.

Appendix II

Additional Associations of Toddlers' ADHD Symptoms and Perinatal Risk Factors

It was shown in Chapter 1 that many perinatal risk factors have been associated with the development of ADHD. However, whilst associations have been found with both genetic and environmental risk factors (Faraone et al., 1995; Nikolas et al., 2011; Thapar, Cooper, Eyre, & Langley, 2013), little is known about how these risk factors might interact to produce ADHD. In this respect, the study of intrauterine and perinatal circumstances has been particularly challenging, since environmental and genetic effect are difficult to separate. This might explain why the literature on obstetric complications is characterised by inconsistent findings.

In this thesis, only those risk factors that were consistently shown to influence ADHD symptoms, i.e. stress and smoking during pregnancy and birth weight, were examined. In addition to these prenatal risk factors, connections between ADHD, other toxic substances in pregnancy and complications during birth have been studied extensively. Whilst the literature often remains inconclusive with some researchers finding an effect and others failing to find a link, some studies have found significant associations between symptoms of ADHD and several complications, including the presence of delivery complications (Claycomb et al., 2004), a longer time between onset of labour and birth (Claycomb et al., 2004;), unusually short or long labour, foetal distress, forceps delivery and toxaemia or eclampsia (Hartsough & Lambert, 1985; Minde, Webb, & Sykes, 1968), emergency caesarean sections (Gurevitz et al., 2014), neonatal complications and early contractions (Amor et al., 2005). Moreover, a longitudinal study, which assessed the medical and neurological status of 5 perinatal groups of infants (full term, healthy preterm, medical preterm, neurological preterm and small for gestational age preterm) found that lower gestational age, lower birth weight, male gender,

higher neonatal risk, abnormal medical and neurological status at 18 and 30 months and lower socioeconomic status were all related to high activity and poorer attention at 4 years of age (McGrath et al., 2005). Exactly how these factors might influence later behavioural problems is unknown and caution needs to be taken when interpreting these findings, since the fact that problems occur during labour might be the result of other (unknown) risk factors (Chandler, 2010). Data on a number of these perinatal risk factors was collected during the first and second wave of data-collection of the CCDS. However, since these variables could not be used to assess the validity of the proposed precursor in this thesis, they will be examined in this Appendix. Here, it will be examined in which way risk factors are associated with one another, and whether they are related to toddlers' ADHD symptoms.

My argument is that certain gaps in the current literature and our understanding make it difficult to interpret the findings that connect perinatal adversity to ADHD symptoms. The most important issue is that many of the studies have not accounted for possible confounding variables sufficiently. This is especially problematic in studies which have used at risk populations, since women from deprived neighbourhoods are at an almost double risk of adverse pregnancy outcome (defined as ≥1 perinatal event; perinatal death, congenital malformations, prematurity, low birth weight and/or Apgar score < 7) (Timmermans et al., 2011). This increased risk can be explained by an accumulation of socio-demographic, lifestyle, obstetric and health-related risk factors, which are more often found in deprived areas. Without taking these confounding variables into account, it is almost impossible to conclude whether found associations are due to the risk factor under investigation or affected by other 'unknown' influences.

It is also known that exposure to the maternally provided prenatal environment is not independent of maternal characteristics and genotype, therefore prenatal risk factors, such as gestational stress and cigarette smoking in pregnancy, could arise either through maternally

provided genetic factors and/or a 'true' environmentally mediated effect (Thapar et al., 2007). These risk factors could also affect further exposure to risk that occurs in later pregnancy, such as prematurity, low birth weight and birth complications. Smoking during pregnancy for example is associated with low birth weight and prematurity (Jaddoe et al., 2008). The effect of smoking as well as stress in late pregnancy on birth weight appears truly environmental, since this association is similar in children of both genetically unrelated (as a result of in vitro fertilization) and related mothers (Rice et al., 2008; Rice et al., 2009). However, the same design showed that the relationship between prenatal stress and ADHD symptoms and smoking and ADHD symptoms was only found in children of genetically related mothers, suggesting that a gene-environment interaction must affect these associations (Rice et al., 2009; Thapar et al., 2009). Given that low birth weight has been found to affect attention problems in MZ, DZ and unrelated children pairs similarly and is therefore likely to play a causal role (Groen-Blokhuis et al., 2011), it might also be possible that birth weight mediates the relationship between prenatal risk factors and later behavioural outcomes. Birth weight is affected by many risk factors, including prenatal alcohol exposure, episodic illness, low pre-pregnancy weight, young maternal age, SE background, infant sex and poor gestational nutrition (Kramer, 1987); however it is also influenced by genetic factors and an environmental effect of maternal height and stature (which affects foetal growth and gestational age; Rice & Thapar, 2010).

Moreover, most studies have used retrospective measures of the intrauterine and perinatal circumstances, using interviews or questionnaires completed by mothers. It has been found that mothers tend to underreport exposure to toxins during pregnancy and birth complications using these methods (Buka, Goldstein, Seidman, & Tsuang, 2000) and it has therefore been argued that these reports might not be reliable. A recent study which compared maternal retrospective reports of pre and peri-natal events with medical records however,

found that agreement was very good for the majority of outcomes (with the exception of length of labour and alcohol use during pregnancy) (Rice et al., 2007). Nevertheless, prospective collection of data minimises the risk of recall bias and misclassification and is therefore a preferred method.

Furthermore, it might be that certain risk factors are specific to one symptom only, whilst others are associated with differing symptoms. It might therefore be warranted to look at associations with specific symptoms ofADHD, rather than at the disorder as a whole. Linnet et al. (2003) note that the time of assessment may be important, because symptoms become less conspicuous over time and only 30-40% of children with ADHD retain their diagnosis into adulthood. Therefore, it might be that the effects of obstetric complications are more or less detectable across developmental ages. Indeed, smaller differences in birth weight for twins have been found to contribute to subclinical ADHD symptoms present in early age, whilst larger differences in birth weight contributed to a more persistent twin-discordance in ADHD symptoms (Hultman et al., 2007). More refined effects of pre- and perinatal risk factors might therefore be detected in a younger sample. Assessing children in early childhood is also likely to minimise further confounding effects of the environment, as these effects accumulate over time.

It is argued here that examining risk factors in isolation might not be helpful, since it is clear that more than one environmental factor contributes to the same behavioural outcome and that these risk factors have an influence on each other as well. It appears safe to conclude that *more* adversity experienced in infancy is related to symptoms of ADHD (Lehn et al., 2007) and that environmental risk factors, present during the vulnerable period of development prior to and around birth, can have a strong impact on children's behaviour. However, whilst pregnancy and birth complications are likely to have a detrimental effect on brain development, it would not be justified to deduce that they cause ADHD; not all children

who have ADHD experience birth complications and vice versa, not all children who experience birth complications develop ADHD.

Therefore, in order to better understand the influence of pre- and perinatal circumstances on symptoms of ADHD and address some of the inconsistencies in the literature, the effect of a number of pregnancy and birth complications on symptoms of ADHD and cognitive task performance in toddlerhood is examined here, whilst controlling for parental ADHD symptoms and other confounding variables. Of particular interest was the way in which risk factors interact (i.e. does the presence of one risk factor increase the likelihood of another), which was explored in order to better understand the mechanism through which pregnancy and birth complications affect the development of ADHD symptoms.

Method

Participants and Procedure

The participants and procedure used were discussed in Chapter 2 and 4 and are therefore not repeated here. This appendix includes data from the first, second and fifth wave of data collection. For the purpose of this appendix some additional variables were used in addition to the tasks described earlier. Firstly, information from questionnaires and interview data, collected during the antenatal visit was used. Mothers were asked questions, which covered socio-economic risk factors, familial and personal medical history, measures of parental psychopathology and their pregnancy. Pregnancy-related questions covered areas such as their consumption of toxins during different stages of their pregnancy (smoking, alcohol and drugs), their psychological (stress, psychopathology) and physical health (illnesses, complications, medication taken, etc.). These data were collected prospectively during pregnancy in order to minimise the risk of recall bias. During the six-month

assessment, a tape-recorded interview was conducted with the mother, concerning questions surrounding the last part of the pregnancy, the labour and the health and development of the baby during the first six months of life.

Measures

Social risk and maternal psychopathology. Information about social circumstances was collected during Wave 1 (see Chapter 2, section 2.2.3.1.1). A retrospective questionnaire called 'What I was like as a Child', was completed by mothers during pregnancy and included questions which were indicative of Conduct Disorder, which is a prerequisite for a diagnosis of Antisocial Personality Disorder (ASPD). Items corresponding to DSM-IV criteria of ASPD were included in a questionnaire about current behaviours (called the 'What I am like' questionnaire). All relevant items were combined to form a composite variable representing antisocial behaviour in mothers, with an internal consistency of α = .79 (Hay et al., 2014). The same set of questionnaires also asked about prenatal stress during all trimesters (see Chapter 4, section 4.2.3). Diagnoses for life-time depression and depression during pregnancy were made on the basis of the maternal interview during pregnancy. This interview included the affect disorder section of the Schedules for Clinical Assessment in Neuropsychiatry (Wing et al., 1990) with an additional screen for psychotic symptomatology. Maternal reports of symptoms were reviewed in consultation with a psychiatrist when mothers responded positively to screening questions for a DSM-IV diagnosis of depressive illness (i.e. dysphoria or loss of interest in usual activities).

Pregnancy and birth complications. Pregnancy complications present during each trimester were reported at Wave 1 and the number of complications was added up to form a complication-score for early, mid- and late pregnancy. The complications included in the Wave 1 questionnaire were gestational diabetes, high blood pressure (toxaemia/pre-

eclampsia), low blood pressure, haemorrhoids (piles), severe constipation, stomach pains, hip pain, pelvic pain, back pain, swelling of hands or feet, varicose veins/thread veins, leg cramps, heartburn, kidney infection, bladder infection, recurrent urinary tract infections, premature rupturing of membranes, vaginal bleeding, cervical problems, uterine abnormalities and too little amniotic fluid.

At Wave 2, participants were asked whether they experienced any complications towards the end of their pregnancy. The following complications were reported at this stage: urine infection, cold, flu, anaemia, heartburn, diabetes, skin rash, low/high blood pressure, vaginal bleeding, high blood sugar, swollen hands/feet, (pre-)eclampsia, carpal tunnel syndrome, sciatica, early contraction/Braxton Hicks, low amniotic fluid, pelvic/back pain, cholestasis, breech, severe morning sickness, a fall, fainting/dizziness and a cessation of baby growth. The reported complications again were added up to form a complication-score for the end of pregnancy (i.e. the period before birth, but after the first interview).

Similarly, a score for problems immediately after birth was calculated by adding up the reported problems, which included jaundice, respiratory problems, heart problems, feeding problems, baby was cold/needed heat lamp, baby in Special Care Baby Unit (SCBU) or Neonatal Intensive Care Unit (NICU) and other problems. Mothers also reported on illnesses that the baby experienced during the first 6 months of life and a total number of illnesses-score was once again created, which included diarrhoea, blood in stools, vomiting, cough, high temperature, cold, ear ache, ear discharge, convulsions/fits, colic, rash, wheezing, breathlessness, stopping breathing, respiratory (chest) infections, eczema, allergies, bug/virus, gastric reflux, possible asthma and any other illnesses. Finally, a total score for sleeping problems during the same period was created, which included not settling easily, time to settle > 10 min., toys required to settle, night waking (> 2 times per night, awake for > 10 min.) and not settling back to sleep after night waking.

Toxins. The pregnant women were asked at Wave 1 to report on substances that they were using during their pregnancy, including smoking, alcohol, cannabis, illicit and other drugs. They were also asked to report the number of cigarettes smoked per day and units of alcohol drunk per week for the three semesters of pregnancy.

Further maternal and child characteristics. Several other variables were taken into account. Firstly, mothers reported their height and weight before pregnancy and from this their BMI was calculated using the following formula: BMI = (Weight in kilograms/ (Height in meters * Height in meters). Secondly, standardised scores for birth weight (adjusted for gestational age and gender) were used, since birth weight was highly correlated with gestational age. Thirdly, during the W2 mother interview mothers reported whether they breastfed their child after birth and for how long; a dichotomous score was created based on these reports (0 = never breastfed; 1 = breastfed). Similarly, mothers were asked at 6 months whether the child had experienced any feeding difficulties, and again a dichotomous score was created based on these reports (0 = no feeding difficulties; 1 = feeding difficulties). Finally, during the 6 month interview mothers reported on the type of delivery they experienced. Four types of deliveries were differentiated: a normal delivery, an assisted vaginal delivery (e.g. forceps), an unplanned caesarean and a planned caesarean.

Measurement of birth weight and gestational age. The measurement of this variable was discussed in Chapter 4 and are therefore not repeated here.

Data Analysis

The screening of violations in assumptions of parametric tests of the dependent variables was described earlier. Inter-correlations between prenatal and perinatal risk factors (use of toxins, stress, birth weight, etc.) were examined. Maternal ADHD was used as a starting point, since this could act as a proxy for both environmental and genetic risk for

ADHD. Regression analysis was performed to establish the influence of these risk factors on birth weight. Then the relationship between prenatal and perinatal risk factors and possible ADHD precursors and symptoms was examined using correlation tables. Several regression analyses were conducted in order to assess the contribution of individual risk factors to ADHD symptoms and cognitive task performance in toddlers, whilst controlling for social risk and familial factors. Finally, it was investigated whether any differences could be found for the dependent variables, depending on what type of delivery the child experienced. Conventional significance levels are observed in this appendix, given that these analyses are exploratory. It must of course be taken into account, that false positives might have occured, since a large number of correlations are examined in this appendix.

Results

Correlates of Mothers' ADHD Symptoms

Mothers' social circumstances and psychopathology. The social circumstances of mothers in the CCDS were comparable to those of the general population (see Table 1 for descriptive statistics). Parental ADHD symptoms could act as a proxy for both environmental and genetic risk for ADHD and the relationship between maternal ADHD symptoms and perinatal risk factors was of particular interest, since these symptoms might relate to the prenatal environment that infants are exposed to. Table 2 shows that maternal ADHD was highly correlated with increased social risk and more antisocial behaviour. Mothers with more ADHD symptoms were also significantly more likely to experience depression in pregnancy. Interestingly, fathers' ADHD was also significantly associated with these maternal risk factors.

Table 1. Mothers' social circumstances and psychopathology: descriptive statistics (excluding twins).

Variable		Descriptive statistics
Maternal ADHD symptoms	*Mean, SD (range)*	3.50, 2.27 (0-10), *N* = 325
Paternal ADHD symptoms	*Mean, SD (range)*	4.31, 2.19 (0-10), *N* = 281
Antisocial Behaviour	*Mean, SD (range)*	4.46, 4.13 (0-20), *N* = 325
Social Risk Index	*Mean, SD (range)*	1.49, 1.50 (0-5), *N* = 325
	0	109 (33.5%)
	1	84 (25.8%)
	2	57 (17.5%)
	3	31 (9.5%)
	4	27 (8.3%)
	5	17 (5.2%)
Smoking in pregnancy	*Yes*	79 (25.6%)
N = 309	*No*	230 (74.4%)
Alcohol in pregnancy	*Yes*	133 (42.8%)
N = 311	*No*	178 (57.2%)
Cannabis in pregnancy	*Yes*	8 (2.6%)
N = 311	*No*	303 (97.4%)
Other drugs in pregnancy	*Yes*	4 (1.3%)
N = 311	*No*	307 (98.7%)
Illicit drugs in pregnancy	*Yes*	10 (3.2%)
N = 311	*No*	301 (96.8%)
Depression in pregnancy	*Yes*	53 (16.3%)
N = 325	*No*	272 (83.7%)

Table 2. Pearson's correlations between maternal risk factors.

	1	2	3	4	5	6	7	8	9
1. Maternal ADHD	-	-	-	-	-	-	-	-	-
2. Paternal ADHD	.17*	-	-	-	-	-	-	-	-
3. Social Risk Index	.35**	.21**	-	-	-	-	-	-	-
4. Antisocial bhv (M)	.55**	.12*	.49**	-	-	-	-	-	-
5. Depression (preg)	.33**	.18**	.43**	.36**	-	-	-	-	-
6. Smoking (preg)	.27**	.15*	.49**	.46**	.27**	-	-	-	-
7. Alcohol (preg)	-.08	.002	-.16**	-.04	-.10†	.09	-	-	-
8. Cannabis (preg)	.08	.06	.22**	.26**	.26**	.23**	.07	-	-
9. Other drugs (preg)	.10†	-.01	.08	.25**	.03	.20**	.13*	.34**	-
10. Illicit drugs (preg)	.08	.05	.20**	.29**	.22**	.27**	.10†	.89**	.63**

NB: significance level * < .05 ** < .01, † < .10

Mothers' use of substances. During pregnancy, children were most frequently exposed to alcohol, followed by cigarettes, whilst only a small percentage of participants consumed other drugs (see Table 1). The consumption of substances differed over the course of pregnancy. Alcohol varied from an average of 3.70 units per week (range 0-30) in early

pregnancy to 1.27 (range 0-28) in mid- and 1.21 (range 0-28) in late pregnancy, whilst smoking followed a similar pattern, from an average of 9.89 cigarettes per day (range 0-30) in early pregnancy, to 5.68 (range 0-30) in mid- and 4.44 (range 0-20) in late pregnancy. Maternal ADHD symptoms were significantly related to smoking throughout pregnancy (see Table 2 and 3) as well as to stress in mid- and late pregnancy. Maternal ADHD symptoms were not significantly associated with the use of other substances, although a marginal correlation with the increased use of 'other drugs' was found. Exposure to one particular toxin however, correlated to increased use of other toxins and the use of substances, and smoking in particular, was strongly related to increased antisocial behaviour, depression during pregnancy and social risk factors. Fathers' ADHD symptoms were significantly related to smoking in early pregnancy and marginally associated with smoking in mid pregnancy (see Table 3).

Table 3. Maternal risk factors during pregnancy (Pearson's correlations).

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1. Maternal ADHD	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2. Paternal ADHD	.17**	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3. BMI mother	-.05	.002	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4. Birth weight[a]	-.03	-.02	.18**	-	-	-	-	-	-	-	-	-	-	-	-	-
5. Cigs early preg	.27**	.13*	-.09	-.16**	-	-	-	-	-	-	-	-	-	-	-	-
6. Cigs mid preg	.28**	.10†	-.09	-.19**	.82**	-	-	-	-	-	-	-	-	-	-	-
7. Cigs late preg	.23**	.09	-.07	-.25**	.65**	.74**	-	-	-	-	-	-	-	-	-	-
8. Alcohol early preg	-.01	-.02	-.02	-.07	.23**	.17**	.17**	-	-	-	-	-	-	-	-	-
9. Alcohol mid preg	.03	-.01	.03	-.11†	.15**	.17**	.22**	.52**	-	-	-	-	-	-	-	-
10. Alcohol late preg	.04	-.08	-.001	-.15*	.15**	.17**	.23**	.50**	.96**	-	-	-	-	-	-	-
11. Stress early preg	.10	.02	.05	-.04	-.06	-.10	-.05	.01	.003	.01	-	-	-	-	-	-
12. Stress mid preg	.20**	.09	.06	-.07	.13*	.15*	.09	.01	-.03	-.03	.38**	-	-	-	-	-
13. Stress late preg	.21**	.13*	.14*	.02	-.09	.09	.05	-.03	.03	.01	.12**	.46**	-	-	-	-
14. Compl. early preg	.06	-.01	.07	-.03	-.01	-.03	-.01	-.11†	-.09	-.10	.30**	.15*	.07	-	-	-
15. Compl. mid preg	.07	.07	.06	-.03	.08	.08	.14*	.01	-.10†	-.09	.16**	.24**	.16**	.54**	-	-
16. Compl. late preg	.07	-01	.12*	.03	.05	-.002	.004	.001	-.08	-.06	.14*	.14*	.18**	.33**	.47**	-
17. Compl. end preg	.04	.17**	.14*	.01	.08	.09	.06	.01	-.07	-.10†	.06	.26**	.07	.16**	.12*	.14*

NB: significance level * < .05 ** < .01, † < .10

[a] birth weight was adjusted for gestational age

Table 4. Pearson's correlations between risk factors in pregnancy and problems during delivery and the first six months of life.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1. Maternal ADHD	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2. Paternal ADHD	.17**	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3. Social Risk Index	.35**	.21**	-	-	-	-	-	-	-	-	-	-	-	-	-
4. Antisocial Bhv (M)	.55**	.12*	.49**	-	-	-	-	-	-	-	-	-	-	-	-
5. Depression (preg)	.33**	.18**	.43**	.36**	-	-	-	-	-	-	-	-	-	-	-
6. BMI (M)	-.05	.002	-.07	-.03	-.05	-	-	-	-	-	-	-	-	-	-
7. Mean# cigs	.29**	.12*	.48**	.45**	.25**	-.09	-	-	-	-	-	-	-	-	-
8. Mean units alcohol	.02	-.03	.03	.10†	.01	-.002	-.21**	-	-	-	-	-	-	-	-
9. Mean stress	.25**	.11†	.11†	.20**	.26**	.10	.08	-.02	-	-	-	-	-	-	-
10. Mean compl. (preg)	.09	.03	.05	.07	.25**	.11†	.03	-.09	.31**	-	-	-	-	-	-
11. Compl. end of preg	.04	.17*	.06	.11*	.14*	.14*	.06	-.04	.16**	.17**	-	-	-	-	-
12. Birth weight[a]	-.03	-.02	.11†	-.10†	-.13*	.18**	-.22**	-.11†	-.07	-.01	.01	-	-	-	-
13. Breastfeeding	-.27**	-.08	-.40**	-.27**	-.24**	-.02	-.32**	.09	.05	-.18**	-.04	.08	-	-	-
14. Illnesses 6 months	.15*	-.01	.03	.07	.19**	.06	.11	.05	.10	.21**	-.22**	-.01	-.07	-	-
15. Feeding difficulties	.09	.17**	.001	-.03	-.02	-.02	.05	-.09	-.04	-.03	.03	-.09	.02	.13*	-
16. Sleeping problems	-.05	-.02	-.04	-.05	.06	-.02	-.05	.02	.04	.04	.04	.05	.04	.21**	.01

NB: significance level * < .05 ** < .01 † < .10

[a] Birth weight was adjusted for gestational age.

Risk factors and complications towards the end of the pregnancy. Complications in pregnancy were most notably associated with increased levels of stress in mothers during the respective part of the pregnancy. Increased stress during mid-pregnancy and more complications throughout the pregnancy were significantly related to complications experienced during the final part of the pregnancy, whilst more smoking in late pregnancy was associated with complications in mid-pregnancy (see Table 3). Complications during pregnancy were also significantly associated with various risk factors, including father's ADHD symptoms, increased BMI, more depression in pregnancy and increased antisocial behaviour (see Table 4; and see Table 5 for descriptive statistics of risk factors).

Table 5. Risk factors of pregnancy and early life: descriptive statistics (excluding twins).

Variable		**Descriptive statistics**
Maternal Body Mass Index	*Mean, SD (range)*	23.65, 4.31 (14.88-40.67), *N* = 276
Stress in pregnancy	*Mean, SD (range)*	
	First trimester	4.74, 2.62 (0-10), *N* = 277
	Second trimester	3.43, 2.16 (0-10), *N* = 278
	Third trimester	3.03, 2.15 (0-10), *N* = 263
Number of complications in pregnancy	*Mean, SD (range)*	
	First trimester	1.55, 1.38 (0-8), *N* = 301
	Second trimester	2.37, 1.82 (0-8), *N* = 301
	Third trimester	2.89, 2.01 (0-11), *N* = 301
	End of pregnancy	0.61, 0.82 (0-4), *N* = 325
Problems with baby directly after birth	*Mean, SD (range)*	0.46, 0.66 (0-3), *N* = 325
Number of illnesses in first 6 months of life	*Mean, SD (range)*	1.31, 1.48 (0-9), *N* =298
Sleeping problems score	*Mean, SD (range)*	1.51, 1.06 (0-6), *N* =298
Breastfeeding (ever)	*Yes*	244 (82.2%)
N =297	*No*	53 (16.3%)
Feeding difficulties	*Yes*	71 (25%)
N= 284	*No*	213 (75%)

Children's Birth Weight in Relation to Maternal Risk Factors

Table 3 shows that birth weight is significantly associated with smoking and that this relationship gets stronger as the pregnancy progresses. A significant relationship between alcohol and birth weight is only found during mid and late pregnancy. Maternal body mass index (BMI) and depression during pregnancy further correlated positively with birth weight, whilst a marginal relationship was found with antisocial behaviour and social risk (see Table 4). In order to explore the unique contribution of these risk factors to birth weight, a regression analysis was undertaken (see Table 6). In the first step, maternal psychopathology was entered, a second step included maternal characteristics (BMI), whilst in a final step risk factors that occurred during pregnancy were entered. Table 6 shows that maternal BMI significantly predicts birth weight and that this relationship remains significant after other risk factors are added to the model. Use of cigarettes throughout pregnancy and alcohol during the third semester also significantly predicts birth weight, whilst depression during pregnancy shows a marginally significant effect.

Table 6. Relationship between maternal BMI, smoking and alcohol during pregnancy and birth weight.

Predictor	**B coef**	**(95% CI)**	**Beta**	***p***
Social Risk Index	-0.01	(-0.11 to 0.10)	-0.01	.90
Antisocial Behaviour (M)[1]	-0.03	(-0.07 to 0.02)	-0.08	.24
Social Risk Index	0.004	(-0.10 to 0.11)	0.01	.94
Antisocial Behaviour (M)	-0.03	(-0.07 to 0.02)	-0.09	.21
Mothers' BMI (M)[2]	0.04	(0.01 to 0.07)	0.17	.01*
Social Risk Index	0.08	(-0.03 to 0.20)	0.11	.15
Antisocial Behaviour (M)	-0.004	(-0.05 to 0.04)	-0.01	.86
Mothers' BMI (M)	0.04	(0.01 to 0.06)	0.16	.01*
Depression in pregnancy (M)	-0.33	(-0.72 to 0.06)	-0.11	.09†
Mean no. of cigarettes in pregnancy	-0.07	(-0.11 to -0.03)	-0.22	.002**
Mean unit of alcohol in late pregnancy[2]	-0.08	(-0.14 to -0.01)	-0.14	.02*

[1] Dependent variable: Birth weight. N= 259, R^2 = .01, p = .01*
[2] Dependent variable: Birth weight. N= 259, R^2 = .04, p = .03*
[3] Dependent variable: Birth weight. N= 259, R^2 = .11, p = .07†

Infant's Health and Wellbeing

Since prenatal factors could also be related to problems after birth, we asked mothers about the health and wellbeing of the infant during the first six months. Correlations can be found in Table 4; levels of stress, cigarette and alcohol use and complications during pregnancy are averaged in this table to save space. This table shows mothers that were less likely to breastfeed had more ADHD symptoms, increased social risk, increased antisocial behaviour, had been smoking, were depressed and experienced more complications during pregnancy. Experiencing an increased number of illnesses during early life was related to maternal ADHD symptoms as well as depression and complications during pregnancy. Children who experienced more illness were also found to have significantly more sleeping and feeding difficulties. Feeding difficulties were furthermore significantly related to fathers' ADHD symptoms.

Toddlers' symptoms of ADHD.

Table 9 shows that toddlers' ADHD symptoms were significantly associated with social risk, maternal and paternal ADHD symptoms, antisocial behaviour, smoking throughout pregnancy and increased levels of stress during mid and late pregnancy. A marginally significant trend was found with complications in late pregnancy, more problems directly after the birth and the absence of breastfeeding.

Table 9. Pearson's correlations between risk factors and toddlers' ADHD symptoms.

	Toddlers' ADHD symptoms		**Toddlers' ADHD symptoms**
Maternal ADHD	.20**	Mean units alcohol pregnancy	-.01
Paternal ADHD	.25**	Stress[1] early pregnancy	.04
Social Risk Index	.21**	Stress[1] mid pregnancy	.13*
Depression in pregnancy	.09	Stress[1] late pregnancy	.18**
Mother's antisocial behaviour	.19**	Complications early preg	.03
BMI mother	.08	Complications mid preg	.08
Cigs early preg	.13*	Complications late preg	.12†
Cigs mid preg	.19**	Complications end of preg	.01
Cigs late preg	.12*	Birth weight [a]	-.10
Mean # cigarettes pregnancy	.14*	Problems directly after birth	.11†
Alcohol early preg	-.03	Breastfeeding	-.12†
Alcohol mid preg	.01	Illnesses 1st 6 months	-.07
Alcohol late preg	.01	Feeding difficulties	.05
Mean units alcohol pregnancy	-.01	Sleeping problems	-.08

NB: significance level * < .05 ** < .01, † < .10

[a] Birth weight was adjusted for gestational age

In order to further explore the independent contribution of each risk factor to the development of ADHD, a regression analysis was undertaken (see Table 10). In the first step social risk was entered. Social risk significantly predicted toddlers' ADHD symptoms, however this effect did not remain when other risk factors were added to the model. In the second step, parental psychopathology was entered into the model (measures of ADHD symptoms and antisocial behaviour) and these factors explained additional variance, with fathers' ADHD symptoms showing an independent significant effect that remained when further variables were entered into the model. A third step, where obstetric data were added, including smoking and stress in mid and late pregnancy, explained further additional variance, and it was stress during mid- and late pregnancy, that showed an independent significant effect on toddlers' ADHD symptoms. Since other risk factors were not significantly associated with ADHD symptoms, they were not included in the analysis.

Table 10. Relationship between risk factors and toddlers' ADHD symptoms.

Predictor	**B coef**	**(95% CI)**	**Beta**	***P***
Social Risk Index[1]	0.14	(0.05 to 0.23)	-0.21	.002**
Social Risk Index	-0.07	(-0.02 to 0.16)	0.11	.13
Maternal ADHD	0.03	(-0.03 to 0.08)	0.07	.36
Paternal ADHD	0.08	(0.03 to 0.12)	0.20	.003*
Antisocial behaviour[2]	0.03	(-0.02 to 0.07)	0.10	.22
Social Risk Index	0.06	(-0.10 to 0.08)	0.08	.27
Maternal ADHD	0.02	(-0.05 to 0.06)	0.04	.60
Paternal ADHD	0.07	(0.02 to 0.11)	0.19	.01*
Antisocial behaviour	0.02	(-0.02 to 0.06)	0.09	.28
Mean # cigs preg	0.02	(-0.03 to 0.05)	0.09	.23
Stress mid/late preg	0.06	(0.01 to 0.13)	0.14	.04*

[1] Dependent variable: Toddlers' ADHD symptoms. N= 218, R^2 = .04, p =.002
[2] Dependent variable: Toddlers' ADHD symptoms. N= 218, R^2 = .11, p = .003
[3] Dependent variable: Toddlers' ADHD symptom. N= 218, R^2 = .13, p = .05

When an additional analysis was performed which included the previous risk factors in a first step (R^2 = .11, p < .001, N = 196) and ODD problems in a second step (R^2 = .36, p < .001; ß = 0.51, p < .001), stress in mid- and late pregnancy no longer explained additional variance in toddlers' symptoms of ADHD (R^2 = .36, p = .50; ß = 0.02, p = .71).

Perinatal risk factors and toddlers' performance on 4 executive functioning tasks. Behavioural regulation scores at 33 months were significantly associated with maternal ADHD symptoms, whilst a marginal relationship with paternal symptoms was found (see Table 11). No association with social risk was found, however it was significantly related to feeding difficulties, whilst a marginal relationship with use of alcohol in early pregnancy (positive) and problems directly after birth was found.

Cognitive flexibility scores at 33 months were not related to parental ADHD symptoms (see Table 11). Complications during mid-pregnancy were significantly associated with poorer cognitive flexibility scores, as was mothers' BMI (marginally significant).

Table 11. Correlations between risk factors and cognitive performance at 33 months of age.

	Raisin	Whisper	BBLB	Tower	Behavioural Regulation	Cognitive Flexibility
Maternal ADHD	-.08	-.14*	-.09	.01	-.16*	-.06
Paternal ADHD	-.14*	-.11	-.05	-.04	-.13†	-.06
Social Risk Index	-.002	.04	-.10	-.09	.07	-.11
Depression in pregnancy	.02	.03	-.04	-.01	.03	-.03
Mothers antisocial behaviour	.004	.03	-.11	-.004	-.01	-.09
BMI mother	.06	.03	-.07	-.13†	.06	-.13†
Cigs early preg	.03	-.01	-.07	.07	.02	.01
Cigs mid preg	.01	.06	-.09	.002	.04	-.06
Cigs late preg	.03	.01	-.08	.001	.03	-.05
Mean # cigarettes pregnancy	.01	.01	-.09	.02	.02	-.04
Alcohol early preg	.11	.15*	.06	-.01	.12†	.01
Alcohol mid preg	.04	.04	.04	.06	.02	.06
Alcohol late preg	.05	-.01	.04	.06	.01	.06
Mean units alcohol pregnancy	.10	.12†	.05	.02	.09	.02
Stress early pregnancy	.03	-.03	-.02	.05	-.001	.02
Stress mid pregnancy	-.02	-.03	-.08	-.02	-.02	-.05
Stress late pregnancy	-.05	-.07	-.09	.03	-.09	-.04
Complications early preg	-.07	-.02	-.05	-.01	-.08	-.05
Complications mid preg	-.08	.18**	-.18**	-.02	.02	-.16*
Complications late preg	.07	.14*	-.02	-.002	.11	-.02
Complications end of preg	-.08	.05	.11	.04	-.04	.08
Birth weight[1]	-.04	.09	.01	.03	.05	.04
Problems directly after birth	-.10	-.08	-.01	-.03	-.13†	-.04
Breastfeeding	.13†	-.03	.07	.02	.06	.05
Illnesses 1st 6 months	-.07	.06	.08	-.002	-.01	.04
Feeding difficulties	-.10	-.13†	-.11	.09	-.17*	-.01
Sleeping problems	.08	-.02	.03	.03	.04	.04

NB: significance level * < .05 ** < .01, † < .10

[1] birth weight was adjusted for gestational age

Once more, in order to further explore the independent contribution of each risk factor to toddlers' cognitive performance, regression analyses were undertaken. Firstly, a regression was performed on behavioural regulation (see Table 12), which included social risk and maternal ADHD symptoms; whilst paternal ADHD symptoms were excluded in order to maximise the sample size. Social risk and mothers' ADHD symptoms significantly predicted behavioural regulation, and this effect remained when further risk factors were added to the model. A final step included alcohol in early pregnancy, problems directly after birth and

feeding difficulties to the model and some additional variance was explained. However, only a marginally significant independent effect of infants' feeding difficulties was found.

Table 12. Relationship between risk factors and Behavioural Regulation at 33 months.

Predictor	**B coef**	**(95% CI)**	**Beta**	***P***
Social Risk Index[1]	0.09	(-0.02 to 0.19)	0.11	.10
Social Risk Index	0.12	(0.02 to 0.23)	0.17	.02*
Maternal ADHD[2]	-0.07	(-0.14 to -0.01)	-0.17	.02*
Social Risk Index	0.11	(0.01 to 0.22)	0.15	.04*
Maternal ADHD	-0.06	(-0.12 to -0.003)	-0.15	.04*
Alcohol early pregnancy	0.02	(-0.02 to 0.05)	0.07	.28
Problems directly after birth	-0.14	(-0.35 to 0.06)	-0.09	.18
Feeding difficulties	-0.28	(-0.59 to 0.03)	-0.12	.08†

[1] Dependent variable: Behavioural Regulation. N= 208, R^2 = .01, p = .10
[2] Dependent variable: Behavioural Regulation. N= 208, R^2 = .04, p = .02
[3] Dependent variable: Behavioural Regulation. N= 208, R^2 = .07, p = .06

A second regression analysis was performed including paternal ADHD symptoms in the second step (*N* =191). This model showed an effect of parental ADHD symptoms in the second step (R^2 = .06, *p* = .01; father's ADHD symptoms: ß = -0.16, *p* = .03; mothers' ADHD symptoms: ß = -0.17, *p* = .03); however, after all predictors (mean units of alcohol in early pregnancy, problems directly after birth and feeding difficulties) were added only marginally significant effects of parental ADHD symptoms remained (R^2 = .08, *p* = .22; father's ADHD symptoms: ß = -0.14, *p* = .07; mothers' ADHD symptoms: ß = -0.14, *p* = .06). Similarly, when an additional analysis was performed which included the previous risk factors in a first step (R^2 = .06, *p* = .01, *N* = 177) and ODD problems in a second step (R^2 = .08, *p* = .07; ß = -0.14, *p* = .07), the perinatal risk factors no longer explained additional variance in toddlers' symptoms of ADHD (R^2 = .09, *p* = .53), whilst only a marginal effect of parental ADHD symptoms was maintained (father's ADHD symptoms: ß = -0.14, *p* = .07; mothers' ADHD symptoms: ß = -0.15, *p* = .06).

Furthermore, two regression analyses were performed on cognitive flexibility (see Table 13). In the first regression analysis no effect of parental ADHD symptoms or social risk

was found, however a final step, including complications in mid-pregnancy and mothers' BMI, explained some additional variance. In particular, a significant independent effect of complications in mid-pregnancy on cognitive flexibility was found, whilst a marginal effect of mothers' BMI was found.

Table 13. Relationship between risk factors and Cognitive Flexibility at 33 months.

Predictor	**B coef**	**(95% CI)**	**Beta**	***P***
Social Risk Index[1]	-0.07	(-0.18 to 0.04)	-0.09	.22
Social Risk Index	-0.07	(-0.18 to 0.05)	-0.08	.25
Maternal ADHD[2]	-0.004	(-0.07 to 0.06)	-0.01	.91
Social Risk Index	-0.06	(-0.18 to 0.06)	-0.07	.30
Maternal ADHD	0.00	(-0.06 to 0.06)	0.00	.99
Complications mid pregnancy	-0.08	(0.16 to -0.002)	-0.14	.04*
Mothers' BMI	-0.03	(-0.06 to 0.003)	-0.12	.08†

[1] Dependent variable: Cognitive Flexibility. N= 207, R^2 = .01, p = .22
[2] Dependent variable: Cognitive Flexibility. N= 207, R^2 = .01, p = .91
[3] Dependent variable: Cognitive Flexibility. N= 207, R^2 = .05, p = .02

A second regression analysis was performed including paternal ADHD symptoms in the second step (*N* =192). This model also showed no effect of social risk (R^2 = .01, *p* = .27) parental ADHD symptoms (R^2 = .01, *p* = .88) and the effect of complications during mid-pregnancy was no longer found (R^2 = .03. *p* = .09; ß = -0.12, *p* = .11). When an additional analysis was performed which included the previous risk factors in a first step (R^2 = .01, *p* = .51, *N* = 176) and ODD problems in a second step (R^2 = .01, *p* = .70; ß = 0.03, *p* = .70), a marginal independent effect of complications during mid-pregnancy was found (R^2 = .04, *p* = .08; ß = -0.14, *p* = .07).

Relationship between type of delivery and precursors of ADHD. It was further examined whether there were any differences between participants who had different types of deliveries. The majority of the participants experienced a normal delivery (57.4%), whilst 19.1% had an assisted vaginal delivery, 19.8% an unplanned caesarean and 3.7% a planned

Caesarean. A one-way ANOVA revealed no significant differences in toddlers' ADHD symptoms between the four groups, F (3,266) = 0.65, p = .59. Similarly, no differences between the four groups were found for behavioural regulation (F (3,220) = 0.99, p = .96) or cognitive flexibility (F (3,220) = 0.28, p = .84).

Discussion

By examining multiple risk factors within one study, we were able to study how these factors were inter-correlated and how they predicted possible early precursors and manifestations of ADHD symptoms. Most striking is the accumulative nature of risk factors. The associations found between maternal ADHD and social risk factors, psychological problems as well as exposure to toxicity in pregnancy illustrate this point clearly. The analyses in this appendix have attempted to take some of these accumulative effects into account while investigating the influence of perinatal adversity on symptoms of ADHD and cognitive task performance in toddlerhood. It must be acknowledged that the exploratory nature of these analyses limits the conclusions that can be drawn from these findings.

Whilst it was hypothesised that low birth weight might mediate some of the accumulative effects of prenatal risk factors, the current study did not support this hypothesis. Birth weight was affected by smoking and alcohol use in pregnancy, however no significant correlations with ADHD symptoms or cognitive task performance in toddlerhood were found. Of course, a lack of power might have been responsible for this finding; however it is also possible that the correction for gestational age played a role. Since gestational age and birth weight are highly correlated, it is suggested here that controlling for this provides us with a more reliable predictor.

Next, the effect of risk factors on toddlers' ADHD symptoms was examined and it was found that toddlers' symptoms were significantly related to social risk, parental ADHD symptoms, antisocial behaviour, use of cigarettes in pregnancy and levels of stress during pregnancy. A marginally significant trend was found for complications in late pregnancy, more problems directly after birth and the absence of breastfeeding. However, when other risk factors were taken into account, only paternal ADHD symptoms and stress in mid- and late pregnancy were independently associated with ADHD symptoms in toddlers. When ODD problems were controlled for, stress in mid- and late pregnancy no longer explained any additional variance. These results are in line with those of Chapter 4, and confirm that the variables chosen as 'well-established' risk factors are associated most strongly with ADHD symptoms.

Finally, the effect of risk factors on children's cognitive task performance was examined. Behavioural regulation was significantly associated with maternal ADHD symptoms and feeding difficulties and marginally with paternal ADHD symptoms, alcohol in early pregnancy (positive) and problems directly after birth. After controlling for social risk and parental ADHD symptoms, a significant independent effect of maternal and paternal ADHD symptoms was found, whilst only a marginal effect of feeding difficulties remained. A recent study found that children who later developed ADHD had suffered more frequently from infant colic, gastroesophageal reflux at 3 months and feeding problems up to 9 months of age than a comparison group (Gurevitz et al., 2014). It is possible that feeding difficulties in early infancy are an indicator of poorer behavioural regulation later in childhood, but this requires further investigation. However, it must be noted that after additional control for ODD symptoms only a marginal effect of maternal and paternal ADHD symptoms remained and feeding difficulties no longer showed an association with behavioural regulation.

Cognitive flexibility was significantly associated with complications in mid-pregnancy and marginally with mothers' BMI. The effect of complications persisted after social risk and parental ADHD symptoms were taken into account, and remained marginally significant, when ODD symptoms were also controlled for. It thus appears that complications in mid-pregnancy might have a specific effect on cognitive flexibility, which is not observed for other indicators of ADHD symptoms; however this finding requires further replication before any definite conclusions can be drawn. It must also be noted that there were various types of complications included in the 'complication score' and it would be interesting to investigate whether specific types of complications are more strongly associated with adverse outcomes, so that possible causal mechanisms might be uncovered. Given the infrequent occurrence of some specific complications, this might be best investigated using a different research design.

In conclusion, the results presented in this appendix indicate that after controlling for social risk and parental ADHD symptoms the absence of breastfeeding was independently associated with informant-reported activity levels. Increased measured activity levels during restraint and peer interaction were associated with several risk factors, whilst risk factors related to decreased activity during baseline and attention. Toddlers' ADHD symptoms were independently predicted by stress in mid and late pregnancy and fathers' ADHD symptoms. Behavioural regulation was associated with social risk, parental ADHD symptoms and infants' feeding difficulties, whilst cognitive flexibility was related to complications in mid-pregnancy. The accumulative nature of exposure to risk factors and several possible interactions between risk factors were also discussed. Whilst more work is certainly needed, these findings are highly relevant to the general population and might contribute to improved identification and prevention strategies.

Appendix III

Mplus Output for Informant-Reported Activity Levels Factor Scores

```
Mplus VERSION 7.11
MUTHEN & MUTHEN
06/03/2014   2:56 PM

INPUT INSTRUCTIONS

  TITLE:      factor scores for activity level scale across 3 informants
  DATA:       FILE IS W2IBQscales.dat;
  VARIABLE:   NAMES ARE famcode actM actF actSO dis2limM dis2limF dis2limSO
              dislatM  dislatF  dislatSO  duroriM  duroriF  duroriSO  smileM
smileF
              smileSO sootheM soothF soothSO;
              USEVARIABLES ARE actM actF actSO;
              MISSING IS ALL (-9);
  MODEL:      f by actM* actF actSO;
              f@1 ; [f@0];
  ANALYSIS:   Estimator=MLR;
  OUTPUT:     STANDARDIZED sampstat;
  SAVEDATA:   file= IBQactivitylevel.dat;
              missflag=-9;
              save= fscores;

*** WARNING
  Data set contains cases with missing on all variables.
  These cases were not included in the analysis.
  Number of cases with missing on all variables:  67
   1 WARNING(S) FOUND IN THE INPUT INSTRUCTIONS

factor scores for activity level scale across 3 informants

SUMMARY OF ANALYSIS

Number of groups                                                 1
Number of observations                                         265
Number of dependent variables                                    3
Number of independent variables                                  0
Number of continuous latent variables                            1

Observed dependent variables
  Continuous
   ACTM        ACTF        ACTSO

Continuous latent variables
   F

Estimator                                                      MLR
Information matrix                                        OBSERVED
Maximum number of iterations                                 1000
Convergence criterion                                   0.500D-04
Maximum number of steepest descent iterations                  20
Maximum number of iterations for H1                          2000
Convergence criterion for H1                            0.100D-03

Input data file(s)
  W2IBQscales.dat
```

Input data format FREE

SUMMARY OF DATA

Number of missing data patterns 7

COVARIANCE COVERAGE OF DATA

Minimum covariance coverage value 0.100

PROPORTION OF DATA PRESENT

Covariance Coverage

	ACTM	ACTF	ACTSO
ACTM	0.943		
ACTF	0.770	0.781	
ACTSO	0.732	0.634	0.781

SAMPLE STATISTICS

ESTIMATED SAMPLE STATISTICS

Means

	ACTM	ACTF	ACTSO
1	3.961	3.945	3.901

Covariances

	ACTM	ACTF	ACTSO
ACTM	0.686		
ACTF	0.316	0.541	
ACTSO	0.227	0.154	0.733

Correlations

	ACTM	ACTF	ACTSO
ACTM	1.000		
ACTF	0.518	1.000	
ACTSO	0.320	0.245	1.000

MAXIMUM LOG-LIKELIHOOD VALUE FOR THE UNRESTRICTED (H1) MODEL IS -756.269
THE MODEL ESTIMATION TERMINATED NORMALLY

MODEL FIT INFORMATION

Number of Free Parameters	9
Loglikelihood	
H0 Value	-756.269
H0 Scaling Correction Factor for MLR	1.0569
H1 Value	-756.269
H1 Scaling Correction Factor for MLR	1.0569
Information Criteria	
Akaike (AIC)	1530.537
Bayesian (BIC)	1562.755
Sample-Size Adjusted BIC (n* = (n + 2) / 24)	1534.220
Chi-Square Test of Model Fit	
Value	0.000*
Degrees of Freedom	0
P-Value	0.0000

Scaling Correction Factor 1.0000
for MLR

* The chi-square value for MLM, MLMV, MLR, ULSMV, WLSM and WLSMV cannot be used for chi-square difference testing in the regular way. MLM, MLR and WLSM chi-square difference testing is described on the Mplus website. MLMV, WLSMV,and ULSMV difference testing is done using the DIFFTEST option.

RMSEA (Root Mean Square Error Of Approximation)

Estimate	0.000	
90 Percent C.I.	0.000	0.000
Probability RMSEA <= .05	0.000	

CFI/TLI

CFI	1.000
TLI	1.000

Chi-Square Test of Model Fit for the Baseline Model

Value	68.946
Degrees of Freedom	3
P-Value	0.0000

SRMR (Standardized Root Mean Square Residual)

Value	0.000

MODEL RESULTS

		Estimate	S.E.	Est./S.E.	Two-Tailed P-Value
F	BY				
	ACTM	0.682	0.106	6.441	0.000
	ACTF	0.463	0.075	6.165	0.000
	ACTSO	0.333	0.091	3.668	0.000
Means					
	F	0.000	0.000	999.000	999.000
Intercepts					
	ACTM	3.961	0.052	75.839	0.000
	ACTF	3.945	0.050	78.701	0.000
	ACTSO	3.901	0.059	66.011	0.000
Variances					
	F	1.000	0.000	999.000	999.000
Residual Variances					
	ACTM	0.221	0.127	1.742	0.082
	ACTF	0.327	0.067	4.872	0.000
	ACTSO	0.622	0.079	7.910	0.000

STANDARDIZED MODEL RESULTS

STDYX Standardization

		Estimate	S.E.	Est./S.E.	Two-Tailed P-Value
F	BY				
	ACTM	0.823	0.115	7.142	0.000
	ACTF	0.630	0.096	6.593	0.000
	ACTSO	0.389	0.103	3.774	0.000
Means					
	F	0.000	0.000	999.000	999.000
Intercepts					
	ACTM	4.781	0.214	22.368	0.000
	ACTF	5.361	0.234	22.905	0.000
	ACTSO	4.557	0.220	20.693	0.000
Variances					
	F	1.000	0.000	999.000	999.000
Residual Variances					
	ACTM	0.323	0.190	1.701	0.089

ACTF	0.603	0.120	5.017	0.000
ACTSO	0.849	0.080	10.592	0.000

STDY Standardization

	Estimate	S.E.	Est./S.E.	Two-Tailed P-Value
F BY				
ACTM	0.823	0.115	7.142	0.000
ACTF	0.630	0.096	6.593	0.000
ACTSO	0.389	0.103	3.774	0.000
Means				
F	0.000	0.000	999.000	999.000
Intercepts				
ACTM	4.781	0.214	22.368	0.000
ACTF	5.361	0.234	22.905	0.000
ACTSO	4.557	0.220	20.693	0.000
Variances				
F	1.000	0.000	999.000	999.000
Residual Variances				
ACTM	0.323	0.190	1.701	0.089
ACTF	0.603	0.120	5.017	0.000
ACTSO	0.849	0.080	10.592	0.000

STD Standardization

	Estimate	S.E.	Est./S.E.	Two-Tailed P-Value
F BY				
ACTM	0.682	0.106	6.441	0.000
ACTF	0.463	0.075	6.165	0.000
ACTSO	0.333	0.091	3.668	0.000
Means				
F	0.000	0.000	999.000	999.000
Intercepts				
ACTM	3.961	0.052	75.839	0.000
ACTF	3.945	0.050	78.701	0.000
ACTSO	3.901	0.059	66.011	0.000
Variances				
F	1.000	0.000	999.000	999.000
Residual Variances				
ACTM	0.221	0.127	1.742	0.082
ACTF	0.327	0.067	4.872	0.000
ACTSO	0.622	0.079	7.910	0.000

R-SQUARE

Observed Variable	Estimate	S.E.	Est./S.E.	Two-Tailed P-Value
ACTM	0.677	0.190	3.571	0.000
ACTF	0.397	0.120	3.297	0.001
ACTSO	0.151	0.080	1.887	0.059

QUALITY OF NUMERICAL RESULTS

Condition Number for the Information Matrix 0.111E-01
(ratio of smallest to largest eigenvalue)

SAMPLE STATISTICS FOR ESTIMATED FACTOR SCORES

SAMPLE STATISTICS

Means

	F	F_SE
1	0.000	0.537

```
           Covariances
              F             F_SE
           ________      ________
 F            0.703
 F_SE         0.001         0.008

           Correlations
              F             F_SE
           ________      ________
 F            1.000
 F_SE         0.015         1.000
```

SAVEDATA INFORMATION

```
  Save file
    IBQactivitylevel.dat

  Order and format of variables
    ACTM           F10.3
    ACTF           F10.3
    ACTSO          F10.3
    F              F10.3
    F_SE           F10.3
  Save file format
    5F10.3
  Save file record length    10000
```

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Web: www.StatModel.com
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Appendix IV

Mplus Output for Toddler ADHD Symptoms Factor Scores

```
Mplus VERSION 7.11
MUTHEN & MUTHEN
06/25/2014   1:57 PM

INPUT INSTRUCTIONS

TITLE:            factor scores for adhd scale across 3 informants
DATA:            FILE IS W4W5HYPandCBCL.dat;
VARIABLE: NAMES= famcode mqcbcl fqcbcl soqcbcl mqmshyp fqmshyp  soqmshyp;
          USEVARIABLES ARE mqcbcl fqcbcl soqcbcl mqmshyp fqmshyp soqmshyp;
                        MISSING IS ALL (-9);
MODEL:          f1 by mqcbcl fqcbcl soqcbcl;
                           f1@1 ; [f1@0];
                      f2 by mqmshyp fqmshyp soqmshyp;
                           f2@1 ; [f2@0];
                               f by f1* f2;
                                   f@1 ; [f@0];
ANALYSIS:     Estimator=MLR;
OUTPUT:      STANDARDIZED sampstat MOD;
SAVEDATA:   file= toddlerW4W5adhd.dat;
                       missflag=-9;
                       save= fscores;
*** WARNING
  Data set contains cases with missing on all variables.
  These cases were not included in the analysis.
  Number of cases with missing on all variables:  46
   1 WARNING(S) FOUND IN THE INPUT INSTRUCTIONS
factor scores for adhd scale across 3 informants

SUMMARY OF ANALYSIS

Number of groups                                                 1
Number of observations                                         286
Number of dependent variables                                    6
Number of independent variables                                  0
Number of continuous latent variables                            3
Observed dependent variables

  Continuous
   MQCBCL      FQCBCL      SOQCBCL     MQMSHYP     FQMSHYP     SOQMSHYP

Continuous latent variables
   F1          F2          F

Estimator                                                      MLR
Information matrix                                        OBSERVED
Maximum number of iterations                                 1000
Convergence criterion                                   0.500D-04
Maximum number of steepest descent iterations                  20
Maximum number of iterations for H1                          2000
Convergence criterion for H1                            0.100D-03
Input data file(s)
  W4W5HYPandCBCL.dat

Input data format  FREE
```

SUMMARY OF DATA

Number of missing data patterns 24

COVARIANCE COVERAGE OF DATA

Minimum covariance coverage value 0.100

PROPORTION OF DATA PRESENT

Covariance Coverage

	MQCBCL	FQCBCL	SOQCBCL	MQMSHYP	FQMSHYP
MQCBCL	0.839				
FQCBCL	0.587	0.615			
SOQCBCL	0.601	0.524	0.636		
MQMSHYP	0.832	0.598	0.626	0.965	
FQMSHYP	0.664	0.615	0.559	0.748	0.769
SOQMSHYP	0.717	0.577	0.633	0.811	0.703

Covariance Coverage

	SOQMSHYP
SOQMSHYP	0.829

SAMPLE STATISTICS

ESTIMATED SAMPLE STATISTICS

Means

	MQCBCL	FQCBCL	SOQCBCL	MQMSHYP	FQMSHYP
1	4.326	4.390	3.656	2.385	2.243

Means

	SOQMSHYP
1	1.717

Covariances

	MQCBCL	FQCBCL	SOQCBCL	MQMSHYP	FQMSHYP
MQCBCL	5.947				
FQCBCL	2.729	6.613			
SOQCBCL	2.983	2.255	5.964		
MQMSHYP	2.312	1.389	1.238	2.590	
FQMSHYP	1.775	2.898	1.575	1.246	3.195
SOQMSHYP	1.075	0.955	2.213	0.894	1.057

Covariances

	SOQMSHYP
SOQMSHYP	2.379

Correlations

	MQCBCL	FQCBCL	SOQCBCL	MQMSHYP	FQMSHYP
MQCBCL	1.000				
FQCBCL	0.435	1.000			
SOQCBCL	0.501	0.359	1.000		
MQMSHYP	0.589	0.336	0.315	1.000	
FQMSHYP	0.407	0.631	0.361	0.433	1.000

```
 SOQMSHYP       0.286         0.241         0.587         0.360         0.383

Correlations
              SOQMSHYP
              ________
 SOQMSHYP       1.000

MAXIMUM LOG-LIKELIHOOD VALUE FOR THE UNRESTRICTED (H1) MODEL IS -2582.294
THE MODEL ESTIMATION TERMINATED NORMALLY
```

MODEL FIT INFORMATION

```
Number of Free Parameters                       18
Loglikelihood
          H0 Value                       -2646.380
          H0 Scaling Correction Factor       1.0310
            for MLR
          H1 Value                       -2582.294
          H1 Scaling Correction Factor       1.0304
            for MLR
Information Criteria
          Akaike (AIC)                    5328.761
          Bayesian (BIC)                  5394.569
          Sample-Size Adjusted BIC        5337.489
            (n* = (n + 2) / 24)
Chi-Square Test of Model Fit
          Value                            124.529*
          Degrees of Freedom                    9
          P-Value                          0.0000
          Scaling Correction Factor         1.0293
            for MLR
*    The chi-square value for MLM, MLMV, MLR, ULSMV, WLSM and WLSMV cannot
be used for chi-square difference testing in the regular way.  MLM, MLR and
WLSM chi-square difference testing is described on the Mplus website.
MLMV, WLSMV,and ULSMV difference testing is done using the DIFFTEST option.

RMSEA (Root Mean Square Error Of Approximation)
          Estimate                         0.212
          90 Percent C.I.                  0.180  0.246
          Probability RMSEA <= .05         0.000
CFI/TLI
          CFI                              0.670
          TLI                              0.450
Chi-Square Test of Model Fit for the Baseline Model
          Value                          364.961
          Degrees of Freedom                 15
          P-Value                          0.0000
SRMR (Standardized Root Mean Square Residual)
          Value                            0.127
```

MODEL RESULTS

```
                                                    Two-Tailed
                  Estimate       S.E.  Est./S.E.    P-Value
 F1       BY
    MQCBCL           1.000      0.000    999.000    999.000
    FQCBCL           0.593      0.134      4.438      0.000
    SOQCBCL          0.661      0.108      6.133      0.000
 F2       BY
    MQMSHYP          1.000      0.000    999.000    999.000
    FQMSHYP          0.676      0.133      5.072      0.000
    SOQMSHYP         0.485      0.113      4.292      0.000
```

F BY				
F1	1.987	0.163	12.196	0.000
F2	1.097	0.096	11.438	0.000
Means				
F	0.000	0.000	999.000	999.000
Intercepts				
MQCBCL	4.323	0.153	28.299	0.000
FQCBCL	4.410	0.188	23.507	0.000
SOQCBCL	3.631	0.175	20.787	0.000
MQMSHYP	2.383	0.097	24.689	0.000
FQMSHYP	2.238	0.118	18.985	0.000
SOQMSHYP	1.717	0.099	17.323	0.000
F1	0.000	0.000	999.000	999.000
F2	0.000	0.000	999.000	999.000
Variances				
F	1.000	0.000	999.000	999.000
Residual Variances				
MQCBCL	1.136	0.498	2.280	0.023
FQCBCL	4.708	0.581	8.097	0.000
SOQCBCL	3.874	0.552	7.021	0.000
MQMSHYP	0.642	0.307	2.093	0.036
FQMSHYP	2.223	0.287	7.736	0.000
SOQMSHYP	1.885	0.230	8.179	0.000
F1	1.000	0.000	999.000	999.000
F2	1.000	0.000	999.000	999.000

STANDARDIZED MODEL RESULTS

STDYX Standardization

	Estimate	S.E.	Est./S.E.	Two-Tailed P-Value
F1 BY				
MQCBCL	0.902	0.044	20.313	0.000
FQCBCL	0.519	0.091	5.732	0.000
SOQCBCL	0.598	0.077	7.749	0.000
F2 BY				
MQMSHYP	0.880	0.053	16.481	0.000
FQMSHYP	0.558	0.088	6.345	0.000
SOQMSHYP	0.465	0.094	4.927	0.000
F BY				
F1	0.893	0.015	60.325	0.000
F2	0.739	0.029	25.202	0.000
Means				
F	0.000	0.000	999.000	999.000
Intercepts				
MQCBCL	1.753	0.086	20.488	0.000
FQCBCL	1.737	0.099	17.506	0.000
SOQCBCL	1.478	0.081	18.291	0.000
MQMSHYP	1.413	0.074	19.207	0.000
FQMSHYP	1.245	0.066	18.814	0.000
SOQMSHYP	1.107	0.066	16.713	0.000
F1	0.000	0.000	999.000	999.000
F2	0.000	0.000	999.000	999.000
Variances				
F	1.000	0.000	999.000	999.000
Residual Variances				
MQCBCL	0.187	0.080	2.332	0.020
FQCBCL	0.730	0.094	7.764	0.000
SOQCBCL	0.642	0.092	6.954	0.000
MQMSHYP	0.226	0.094	2.400	0.016
FQMSHYP	0.688	0.098	7.002	0.000

SOQMSHYP	0.784	0.088	8.947	0.000
F1	0.202	0.026	7.643	0.000
F2	0.454	0.043	10.471	0.000

STDY Standardization

	Estimate	S.E.	Est./S.E.	Two-Tailed P-Value
F1 BY				
MQCBCL	0.902	0.044	20.313	0.000
FQCBCL	0.519	0.091	5.732	0.000
SOQCBCL	0.598	0.077	7.749	0.000
F2 BY				
MQMSHYP	0.880	0.053	16.481	0.000
FQMSHYP	0.558	0.088	6.345	0.000
SOQMSHYP	0.465	0.094	4.927	0.000
F BY				
F1	0.893	0.015	60.325	0.000
F2	0.739	0.029	25.202	0.000
Means				
F	0.000	0.000	999.000	999.000
Intercepts				
MQCBCL	1.753	0.086	20.488	0.000
FQCBCL	1.737	0.099	17.506	0.000
SOQCBCL	1.478	0.081	18.291	0.000
MQMSHYP	1.413	0.074	19.207	0.000
FQMSHYP	1.245	0.066	18.814	0.000
SOQMSHYP	1.107	0.066	16.713	0.000
F1	0.000	0.000	999.000	999.000
F2	0.000	0.000	999.000	999.000
Variances				
F	1.000	0.000	999.000	999.000
Residual Variances				
MQCBCL	0.187	0.080	2.332	0.020
FQCBCL	0.730	0.094	7.764	0.000
SOQCBCL	0.642	0.092	6.954	0.000
MQMSHYP	0.226	0.094	2.400	0.016
FQMSHYP	0.688	0.098	7.002	0.000
SOQMSHYP	0.784	0.088	8.947	0.000
F1	0.202	0.026	7.643	0.000
F2	0.454	0.043	10.471	0.000

STD Standardization

	Estimate	S.E.	Est./S.E.	Two-Tailed P-Value
F1 BY				
MQCBCL	2.224	0.145	15.286	0.000
FQCBCL	1.318	0.270	4.890	0.000
SOQCBCL	1.469	0.223	6.590	0.000
F2 BY				
MQMSHYP	1.484	0.071	20.943	0.000
FQMSHYP	1.004	0.181	5.530	0.000
SOQMSHYP	0.721	0.157	4.583	0.000
F BY				
F1	0.893	0.015	60.325	0.000
F2	0.739	0.029	25.202	0.000
Means				
F	0.000	0.000	999.000	999.000
Intercepts				
MQCBCL	4.323	0.153	28.299	0.000
FQCBCL	4.410	0.188	23.507	0.000
SOQCBCL	3.631	0.175	20.787	0.000

MQMSHYP	2.383	0.097	24.689	0.000
FQMSHYP	2.238	0.118	18.985	0.000
SOQMSHYP	1.717	0.099	17.323	0.000
F1	0.000	0.000	999.000	999.000
F2	0.000	0.000	999.000	999.000
Variances				
F	1.000	0.000	999.000	999.000
Residual Variances				
MQCBCL	1.136	0.498	2.280	0.023
FQCBCL	4.708	0.581	8.097	0.000
SOQCBCL	3.874	0.552	7.021	0.000
MQMSHYP	0.642	0.307	2.093	0.036
FQMSHYP	2.223	0.287	7.736	0.000
SOQMSHYP	1.885	0.230	8.179	0.000
F1	0.202	0.026	7.643	0.000
F2	0.454	0.043	10.471	0.000

R-SQUARE

Observed Variable	Estimate	S.E.	Est./S.E.	Two-Tailed P-Value
MQCBCL	0.813	0.080	10.157	0.000
FQCBCL	0.270	0.094	2.866	0.004
SOQCBCL	0.358	0.092	3.874	0.000
MQMSHYP	0.774	0.094	8.240	0.000
FQMSHYP	0.312	0.098	3.173	0.002
SOQMSHYP	0.216	0.088	2.464	0.014

Latent Variable	Estimate	S.E.	Est./S.E.	Two-Tailed P-Value
F1	0.798	0.026	30.163	0.000
F2	0.546	0.043	12.601	0.000

QUALITY OF NUMERICAL RESULTS

Condition Number for the Information Matrix 0.919E-02
(ratio of smallest to largest eigenvalue)

MODEL MODIFICATION INDICES

NOTE: Modification indices for direct effects of observed dependent variables regressed on covariates may not be included. To include these, request MODINDICES (ALL).

Minimum M.I. value for printing the modification index 10.000

		M.I.	E.P.C.	Std E.P.C.	StdYX E.P.C.
BY Statements					
F1	BY MQCBCL	22.361	-2.524	-5.614	-2.276
F2	BY MQMSHYP	22.398	-0.770	-1.143	-0.678
ON/BY Statements					
F1	ON F1 /				
F1	BY F1	22.394	-2.526	-2.526	-2.526
F1	ON F2 /				
F2	BY F1	22.392	1.395	0.931	0.931
F2	ON F1 /				
F1	BY F2	22.380	1.394	2.089	2.089
F2	ON F2 /				
F2	BY F2	22.399	-0.770	-0.770	-0.770

WITH Statements

MQMSHYP	WITH	MQCBCL	30.797	1.575	1.575	1.844
FQMSHYP	WITH	FQCBCL	38.086	1.650	1.650	0.510
FQMSHYP	WITH	MQMSHYP	16.908	-0.961	-0.961	-0.804
SOQMSHYP	WITH	SOQCBCL	43.133	1.444	1.444	0.534
F2	WITH	F1	22.392	1.395	1.395	1.395

Variances/Residual Variances

F1	22.393	-5.052	-1.021	-1.021
F2	22.395	-1.540	-0.699	-0.699

SAMPLE STATISTICS FOR ESTIMATED FACTOR SCORES

SAMPLE STATISTICS

Means

	F1	F1_SE	F2	F2_SE	F
1	0.000	1.012	0.000	0.652	0.000

Means

	F_SE
1	0.554

Covariances

	F1	F1_SE	F2	F2_SE	F
F1	3.782				
F1_SE	0.013	0.108			
F2	2.061	0.003	1.663		
F2_SE	-0.009	0.017	-0.004	0.011	
F	1.589	0.005	0.962	-0.004	0.685
F_SE	0.002	0.029	0.000	0.006	0.001

Covariances

	F_SE
F_SE	0.008

Correlations

	F1	F1_SE	F2	F2_SE	F
F1	1.000				
F1_SE	0.020	1.000			
F2	0.822	0.008	1.000		
F2_SE	-0.045	0.495	-0.032	1.000	
F	0.987	0.017	0.902	-0.043	1.000
F_SE	0.012	0.990	0.004	0.605	0.010

Correlations

	F_SE
F_SE	1.000

SAVEDATA INFORMATION

Save file

toddlerW4W5adhd.dat

Order and format of variables

MQCBCL	F10.3
FQCBCL	F10.3
SOQCBCL	F10.3
MQMSHYP	F10.3

```
    FQMSHYP             F10.3
    SOQMSHYP            F10.3
    F1                  F10.3
    F1_SE               F10.3
    F2                  F10.3
    F2_SE               F10.3
    F                   F10.3
    F_SE                F10.3

Save file format
12F10.3

Save file record length    10000

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```

Appendix V

Mplus Output for Toddler ODD Symptoms Factor Scores

```
Mplus VERSION 7.11
MUTHEN & MUTHEN
06/03/2014   3:16 PM

INPUT INSTRUCTIONS
  TITLE:            factor scores for odd scale across 3 informants
  DATA:            FILE IS CBCLscales.dat;
  VARIABLE:   NAMES ARE famcode emotreactM emotreactF emotreactSO anxiousM
                        anxiousF anxiousSO emotprobM emotprobF emotprobSO
                        aggM aggF aggSO adhdM adhdF adhdSO oddM oddF oddSO
                        anyM anyF anySO anyCBCL meanemotreact meananxious
                        meanemotprob meanagg meanadhd meanodd;
                        USEVARIABLES ARE oddM oddF oddSO;
                        MISSING IS ALL (-9);
  MODEL:         f by oddM* oddF oddSO;
            f@1 ; [f@0];
  ANALYSIS:      Estimator=MLR;
  OUTPUT:      STANDARDIZED sampstat MOD;
  SAVEDATA:   file= CBCLodd.dat;
                       missflag=-9;
                       save= fscores;
*** WARNING
  Data set contains cases with missing on all variables.
  These cases were not included in the analysis.
  Number of cases with missing on all variables:  78
   1 WARNING(S) FOUND IN THE INPUT INSTRUCTIONS

factor scores for odd scale across 3 informants

SUMMARY OF ANALYSIS
Number of groups                                                 1
Number of observations                                         254
Number of dependent variables                                    3
Number of independent variables                                  0
Number of continuous latent variables                            1
Observed dependent variables
  Continuous
   ODDM        ODDF        ODDSO
Continuous latent variables
   F

Estimator                                                      MLR
Information matrix                                        OBSERVED
Maximum number of iterations                                 1000
Convergence criterion                                   0.500D-04
Maximum number of steepest descent iterations                  20
Maximum number of iterations for H1                          2000
Convergence criterion for H1                            0.100D-03

Input data file(s)
  CBCLscales.dat
Input data format  FREE

SUMMARY OF DATA
     Number of missing data patterns             7
```

COVARIANCE COVERAGE OF DATA

Minimum covariance coverage value 0.100

PROPORTION OF DATA PRESENT

Covariance Coverage

	ODDM	ODDF	ODDSO
ODDM	0.945		
ODDF	0.661	0.693	
ODDSO	0.677	0.591	0.717

SAMPLE STATISTICS

ESTIMATED SAMPLE STATISTICS

Means

	ODDM	ODDF	ODDSO
1	3.484	3.365	2.774

Covariances

	ODDM	ODDF	ODDSO
ODDM	6.239		
ODDF	2.613	6.777	
ODDSO	2.711	2.630	4.888

Correlations

	ODDM	ODDF	ODDSO
ODDM	1.000		
ODDF	0.402	1.000	
ODDSO	0.491	0.457	1.000

MAXIMUM LOG-LIKELIHOOD VALUE FOR THE UNRESTRICTED (H1) MODEL IS -1333.835
THE MODEL ESTIMATION TERMINATED NORMALLY

MODEL FIT INFORMATION

Number of Free Parameters	9
Loglikelihood	
H0 Value	-1333.835
H0 Scaling Correction Factor for MLR	1.0190
H1 Value	-1333.835
H1 Scaling Correction Factor for MLR	1.0190
Information Criteria	
Akaike (AIC)	2685.671
Bayesian (BIC)	2717.507
Sample-Size Adjusted BIC (n* = (n + 2) / 24)	2688.975
Chi-Square Test of Model Fit	
Value	0.000*
Degrees of Freedom	0
P-Value	0.0000
Scaling Correction Factor for MLR	1.0000

* The chi-square value for MLM, MLMV, MLR, ULSMV, WLSM and WLSMV cannot be used for chi-square difference testing in the regular way. MLM, MLR and WLSM chi-square difference testing is described on the Mplus website. MLMV, WLSMV,and ULSMV difference testing is done using the DIFFTEST option.

RMSEA (Root Mean Square Error Of Approximation)

Estimate	0.000	
90 Percent C.I.	0.000	0.000
Probability RMSEA <= .05	0.000	

CFI/TLI

CFI	1.000
TLI	1.000

Chi-Square Test of Model Fit for the Baseline Model

Value	76.973
Degrees of Freedom	3
P-Value	0.0000

SRMR (Standardized Root Mean Square Residual)

Value	0.000

MODEL RESULTS

		Estimate	S.E.	Est./S.E.	Two-Tailed P-Value
F	BY				
	ODDM	1.641	0.206	7.976	0.000
	ODDF	1.592	0.268	5.949	0.000
	ODDSO	1.652	0.203	8.158	0.000
Means					
	F	0.000	0.000	999.000	999.000
Intercepts					
	ODDM	3.484	0.161	21.658	0.000
	ODDF	3.365	0.191	17.630	0.000
	ODDSO	2.774	0.157	17.673	0.000
Variances					
	F	1.000	0.000	999.000	999.000
Residual Variances					
	ODDM	3.545	0.596	5.950	0.000
	ODDF	4.242	0.711	5.968	0.000
	ODDSO	2.158	0.537	4.016	0.000

STANDARDIZED MODEL RESULTS

STDYX Standardization

		Estimate	S.E.	Est./S.E.	Two-Tailed P-Value
F	BY				
	ODDM	0.657	0.069	9.549	0.000
	ODDF	0.612	0.087	7.021	0.000
	ODDSO	0.747	0.075	9.901	0.000
Means					
	F	0.000	0.000	999.000	999.000
Intercepts					
	ODDM	1.395	0.069	20.294	0.000
	ODDF	1.293	0.079	16.461	0.000
	ODDSO	1.255	0.074	16.875	0.000
Variances					
	F	1.000	0.000	999.000	999.000
Residual Variances					
	ODDM	0.568	0.090	6.283	0.000
	ODDF	0.626	0.107	5.874	0.000
	ODDSO	0.441	0.113	3.912	0.000

STDY Standardization

	Estimate	S.E.	Est./S.E.	Two-Tailed P-Value
F BY				
ODDM	0.657	0.069	9.549	0.000
ODDF	0.612	0.087	7.021	0.000
ODDSO	0.747	0.075	9.901	0.000
Means				
F	0.000	0.000	999.000	999.000
Intercepts				
ODDM	1.395	0.069	20.294	0.000
ODDF	1.293	0.079	16.461	0.000
ODDSO	1.255	0.074	16.875	0.000
Variances				
F	1.000	0.000	999.000	999.000
Residual Variances				
ODDM	0.568	0.090	6.283	0.000
ODDF	0.626	0.107	5.874	0.000
ODDSO	0.441	0.113	3.912	0.000

STD Standardization

	Estimate	S.E.	Est./S.E.	Two-Tailed P-Value
F BY				
ODDM	1.641	0.206	7.976	0.000
ODDF	1.592	0.268	5.949	0.000
ODDSO	1.652	0.203	8.158	0.000
Means				
F	0.000	0.000	999.000	999.000
Intercepts				
ODDM	3.484	0.161	21.658	0.000
ODDF	3.365	0.191	17.630	0.000
ODDSO	2.774	0.157	17.673	0.000
Variances				
F	1.000	0.000	999.000	999.000
Residual Variances				
ODDM	3.545	0.596	5.950	0.000
ODDF	4.242	0.711	5.968	0.000
ODDSO	2.158	0.537	4.016	0.000

R-SQUARE

Observed Variable	Estimate	S.E.	Est./S.E.	Two-Tailed P-Value
ODDM	0.432	0.090	4.774	0.000
ODDF	0.374	0.107	3.510	0.000
ODDSO	0.559	0.113	4.950	0.000

QUALITY OF NUMERICAL RESULTS

Condition Number for the Information Matrix 0.180E-01
(ratio of smallest to largest eigenvalue)

MODEL MODIFICATION INDICES

NOTE: Modification indices for direct effects of observed dependent variables regressed on covariates may not be included. To include these, request MODINDICES (ALL).

Minimum M.I. value for printing the modification index 10.000

	M.I.	E.P.C.	Std E.P.C.	StdYX E.P.C.

No modification indices above the minimum value.

```
SAMPLE STATISTICS FOR ESTIMATED FACTOR SCORES
     SAMPLE STATISTICS
           Means
              F             F_SE
              ________      ________
 1              0.000         0.591
           Covariances
              F             F_SE
              ________      ________
 F              0.642
 F_SE           0.000         0.008
           Correlations
              F             F_SE
              ________      ________
 F              1.000
 F_SE           0.004         1.000

SAVEDATA INFORMATION
  Save file
    CBCLodd.dat
  Order and format of variables
    ODDM           F10.3
    ODDF           F10.3
    ODDSO          F10.3
    F              F10.3
    F_SE           F10.3
  Save file format
    5F10.3
  Save file record length    10000

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```

Appendix VI

Mplus Output for Childhood ADHD Symptoms Factor Scores

```
Mplus VERSION 7.11
MUTHEN & MUTHEN
09/19/2014   3:53 PM

INPUT INSTRUCTIONS

  TITLE:            factor scores for Wave 6
  DATA:            FILE IS W6data.dat;
  VARIABLE:   NAMES ARE famcode Madhd Fadhd Tadhd Mconners;
                        USEVARIABLES ARE Madhd Fadhd Tadhd Mconners;
                        MISSING IS ALL (-9);
  MODEL:         f by Madhd* Fadhd Tadhd Mconners;
                   f@1 ; [f@0];
  ANALYSIS:     Estimator=MLR;
  OUTPUT:       STANDARDIZED sampstat MOD;
  SAVEDATA:   file= W6adhdfactor.dat;
                      missflag=-9;
                      save= fscores;

*** WARNING
  Data set contains cases with missing on all variables.
  These cases were not included in the analysis.
  Number of cases with missing on all variables:  128

SUMMARY OF ANALYSIS

Number of groups                                                 1
Number of observations                                         204
Number of dependent variables                                    4
Number of independent variables                                  0
Number of continuous latent variables                            1
Observed dependent variables
  Continuous
   MADHD       FADHD       TADHD       MCONNERS
Continuous latent variables
   F
Estimator                                                      MLR
Information matrix                                        OBSERVED
Maximum number of iterations                                 1000
Convergence criterion                                   0.500D-04
Maximum number of steepest descent iterations                  20
Maximum number of iterations for H1                          2000
Convergence criterion for H1                            0.100D-03
Input data file(s)
       W6data.dat
Input data format  FREE

SUMMARY OF DATA

    Number of missing data patterns             8

COVARIANCE COVERAGE OF DATA

Minimum covariance coverage value   0.100
     PROPORTION OF DATA PRESENT
```

Covariance Coverage

	MADHD	FADHD	TADHD	MCONNERS
MADHD	0.980			
FADHD	0.598	0.608		
TADHD	0.672	0.446	0.686	
MCONNERS	0.975	0.593	0.667	0.975

SAMPLE STATISTICS

ESTIMATED SAMPLE STATISTICS

Means

	MADHD	FADHD	TADHD	MCONNERS
1	3.375	3.688	4.324	2.428

Covariances

	MADHD	FADHD	TADHD	MCONNERS
MADHD	7.911			
FADHD	4.834	6.567		
TADHD	8.321	6.375	27.140	
MCONNERS	7.628	5.953	10.238	16.386

Correlations

	MADHD	FADHD	TADHD	MCONNERS
MADHD	1.000			
FADHD	0.671	1.000		
TADHD	0.568	0.478	1.000	
MCONNERS	0.670	0.574	0.485	1.000

MAXIMUM LOG-LIKELIHOOD VALUE FOR THE UNRESTRICTED (H1) MODEL IS -1645.142
THE MODEL ESTIMATION TERMINATED NORMALLY

MODEL FIT INFORMATION

Number of Free Parameters	12
Loglikelihood	
H0 Value	-1645.148
H0 Scaling Correction Factor for MLR	1.3414
H1 Value	-1645.142
H1 Scaling Correction Factor for MLR	1.2878
Information Criteria	
Akaike (AIC)	3314.296
Bayesian (BIC)	3354.113
Sample-Size Adjusted BIC (n* = (n + 2) / 24)	3316.094
Chi-Square Test of Model Fit	
Value	0.013*
Degrees of Freedom	2
P-Value	0.9935
Scaling Correction Factor for MLR	0.9664

* The chi-square value for MLM, MLMV, MLR, ULSMV, WLSM and WLSMV cannot be used for chi-square difference testing in the regular way. MLM, MLR and WLSM chi-square difference testing is described on the Mplus website.

MLMV, WLSMV, and ULSMV difference testing is done using the DIFFTEST option.

RMSEA (Root Mean Square Error Of Approximation)

Estimate	0.000	
90 Percent C.I.	0.000	0.000
Probability RMSEA <= .05	0.996	

CFI/TLI

CFI	1.000
TLI	1.025

Chi-Square Test of Model Fit for the Baseline Model

Value	240.258
Degrees of Freedom	6
P-Value	0.0000

SRMR (Standardized Root Mean Square Residual)

Value	0.002

MODEL RESULTS

		Estimate	S.E.	Est./S.E.	Two-Tailed P-Value
F	BY				
	MADHD	2.492	0.183	13.638	0.000
	FADHD	1.938	0.232	8.351	0.000
	TADHD	3.331	0.618	5.386	0.000
	MCONNERS	3.063	0.448	6.840	0.000
Means					
	F	0.000	0.000	999.000	999.000
Intercepts					
	MADHD	3.375	0.198	17.006	0.000
	FADHD	3.689	0.208	17.726	0.000
	TADHD	4.322	0.429	10.069	0.000
	MCONNERS	2.428	0.289	8.411	0.000
Variances					
	F	1.000	0.000	999.000	999.000
Residual Variances					
	MADHD	1.703	0.579	2.940	0.003
	FADHD	2.810	0.464	6.055	0.000
	TADHD	16.024	2.682	5.974	0.000
	MCONNERS	7.001	1.202	5.824	0.000

STANDARDIZED MODEL RESULTS

STDYX Standardization

		Estimate	S.E.	Est./S.E.	Two-Tailed P-Value
F	BY				
	MADHD	0.886	0.039	22.462	0.000
	FADHD	0.756	0.055	13.712	0.000
	TADHD	0.640	0.079	8.116	0.000
	MCONNERS	0.757	0.054	13.992	0.000
Means					
	F	0.000	0.000	999.000	999.000
Intercepts					
	MADHD	1.200	0.063	19.130	0.000
	FADHD	1.440	0.094	15.384	0.000
	TADHD	0.830	0.053	15.796	0.000
	MCONNERS	0.600	0.036	16.591	0.000
Variances					
	F	1.000	0.000	999.000	999.000
Residual Variances					
	MADHD	0.215	0.070	3.080	0.002

FADHD	0.428	0.083	5.132	0.000
TADHD	0.591	0.101	5.862	0.000
MCONNERS	0.427	0.082	5.220	0.000

STDY Standardization

	Estimate	S.E.	Est./S.E.	Two-Tailed P-Value
F BY				
MADHD	0.886	0.039	22.462	0.000
FADHD	0.756	0.055	13.712	0.000
TADHD	0.640	0.079	8.116	0.000
MCONNERS	0.757	0.054	13.992	0.000
Means				
F	0.000	0.000	999.000	999.000
Intercepts				
MADHD	1.200	0.063	19.130	0.000
FADHD	1.440	0.094	15.384	0.000
TADHD	0.830	0.053	15.796	0.000
MCONNERS	0.600	0.036	16.591	0.000
Variances				
F	1.000	0.000	999.000	999.000
Residual Variances				
MADHD	0.215	0.070	3.080	0.002
FADHD	0.428	0.083	5.132	0.000
TADHD	0.591	0.101	5.862	0.000
MCONNERS	0.427	0.082	5.220	0.000

STD Standardization

	Estimate	S.E.	Est./S.E.	Two-Tailed P-Value
F BY				
MADHD	2.492	0.183	13.638	0.000
FADHD	1.938	0.232	8.351	0.000
TADHD	3.331	0.618	5.386	0.000
MCONNERS	3.063	0.448	6.840	0.000
Means				
F	0.000	0.000	999.000	999.000
Intercepts				
MADHD	3.375	0.198	17.006	0.000
FADHD	3.689	0.208	17.726	0.000
TADHD	4.322	0.429	10.069	0.000
MCONNERS	2.428	0.289	8.411	0.000
Variances				
F	1.000	0.000	999.000	999.000
Residual Variances				
MADHD	1.703	0.579	2.940	0.003
FADHD	2.810	0.464	6.055	0.000
TADHD	16.024	2.682	5.974	0.000
MCONNERS	7.001	1.202	5.824	0.000

R-SQUARE

Observed Variable	Estimate	S.E.	Est./S.E.	Two-Tailed P-Value
MADHD	0.785	0.070	11.231	0.000
FADHD	0.572	0.083	6.856	0.000
TADHD	0.409	0.101	4.058	0.000
MCONNERS	0.573	0.082	6.996	0.000

QUALITY OF NUMERICAL RESULTS
Condition Number for the Information Matrix 0.184E-01
ratio of smallest to largest eigenvalue)

MODEL MODIFICATION INDICES

NOTE: Modification indices for direct effects of observed dependent variables regressed on covariates may not be included. To include these, request MODINDICES (ALL).
Minimum M.I. value for printing the modification index 10.000

	M.I.	E.P.C.	Std E.P.C.	StdYX E.P.C.

No modification indices above the minimum value.

SAMPLE STATISTICS FOR ESTIMATED FACTOR SCORES

SAMPLE STATISTICS

Means

	F	F_SE
1	0.000	0.379

Covariances

	F	F_SE
F	0.854	
F_SE	0.005	0.003

Correlations

	F	F_SE
F	1.000	
F_SE	0.114	1.000

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Appendix VII

Mplus Output for Childhood ODD Symptoms Factor Scores

```
Mplus VERSION 7.11
MUTHEN & MUTHEN
11/18/2014   4:46 PM

INPUT INSTRUCTIONS

TITLE:            factor scores for W6 odd scale across 3 informants
DATA:            FILE IS ODD.dat;
VARIABLE:   NAMES ARE famcode Modd Fodd Todd;
                  USEVARIABLES ARE Modd Fodd Todd;
                        MISSING IS ALL (-9);
MODEL:        f by Modd* Fodd Todd;
            f@1 ; [f@0];
ANALYSIS:      Estimator=MLR;
OUTPUT:       STANDARDIZED sampstat MOD;
SAVEDATA:   file= W6odd.dat;
                       missflag=-9;
                       save= fscores;

*** WARNING
  Data set contains cases with missing on all variables.
  These cases were not included in the analysis.
  Number of cases with missing on all variables:  128
   1 WARNING(S) FOUND IN THE INPUT INSTRUCTIONS

factor scores for W6 odd scale across 3 informants

SUMMARY OF ANALYSIS

Number of groups                                                 1
Number of observations                                         204
Number of dependent variables                                    3
Number of independent variables                                  0
Number of continuous latent variables                            1
Observed dependent variables
  Continuous
   MODD        FODD        TODD
Continuous latent variables
   F

Estimator                                                      MLR
Information matrix                                        OBSERVED
Maximum number of iterations                                 1000
Convergence criterion                                   0.500D-04
Maximum number of steepest descent iterations                  20
Maximum number of iterations for H1                          2000
Convergence criterion for H1                            0.100D-03
Input data file(s)
  ODD.dat
Input data format  FREE
```

SUMMARY OF DATA

Number of missing data patterns 7

COVARIANCE COVERAGE OF DATA

Minimum covariance coverage value 0.100

PROPORTION OF DATA PRESENT

Covariance Coverage

	MODD	FODD	TODD
MODD	0.980		
FODD	0.588	0.598	
TODD	0.672	0.446	0.686

SAMPLE STATISTICS

ESTIMATED SAMPLE STATISTICS

Means

	MODD	FODD	TODD
1	2.642	2.761	0.962

Covariances

	MODD	FODD	TODD
MODD	7.005		
FODD	4.269	7.404	
TODD	3.828	3.607	6.421

Correlations

	MODD	FODD	TODD
MODD	1.000		
FODD	0.593	1.000	
TODD	0.571	0.523	1.000

MAXIMUM LOG-LIKELIHOOD VALUE FOR THE UNRESTRICTED (H1) MODEL IS -1045.711. THE MODEL ESTIMATION TERMINATED NORMALLY

MODEL FIT INFORMATION

Number of Free Parameters	9
Loglikelihood	
H0 Value	-1045.711
H0 Scaling Correction Factor for MLR	1.5785
H1 Value	-1045.711
H1 Scaling Correction Factor for MLR	1.5785
Information Criteria	
Akaike (AIC)	2109.421
Bayesian (BIC)	2139.285
Sample-Size Adjusted BIC (n* = (n + 2) / 24)	2110.770
Chi-Square Test of Model Fit	
Value	0.000*

```
          Degrees of Freedom                     0
          P-Value                           0.0000
          Scaling Correction Factor         1.0000
            for MLR
*    The chi-square value for MLM, MLMV, MLR, ULSMV, WLSM and WLSMV
cannot be used for chi-square difference testing in the regular way.
MLM, MLR and WLSM chi-square difference testing is described on the
Mplus website.  MLMV, WLSMV,and ULSMV difference testing is done
using the DIFFTEST option.

RMSEA (Root Mean Square Error Of Approximation)
          Estimate                           0.000
          90 Percent C.I.                    0.000  0.000
          Probability RMSEA <= .05           0.000
CFI/TLI
          CFI                                1.000
          TLI                                1.000
Chi-Square Test of Model Fit for the Baseline Model
          Value                            153.860
          Degrees of Freedom                     3
          P-Value                           0.0000
SRMR (Standardized Root Mean Square Residual)
          Value                              0.000
```

MODEL RESULTS

		Estimate	S.E.	Est./S.E.	Two-Tailed P-Value
F	BY				
	MODD	2.128	0.254	8.387	0.000
	FODD	2.006	0.284	7.068	0.000
	TODD	1.799	0.383	4.697	0.000
Means					
	F	0.000	0.000	999.000	999.000
Intercepts					
	MODD	2.642	0.187	14.143	0.000
	FODD	2.761	0.228	12.133	0.000
	TODD	0.961	0.202	4.758	0.000
Variances					
	F	1.000	0.000	999.000	999.000
Residual Variances					
	MODD	2.476	0.576	4.295	0.000
	FODD	3.380	0.868	3.893	0.000
	TODD	3.185	0.735	4.333	0.000

STANDARDIZED MODEL RESULTS

STDYX Standardization

		Estimate	S.E.	Est./S.E.	Two-Tailed P-Value
F	BY				
	MODD	0.804	0.058	13.768	0.000
	FODD	0.737	0.078	9.477	0.000
	TODD	0.710	0.074	9.575	0.000
Means					
	F	0.000	0.000	999.000	999.000

Intercepts				
MODD	0.998	0.059	16.997	0.000
FODD	1.015	0.072	14.021	0.000
TODD	0.379	0.040	9.585	0.000
Variances				
F	1.000	0.000	999.000	999.000
Residual Variances				
MODD	0.353	0.094	3.763	0.000
FODD	0.457	0.115	3.980	0.000
TODD	0.496	0.105	4.714	0.000

STDY Standardization

	Estimate	S.E.	Est./S.E.	Two-Tailed P-Value
F BY				
MODD	0.804	0.058	13.768	0.000
FODD	0.737	0.078	9.477	0.000
TODD	0.710	0.074	9.575	0.000
Means				
F	0.000	0.000	999.000	999.000
Intercepts				
MODD	0.998	0.059	16.997	0.000
FODD	1.015	0.072	14.021	0.000
TODD	0.379	0.040	9.585	0.000
Variances				
F	1.000	0.000	999.000	999.000
Residual Variances				
MODD	0.353	0.094	3.763	0.000
FODD	0.457	0.115	3.980	0.000
TODD	0.496	0.105	4.714	0.000

STD Standardization

	Estimate	S.E.	Est./S.E.	Two-Tailed P-Value
F BY				
MODD	2.128	0.254	8.387	0.000
FODD	2.006	0.284	7.068	0.000
TODD	1.799	0.383	4.697	0.000
Means				
F	0.000	0.000	999.000	999.000
Intercepts				
MODD	2.642	0.187	14.143	0.000
FODD	2.761	0.228	12.133	0.000
TODD	0.961	0.202	4.758	0.000
Variances				
F	1.000	0.000	999.000	999.000
Residual Variances				
MODD	2.476	0.576	4.295	0.000
FODD	3.380	0.868	3.893	0.000
TODD	3.185	0.735	4.333	0.000

R-SQUARE

Observed Variable	Estimate	S.E.	Est./S.E.	Two-Tailed P-Value
MODD	0.647	0.094	6.884	0.000

FODD	0.543	0.115	4.739	0.000
TODD	0.504	0.105	4.788	0.000

QUALITY OF NUMERICAL RESULTS

Condition Number for the Information Matrix 0.267E-01
(ratio of smallest to largest eigenvalue)

MODEL MODIFICATION INDICES

NOTE: Modification indices for direct effects of observed dependent variables regressed on covariates may not be included. To include these, request MODINDICES (ALL).
Minimum M.I. value for printing the modification index 10.000

	M.I.	E.P.C.	Std E.P.C.	StdYX E.P.C.

No modification indices above the minimum value.

SAMPLE STATISTICS FOR ESTIMATED FACTOR SCORES

SAMPLE STATISTICS

Means

	F	F_SE
1	0.000	0.497

Covariances

	F	F_SE
F	0.750	
F_SE	0.004	0.003

Correlations

	F	F_SE
F	1.000	
F_SE	0.089	1.000

SAVEDATA INFORMATION

Save file
W6odd.dat
Order and format of variables

MODD	F10.3
FODD	F10.3
TODD	F10.3
F	F10.3
F_SE	F10.3

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