Social paediatric perspective on Attention-Deficit/Hyperactivity Disorder

SOCIAL PAEDIATRIC PERSPECTIVE ON ATTENTION-DEFICIT/ HYPERACTIVITY DISORDER

From early risk factors to symptom evaluation in the Dutch health care system

Cover Design and Layout: Studio Seef, Séverine van Bun
Cover photography: Birgit Levelink
Production: Gildeprint

ISBN: 978-94-6419-195-0

The research presented in this thesis was conducted at the School for Public Health and Primairy Care: CAPHRI, Department of Paediatrics, Maastricht University

SOCIAL PAEDIATRIC PERSPECTIVE ON ATTENTION-DEFICIT/ HYPERACTIVITY DISORDER

From early risk factors to symptom evaluation in the Dutch health care system

Proefschrift

Ter verkrijging van de graad van doctor aan de Universiteit Maastricht,
op gezag van de Rector Magnificus, Prof. dr. Rianne M. Letschert,
volgens het besluit van het College van Decanen,
in het openbaar te verdedigen
op woensdag 30 juni 2021 om 13:00 uur

door

Birgit Levelink

Promotores
Prof. dr. E. Dompeling
Prof. dr. F.J.M. Feron

Co-promotor
Dr. D.M.C.B. van Zeben-van der Aa

Beoordelingscommissie
Prof. dr. J.J.M.H. Strik (voorzitter)
Prof. dr. M.E.A. Spaanderman
Prof. dr. E.M. van de Putte (Universiteit Utrecht)
Prof. dr. B.J. van den Hoofdakker (Universiteit Groningen)
Dr. R. Wassenberg

CONTENTS

CHAPTER 1

GENERAL INTRODUCTION

Paediatricians, like many other (health)care professionals, want to contribute to the healthy development of children. Whereas throughout the twentieth century emphasis was placed on physical health, nowadays paediatricians recognize that child health is more than just the absence of physical disease. There is an increasing awareness that physical health, psychological well-being and the (social) environment all play an important role, and can influence each one another. This change in perspective is also apparent in the literature, where a gradual shift away from linear towards more multidirectional models of child development can be observed [1].

Children develop from the moment of conception. Many models have been proposed in which the complex interactions between the individual behaviour of the child and changes in biological and social circumstances are explained. A physician must consider a child as more than the sum of his/her physical problems, and should study a child in relation to the child's own genetic predispositions, and capabilities within his/her environment as a whole [1]. Paediatricians with a focus on social paediatrics specialize in the care of children whose problems are due to interactions between biomedical, social and psychological factors. They are trained to evaluate children with developmental disorders from a broad perspective, and interdisciplinary collaboration is often required. Children often present to a (social) paediatrician with (symptoms related to) attention-deficit/hyperactivity disorder (ADHD), a highly prevalent neurodevelopmental disorder, characterized by symptoms of inattention and impulsivity/hyperactivity that are inconsistent with developmental level. Sometimes they present with a demand for care specifically because of ADHD symptoms, but often they present with other health-related issues. In the last decade, a lot has changed in the care for children with ADHD in the Netherlands. In fact, youth care underwent a major transformation in 2015. Although the role of paediatricians in caring for children with problems related to ADHD has previously been described in the Dutch standard of care for children with ADHD (in Dutch: ADHD zorgstandaard)[2], it is important to evaluate the particular role of (social) paediatricians in the care of children who are impaired due to symptoms of attention deficit and/or hyperactivity or because of ADHD.

ADHD: Classification, prevalence and co-morbid disorders

Symptoms that are nowadays named and classified as ADHD have been described since the early 1900s [3]. Since 1980, a diagnosis of ADHD is based on the diagnostic classification system, first described in the Diagnostic and Statistical Manual of Mental Disorders-III [4]. After several text revisions and adjustments, the DSM-5 was introduced in May 2013 [5]. DSM-5 criteria for ADHD in children are shown in Table 1.

***Table 1** | DSM-5 criteria for ADHD in childrena*

Criterion A: A persistent pattern of inattention and / or hyperactivity impulsivity that interferes with functioning or development, as characterized by (1) and / or (2).
(1) Six (or more) of the following symptoms of inattention have persisted for at least six months to a degree that it has a negative impact on social, school or occupational activities and is inconsistent with the level of development.

Inattention

a. Often fails to give close attention to details or makes careless mistakes in school work, work or other activities
b. Often has difficulty sustaining attention in tasks or play activities
c. Often does not seem to listen if he / she is spoken to directly
d. Often does not follow through on instructions and fails to finish schoolwork, 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 requiring sustained mental effort (such as schoolwork or homework)
g. Often loses things necessary for tasks or activities (for example toys, homework, pencils, books, or tools)
h. Often easily distracted by external stimuli
i. Often forgetful in daily activities

(2) Six (or more) of the following symptoms of hyperactivity and impulsivity have persisted for at least six months to a degree that it has a negative impact on social, school or occupational activities and is inconsistent with the level of development.

Hyperactivity and impulsivity

a. Often fidgets with hands or feet or squirms in seat
b. Often leaves seat in the classroom or in other situations where remaining seated is expected
c. Often runs around or climbs excessively in situations where it is inappropriate (in adolescents or adults this 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 "driven by a motor"
f. Often talks excessively
g. Often blurts out answers before the questions have been completed
h. Often has difficulty awaiting his/her turn
i. Often interrupts or intrudes on others (e.g., interferes in conversations or games)

Criterion B: Some of the symptoms of hyperactivity-impulsivity or inattention that caused impairment were present before age 12 years.
Criterion C: Several inattentive or hyperactive-impulsive symptoms are present in two or more settings (e.g., at school (or work) and at home).
Criterion D: There must be clear evidence of clinically significant impairment in social, school or occupational functioning.
Criterion E: The symptoms do not occur exclusively during the course of a pervasive developmental disorder, schizophrenia or another psychotic disorder and are not better accounted for by another mental disorder (e.g., mood disorder, anxiety disorder, dissociative disorder or personality disorder).

[a] from the American Psychiatric Association 2013, DSM-5

According to the DSM-IV, ADHD is an externalizing mental disorder, whereby the disruptive effect of the behaviour on the environment is a key symptom, while the DSM-5 refers to ADHD as a neurobiological developmental disorder [6, 7]. Over the last twenty years, it has become increasingly accepted that ADHD is a dimensional disorder [8]. That is to say that inattention and hyperactivity/impulsivity are behavioural traits that naturally occur on a continuum, and that symptoms can differ due to, for example, age, gender, or environment [9]. Nowadays, different presentations of the ADHD spectrum are described which better reflect developmental aspects of ADHD. The DSM-5 distinguishes between three different presentations of ADHD which can be combined with three levels of severity, as shown in Table 2.

***Table 2** | Different presentations and levels of severity of ADHD symptoms according to the DSM-5[a]*

Presentations:

a. Combined, if both criterion A1 (inattention) and A2 (hyperactivity-impulsivity) were met in the past six months
b. Mostly inattentive, if criterion A1 was met during the past six months, but not criterion A2
c. Predominantly hyperactive-impulsive, if criterion A2 was met during the past six months, but not criterion A1

Severity

Mild: Few, if any symptoms in excess of those required to attribute the classification are present, and the symptoms only lead to slight limitations in social, academic or professional functioning.
Moderate: There are symptoms or functional limitations between "mild" and "severe".
Severe: Many more symptoms in excess of those required to attribute the classification are present, or several particularly serious symptoms are present, or the symptoms lead to marked impairment in social, academic or occupational functioning.

[a] from the American Psychiatric Association 2013, DSM-5

It is assumed that 3-7% of school-aged children meet ADHD criteria, but prevalence rates vary worldwide [10-13]. Gender ratios (girl: boy) also vary by country, ranging from 1:3 to 1:16 [14]. The core defining features tend to decline with age, but around 65% of patients continue to meet full adult criteria for ADHD or have achieved only partial remission, and pooled prevalence in adulthood is estimated to be around 2-5% [15]. Both epidemiological and clinical studies have found that non-comorbid ADHD only occurs in 13-32.3% of cases [16-18]. Most children have multiple comorbid disorders, such as learning disabilities, conduct disorder, autism spectrum disorder, anxiety, depression, and/or speech problems [16, 19]. In addition, several studies have shown associations between ADHD and physical problems [20, 21]. In particular, associations with enuresis and asthma are regularly described [22, 23].

ADHD: Aetiology

The pattern of inheritance of ADHD is multifactorial for most individuals, meaning that both genetic and environmental factors contribute [24, 25]. No single gene is associated with ADHD and different classes of genomic variants have been associated with ADHD [26, 27]. Although most cases of ADHD are multifactorial in origin, there are several known, rare genetic syndromes (such as fragile X syndrome, tuberous sclerosis, 22q11 microdeletion, and Williams syndrome) characterized by high rates of ADHD and ADHD-like

features [28]. Together with genomic factors, environmental influences contribute to the spectrum of ADHD. Many studies have shown associations between a range of prenatal and postnatal factors (such as extreme prematurity, smoking and alcohol use during pregnancy), as well as dietary factors, but no real causation has been demonstrated so far [26, 29, 30]. However, in many of these studies, perinatal risk factors were assessed in a retrospective way. By studying a birth cohort, in which risk factors are assessed prospectively - starting during pregnancy - associations with pre-, peri- and postnatal risk factors can be studied more reliably.

In addition to pre- and postnatal risk factors, family- and social habits have been identified as environmental factors associated with ADHD [29, 31-34]. The effect of environmental risk factors may depend on genetic liability due to gene-environment interaction [35-37]. It has been suggested that screen time and sleep deprivation may be linked to the pathogenesis of ADHD [38, 39]. However, research so far has predominantly demonstrated a link between these risk factors and ADHD-related behaviour, such as hyperactivity or inattention. Little is known about the longitudinal effect of these new environmental factors (screen time and sleep deprivation) on the risk of developing an attention-deficit/hyperactivity disorder. Knowledge about the long-term effects of screen time and sleep on ADHD is important, so that doctors can give appropriate advice in the consultation room.

ADHD: Diagnosis

The cornerstone of an ADHD diagnosis is based on adequate clinical history taking, addressing all five criteria from the DSM-5 (A to E). This clinical assessment should address core symptoms (A1 and A2 criteria) of ADHD, but also the level of impairment and the occurrence of symptoms in different settings - for example at home, at school and at the sports club. In addition, developmental and family history taking, screening for co-morbidities, and an assessment of social circumstances all form an important part of the diagnostic process. Gathering information about medication use and somatic problems, including hearing and vision, is also important. Semi-structured interviews have proven to be useful in clinical practice [40, 41]. Many questionnaires (in different languages) are available to screen for ADHD core symptoms, behavioural problems or co-morbidities, but these should not be used as a substitute for detailed clinical history taking.

ADHD: Treatment

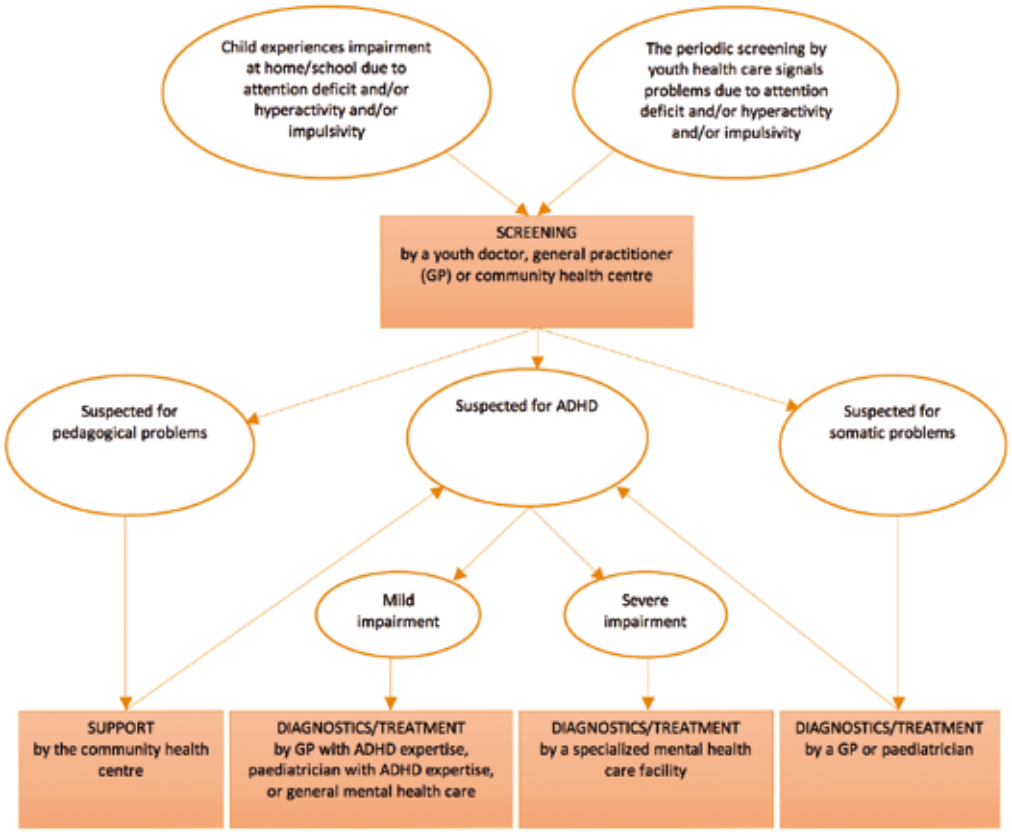
In brief, ADHD treatment consists of behavioural support and pharmacological treatment [2, 28, 42]. The first step in the treatment of ADHD is always to provide comprehensive psycho-education regarding aetiology, behavioural characteristics and co-morbidities, and to discuss possible ways in which impairments can be managed. Step two depends on age, and the presence and type of behavioural problems and / or co-morbidities, but generally includes parent training, or the provision of support at school. When non-pharmacological treatment is not effective, medication may be considered. Medication mainly focuses on reducing core symptoms of ADHD, but never cures ADHD. For children in the Netherlands, the first pharmacological option is methylphenidate, and the second is atomoxetine [2]. In addition to the treatment of ADHD and its psychiatric comorbidities, attention must be paid to any somatic co-morbidity, such as enuresis.

ADHD: The Dutch situation

Current data regarding the prevalence of ADHD in the Netherlands are not available. Based on international research, the Dutch Health Council estimated in 2014 that about 5 to 6% of all children had symptoms of ADHD [43]. It is estimated that in about 2% of all children, ADHD symptoms caused a level of impairment that warranted treatment, while 4% had less severe symptoms. According to the Dutch Health Council, the number of children and adolescents with ADHD did not increase between 2004 and 2014, but more children and young people were diagnosed due to better recognition of ADHD [43]. Since 2005, children were diagnosed and treated according to the *multidisciplinary guidelines for ADHD*, until the *ADHD standard of care* was introduced in 2019 [2, 44]. Neither of these guidelines provide a real 'gold standard' for the diagnosis and treatment of ADHD and co-morbidities, but they do offer evidence-based recommendations. It is usually a teacher or a parent who first signals that core symptoms of ADHD are present. The first step in the diagnostic pathway often starts with the general practitioner (GP) or a youth doctor. When these core symptoms lead to impairment, they can refer children to a wide variety of healthcare institutions and professionals, depending on the healthcare services available in their region, and the level of impairment. Children may be sent to a child and youth psychologist, a general remedial educationalist, a youth doctor at school or working in mental health care, a child and youth psychiatrist in a specialized mental health care institute or private practice, a paediatrician in a hospital or an ADHD treatment centre, or to a combination of the above. Based on expert opinion, diagnoses are made based upon a very extensive (neuropsychological) examination, as well as after a relatively short diagnostic interview. In addition to the previously mentioned nationwide ADHD guidelines, both youth doctors and GPs have their own guidelines, which were introduced in 2014 [45, 46]. The GP guidelines give GPs the opportunity to diagnose ADHD in collaboration with, for example, mental health care services, or to start pharmacological treatment. It is important to be aware which health care professionals are involved in the process of diagnosing ADHD and if they are following particular guidelines. However, in the Netherlands, this information is not available. It is important to gain more insight into the diagnostic decision-making process, in order to optimize care for children with symptoms of inattention and / or hyperactivity.

According to the ADHD standard of care, the care of children with ADHD should be organized as shown in Figure 1.

***Figure 1** | Dutch recommendation for screening, diagnosing and treatment of ADHD*



(translated from the 'ADHD Zorgstandaard' ttps://www.ggzstandaarden.nl/zorgstandaarden/adhd/zorgrondom-adhd)

Since 1st January 2015, all Dutch municipalities are responsible for youth care services, including care for children with ADHD. The Dutch Youth Care Act (2015) provides a legal framework for this transition [47]. This transition of youth care applies to general youth care, and to (specialized) mental health care for children and youth. Before the introduction of the Youth Act, (specialized) mental health care services were paid for by health insurance companies. Since the transformation of youth care services, both youth care and specialized mental health care are paid for by the municipalities.

The premise of the 2015 Youth Act is to focus on the strength of both the parents and the child. Care should be *demand driven*, and should not be based on what the child *has* (the diagnosis) but rather on what the child and the family say they *need*. Care should be easily accessible, and expensive second- and third-line care should only be offered if necessary. With regard to ADHD, policy has been aimed at reducing the number of children who use medication for attention and concentration problems, based on an advisory report from the Dutch Health Council in 2014[43]. Instead of using highly specialized care, the government prefers to provide (preventive) support at an early stage. By supporting families in the community, and providing families with more information, this goal should be achievable.

In addition, a new Education Act was introduced on the 1st August 2014, the so called 'Inclusive Education Act' (in Dutch: Wet Passend Onderwijs) [48]. Before 2014, schools received extra financial support (in Dutch: rugzakje) for children who needed extra support based on a *diagnosis* like ADHD. One goal of the new Inclusive Education Act is to reduce the need for a diagnosis in order to provide the appropriate support to a child. According to the Inclusive Education Act, every school is obliged to provide both education and the right support and care to those children in need of something extra. Regular and special education schools work together in regional partnerships to realise these goals.

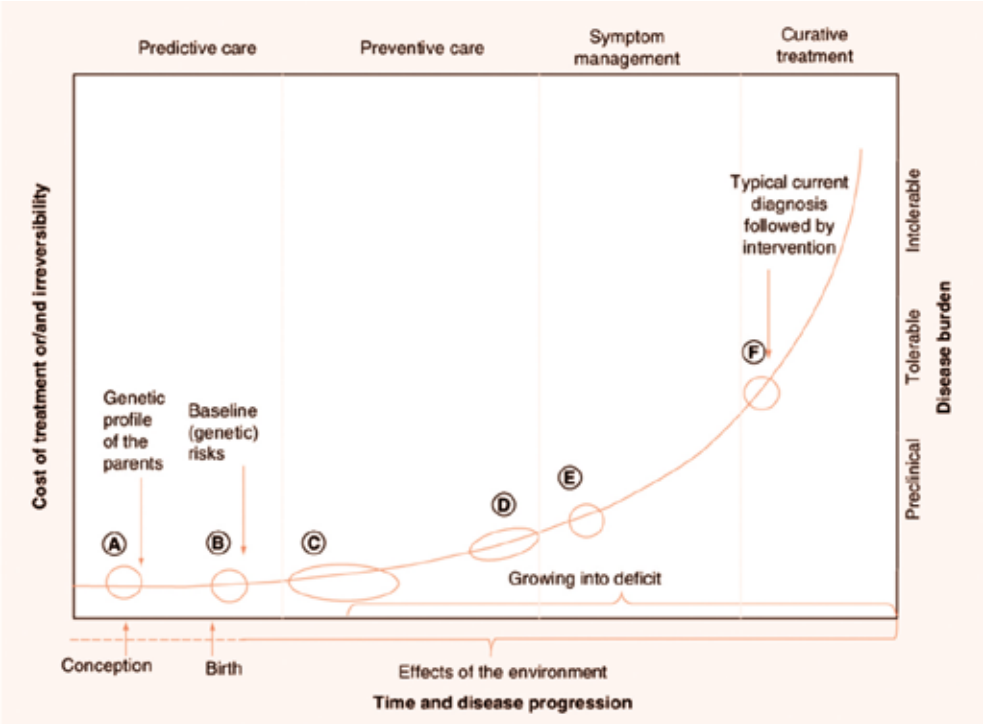
In short, the goal of the government's policy is to provide more support through primary care, and to minimise the use of special education. In order to make this transformation of youth care successful, it is necessary to identify the characteristics of children who were referred with symptoms of inattention and/or hyperactivity before the transformation. As the origins of inattention and/or hyperactivity symptoms are varied, and the aetiology of ADHD multifactorial, it is important to determine what knowledge is necessary to decide whether a child needs primary or specialized care. For example, knowledge of the bio-psycho-social model may help the care provider make the right choices in terms of further care and support. From a paediatric point of view, it is important to know whether somatic screening is only needed for children who meet *all ADHD criteria*, or if it is also needed for children with attention deficit and/or hyperactivity *symptoms*. In addition, knowledge about (early) risk factors, relevant for prevention or early support, will make it easier to meet the goals set out in the transformation of youth care.

Social paediatrics

Social paediatrics is a sub-specialization of general paediatrics. Social paediatrics is based on the principle that sickness and health are always related to the interaction between physical, psychological and social well-being. Social paediatricians work within academic and general hospitals, but also, for example, in mental health institutions, youth care, and other services for children with problems that are a threat to their development. Social paediatricians always team up with a wide range of (health)care providers, including those working in (specialized) mental health care, youth care, preventive youth health care, child and youth rehabilitation, child protection services, and many more. Symptoms and syndromes that are pre-eminently under the care of the social paediatrician include medically unexplained symptoms (MUS), learning, behavioural and developmental disorders (including ADHD, autism, mental disability), eating disorders, and chronic (childhood) illnesses. In addition, social paediatricians are specialized in the care of children in complex social situations that influence the maximum functioning and development of the child. A very important part of the work of social paediatricians is the care of children subject to any form of child abuse. Recently, Brown et al. (2017) showed that children with ADHD tend to have higher exposure to adverse childhood events (ACE, e.g., divorce, incarceration of a parent) compared with children without ADHD [49]. It is important to be aware of ACEs whenever evaluating a child with symptoms of inattention or hyperactivity.

A consultation by a social paediatrician is always based on the bio-psycho-social- transactional model. Unique to social paediatrics is the combination of knowledge about somatic diseases, the influence of these diseases on the environment, and the influence of the environment on diseases. A consultation can take place at different stages in the development of the child, from birth until adolescence. The moment and the way in which symptoms present themselves often depends on the social environment and the psychology of the child and/or his/her family. Sometimes, particular symptoms and their effect on a child's life match a (DSM) diagnosis; often, however, paediatricians observe clinical features of a certain disorder before symptoms meet a full diagnosis. Snyderman and Langheier have summarized this in a graph shown in Figure 2, representing the phenomenon which is later referred to as *growing into deficit*.

***Figure 2** | Adaptation of Snyderman's curve representing growing into deficit and the development of common complex diseases.*



(A) Parental genetic profile. (B) Baseline genetic risks at birth with minimal history of environmental effects. (C) Environmental effects act as initiating events in the process of disease formation. The precise time point may vary. (D) Further cumulative exposure to harmful environmental effects can lead to further preclinical progression of the development of the disease. (E) Gene-environment interaction leads to disease initiation: few symptoms can be seen. They do not cluster to diagnosis, but cause suffering. (F) The symptoms intensify until they structure to a diagnosis [50,51].

Social paediatricians are trained to recognize the impact of certain environmental factors on the health of children which may aggravate symptoms, leading to serious impairment. This offers opportunities for early support, for example for symptoms related to ADHD. Over the past 20 years, much research on ADHD has been carried out, and it is generally agreed that ADHD is a disorder with a wide heterogeneity and complex manifestations. ADHD can present itself differently in various stages of a child's life, as said depending on gender, age, level of development and/or environment [9]. In order to make an accurate diagnosis, symptoms must be correctly interpreted, as symptoms of inattention or hyperactivity can also have many other causes. When a child is referred too late, there is a risk of (major) problems developing, for example, problems with learning or with social contacts [52]. However, the misinterpretation of core symptoms can also lead to overdiagnosis, or increase the likelihood that other possible causes are

overlooked [52-54]. It is important to note that somatic problems may co-occur with ADHD, for example enuresis, or impaired motor skills that affect the total well-being of the child [22,55]. The combination of a multifactorial aetiology and a diverse symptom presentation contributed to the fact that children with symptoms of ADHD were often referred to a (social) paediatrician prior to the transformation of youth care. However, due to the transition and transformation of youth care, care pathways for children have changed. Since 2015, many hospitals are no longer contracted by municipalities to provide ADHD care. In the new *'ADHD standard of care'*, paediatricians are given a clear role whenever physical problems seem to be the reason for inattention and/or hyperactivity (Figure 1). Moreover, when mild ADHD is suspected, children may be diagnosed and treated by paediatricians with expertise in the area. However, bearing in mind the 'growing into deficit model', it can be assumed that paediatricians often see children with ADHD in their consulting room before symptoms meet an ADHD diagnosis. Often these children are referred with a request for help that is not related to ADHD. The reduced involvement of paediatricians in the care of children with ADHD, as a consequence of the transition of youth care, may therefore lead to missed opportunities for the early identification of these children. For this reason, it is important to discuss the role of (social) paediatricians in relation to ADHD in more detail.

Objectives and outline of this thesis

This thesis has two main objectives. First, to discuss the current role of (social) paediatricians in making a complex diagnosis such as ADHD, in relation to the changes implemented due to the introduction of the Youth Act in 2015. The second objective is related to the emphasis social paediatricians place on the interaction between biological, psychological and social factors. By studying the longitudinal effect of several environmental factors on ADHD, possibilities for (early) intervention are examined.

The transition and transformation of youth care in the Netherlands has had a major impact on care pathways for children with symptoms related to ADHD. As one of the goals of the transformation was to reduce referral to specialized care, this policy raises questions about the specific characteristics of children who were assessed by a multidisciplinary team (including a paediatrician), prior to the transformation. Is it possible to identify characteristics that discriminate between children who would benefit from specialized care and those who should be treated in primary care first? In an attempt to answer this question, **Chapters 2 and 3** explore the biomedical, psychological and social characteristics of children who were referred to an ADHD clinic prior to the transformation of youth care. For this study, the data of 261 children who underwent a multidisciplinary best practice evaluation at an ADHD clinic are analysed. Our research question is whether certain child- and parent characteristics and/or screenings tools can be identified which could indicate whether a child with symptoms related to ADHD should be sent to primary or specialized care. To determine the contribution of a medical doctor, the association between physical problems/diagnoses, and symptoms related to ADHD is explored. **Chapter 4** focuses on the professionals a family may encounter during the diagnostic phase of ADHD, which is studied after the transition of youth care. A survey is used to identify which (healthcare) professionals in the Netherlands are involved, and which guidelines they follow. The involvement of paediatricians is evaluated, alongside how closely they adhere to the bio-psycho-social model when diagnosing a child with ADHD.

The mutual influence of environmental factors and a child's constantly developing brain makes the environment an interesting subject of study, particularly in terms of finding possible clues to prevent growing into deficit. Therefore, in **Chapters 5, 6 and 7**, associations between various environmental factors and ADHD are evaluated. In order to study longitudinal associations between environmental

factors and ADHD, data from the prospective KOALA Birth Cohort Study are used. In the KOALA Birth Cohort Study, more than 2.500 children born between the years 2001 and 2003, together with their families, are being followed from early pregnancy into adulthood. This birth cohort study addresses two major themes: allergy/asthma, and growth and development [56]. Data are collected through repeated parent-reported questionnaires starting in pregnancy. In **Chapter 5**, associations between ADHD and pre-, peri -, and postnatal risk factors - such as maternal education level, Body Mass Index, smoking, alcohol use, gestational age, birthweight, gender, initiation and duration of breastfeeding, marital discord, daily routine and perceived psychological stress in the first year after birth - are assessed. In contrast to many other studies, three different models are used to explore associations between the distinct early stages of development and ADHD. For **Chapter 6** data regarding recreational screen time (watching television, computer use) and total sleep duration collected when the child was 2, 4 and 6 years old, are analysed to study the longitudinal association between ADHD and both recreational screen time and total sleep duration. Finally, **Chapter 7** focuses on general parenting in relation to ADHD. Responses to the Comprehensive Parenting Child Questionnaire, which is introduced in the same KOALA questionnaire as the questions about an ADHD diagnosis (age 8 -10 years), are used to describe general parenting in families with a child with ADHD.

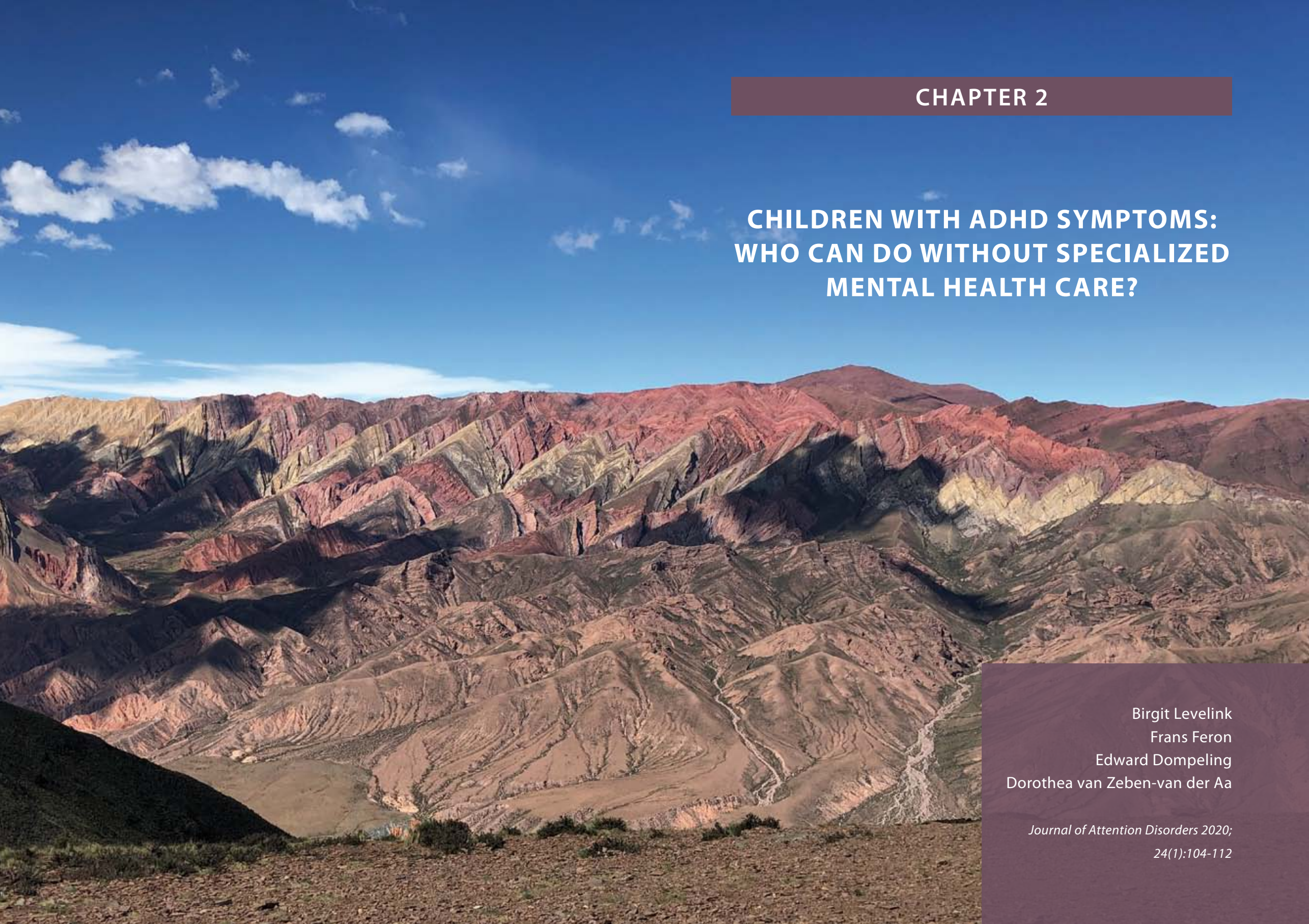
In **Chapter 8**, a general discussion considering the role of (social) paediatricians, and environmental factors in relation to ADHD is provided, based on the results of the studies outlined in previous chapters. Insights from the different studies are discussed in light of existing knowledge about ADHD and in relation to the goals set out in various Dutch policies and preventative programs.

REFERENCES

1. Sameroff A. A unified theory of development: a dialectic integration of nature and nurture. *Child Dev*. 2010 Jan-Feb 2010;81(1):6-22.
2. Trimbos Institute, Zorgstandaard ADHD [ADHD standard of care] Akwa GGZ; 2019. https://www.ggzstandaarden.nl/zorgstandaarden/adhd
3. Lange KW, Reichl S, Tucha O. The history of attention deficit hyperactivity disorder. *Attention deficit hyperactivity disorder* 2010. p. 241-255.
4. American Psychiatric Association, APA. Diagnostic and Statistical Manual of mental Disorders, DSM-III. Washington, DC: APA Press; 1980.
5. American Psychiatric Association, APA. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Arlington, VA2013.
6. American Psychiatric Association, APA. Diagnostic and Statistical Manual of Mental Disorders (DSM IV-TR). 4th edition, text revised ed. Washington, DC2000.
7. American Psychiatric Association, APA. DSM-IV: Diagnostic and Statistical Manual of Mental Disorders. American Psychiatric Press; 1994.
8. Lubke GH, Hudziak JJ, Derks EM, van Bijsterveldt TCEM, Boomsma DI. Maternal ratings of attention problems in ADHD: evidence for the existence of a continuum. *J Am Acad Child Adolesc Psychiatry*. Nov 2009;48(11):1085-1093.
9. Barkley RA, Murphy KR. Attention-Deficit Hyperactivity Disorder: A Clinical Workbook. third edition ed: Guilford Press; 2006.
10. Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA. The worldwide prevalence of ADHD: a systematic review and metaregression analysis. *Am J Psychiatry*. Jun 2007;164(6):942-8.
11. Polanczyk GV, Salum GA, Sugaya LS, Caye A, Rohde LA. Annual research review: A meta-analysis of the worldwide prevalence of mental disorders in children and adolescents. *J Child Psychol Psychiatry*. Mar 2015;56(3):345-65.
12. Willcutt EG. The prevalence of DSM-IV attention-deficit/hyperactivity disorder: a meta-analytic review. *Neurotherapeutics*. Jul 2012;9(3):490-9.
13. Thomas R, Sanders S, Doust J, Beller E, Glasziou P. Prevalence of attention-deficit/hyperactivity disorder: a systematic review and meta-analysis. *Pediatrics*. Apr 2015;135(4):e994-1001.
14. Nøvik TS, Hervas A, Ralston SJ, et al. Influence of gender on attention-deficit/hyperactivity disorder in Europe--ADORE. *Eur Child Adolesc Psychiatry*. Dec 2006;15 Suppl 1:I15-24.
15. Simon V, Czobor P, Bálint S, Mészáros A, Bitter I. Prevalence and correlates of adult attention-deficit hyperactivity disorder: meta-analysis. *Br J Psychiatry*. Mar 2009;194(3):204-11.
16. Larson K, Russ SA, Kahn RS, Halfon N. Patterns of comorbidity, functioning, and service use for US children with ADHD, 2007. *Pediatrics*. Mar 2011;127(3):462-70.
17. Kraut AA, Langner I, Lindemann C, et al. Comorbidities in ADHD children treated with methylphenidate: a database study. *BMC Psychiatry*. Jan 2013;13:11.
18. Ghanizadeh A. Psychiatric comorbidity differences in clinic-referred children and adolescents with ADHD according to the subtypes and gender. *J Child Neurol*. Jun 2009;24(6):679-84.
19. Jensen CM, Steinhausen HC. Comorbid mental disorders in children and adolescents with attention-deficit/hyperactivity disorder in a large nationwide study. *Atten Defic Hyperact Disord*. Mar 2015;7(1):27-38.
20. Jameson ND, Sheppard BK, Lateef TM, Vande Voort JL, He JP, Merikangas KR. Medical Comorbidity of Attention-Deficit/Hyperactivity Disorder in US Adolescents. *J Child Neurol*. 10 2016;31(11):1282-9.

21. Muskens JB, Velders FP, Staal WG. Medical comorbidities in children and adolescents with autism spectrum disorders and attention deficit hyperactivity disorders: a systematic review. *Eur Child Adolesc Psychiatry.* Sep 2017;26(9):1093-1103.
22. Von Gontard A, Equit M. Comorbidity of ADHD and incontinence in children. *Eur Child Adolesc Psychiatry*. Feb 2015;24(2):127-40.
23. Mogensen N, Larsson H, Lundholm C, Almqvist C. Association between childhood asthma and ADHD symptoms in adolescence--a prospective population-based twin study. *Allergy.* Sep 2011;66(9):1224-30.
24. Faraone SV, Asherson P, Banaschewski T, et al. Attention-deficit/hyperactivity disorder. *Nat Rev Dis Primers*. 08 2015;1:15020.
25. Faraone SV, Larsson H. Genetics of attention deficit hyperactivity disorder. *Mol Psychiatry.* 04 2019;24(4):562-575.
26. Thapar A, Cooper M, Eyre O, Langley K. What have we learnt about the causes of ADHD? *J Child Psychol Psychiatry*. Jan 2013;54(1):3-16.
27. Demontis D, Walters RK, Martin J, et al. Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. *Nat Genet.* 01 2019;51(1):63-75.
28. Thapar A, Cooper M. Attention deficit hyperactivity disorder. *Lancet.* Mar 2016;387(10024):1240-50.
29. Russell AE, Ford T, Williams R, Russell G. The Association Between Socioeconomic Disadvantage and Attention Deficit/Hyperactivity Disorder (ADHD): A Systematic Review. *Child Psychiatry Hum Dev.* 06 2016;47(3):440-58.
30. Sciberras E, Mulraney M, Silva D, Coghill D. Prenatal Risk Factors and the Etiology of ADHD-Review of Existing Evidence. *Curr Psychiatry Rep.* Jan 2017;19(1):1.
31. Lifford KJ, Harold GT, Thapar A. Parent-child relationships and ADHD symptoms: a longitudinal analysis. *J Abnorm Child Psychol.* Feb 2008;36(2):285-96.
32. Modesto-Lowe V, Danforth JS, Brooks D. ADHD: does parenting style matter? *Clin Pediatr (Phila).* Nov 2008;47(9):865-72.
33. Beyens I, Valkenburg PM, Piotrowski JT. Screen media use and ADHD-related behaviors: Four decades of research. *Proc Natl Acad Sci U S A.* 10 2018;115(40):9875-9881.
34. Russell G, Ford T, Rosenberg R, Kelly S. The association of attention deficit hyperactivity disorder with socioeconomic disadvantage: alternative explanations and evidence. *J Child Psychol Psychiatry.* May 2014;55(5):436-45.
35. Clifton EAD, Perry JRB, Imamura F, et al. Genome-wide association study for risk taking propensity indicates shared pathways with body mass index. *Commun Biol.* 2018;1:36.
36. Martins-Silva T, Vaz JDS, Hutz MH, et al. Assessing causality in the association between attention-deficit/hyperactivity disorder and obesity: a Mendelian randomization study. *Int J Obes (Lond).* Apr 2019
37. Strawbridge RJ, Ward J, Cullen B, et al. Genome-wide analysis of self-reported risk-taking behaviour and cross-disorder genetic correlations in the UK Biobank cohort. *Transl Psychiatry.* 02 2018;8(1):39.
38. Christakis DA. The effects of infant media usage: what do we know and what should we learn? *Acta Paediatr.* Jan 2009;98(1):8-16.
39. Lingineni RK, Biswas S, Ahmad N, Jackson BE, Bae S, Singh KP. Factors associated with attention deficit/hyperactivity disorder among US children: results from a national survey. *BMC Pediatr.* May 2012;12:50.
40. Parker A, Corkum P. ADHD Diagnosis: As Simple As Administering a Questionnaire or a Complex Diagnostic Process? *J Atten Disord.* 06 2016;20(6):478-86.

41. Ickowicz A, Schachar RJ, Sugarman R, Chen SX, Millette C, Cook L. The parent interview for child symptoms: a situation-specific clinical research interview for attention-deficit hyperactivity and related disorders. *Can J Psychiatry.* Apr 2006;51(5):325-8.
42. Martínez-Núñez B, Quintero J. Update the Multimodal Treatment of ADHD (MTA): twenty years of lessons. *Actas Esp Psiquiatr.* Jan 2019;47(1):16-22.
43. *ADHD: medicatie en maatschappij.* [ADHD: medication and society] (2014).
44. Richtlijnontwikkeling LSM. *Multidisciplinaire Richtlijn voor diagnostiek en behandeling van ADHD bij kinderen en jeugdigen* [Multidisciplinar Guideline for diagnosis and management of ADHD in children and adolescents]. Trimbos instituut, Utrecht2005.
45. Boer F, Glind vdG. *JGZ-richtlijn ADHD; Signalering, begeleiding en toeleiding naar diagnostiek* [Youth Health Care guideline ADHD: signalling, guiding and leading towards diagnosis]. https://www.ncj.nl/richtlijnen/alle-richtlijnen/richtlijn/?richtlijn=24: Trimbos Institute; 2015.
46. Van Avendonk MJ, Hassink-Franke LJ, Stijntjes F, Wiersma T, Burgers JS. *Samenvatting NHG standaard 'ADHD bij kinderen'* [Summary of the Dutch College of General Practitioners' (NHG) practice guideline 'ADHD in children']. *Ned Tijdschr Geneeskd.* 2015;159:A8395.
47. Ministerie Volksgezondheid WeSMoHaS. [National Youth Law The Netherlands]. https://eacea.ec.europa.eu/national-policies/en/content/youthwiki/12-national-youth-law-netherlands: EACEA National Policies Platform; European Commission; 2014.
48. Rijksoverheid. Wet Passend Onderwijs. [Inclusive Education Act: ' Retrieved from https://www.nji.nl/nl/Download-NJi/Publicatie-NJi/Children-and-youth-support-and-care-in-The-Netherlands.pdf]
49. Brown NM, Brown SN, Briggs RD, Germán M, Belamarich PF, Oyeku SO. Associations Between Adverse Childhood Experiences and ADHD Diagnosis and Severity. *Acad Pediatr.* 2017 May - Jun 2017;17(4):349-355.
50. Snyderman R, Langheier J. Prospective health care: the second transformation of medicine. *Genome Biol.* 2006;7(2):104.
51. Syurina EV, Gerritsen AJ, Hens K, Feron FJ. "What about FH of my child?" parents' opinion on family history collection in preventive primary pediatric care. *Per Med.* Aug 2015;12(4):327-337.
52. Wehmeier PM, Schacht A, Barkley RA. Social and emotional impairment in children and adolescents with ADHD and the impact on quality of life. *J Adolesc Health.* Mar 2010;46(3):209-17.
53. Coon ER, Quinonez RA, Moyer VA, Schroeder AR. Overdiagnosis: how our compulsion for diagnosis may be harming children. *Pediatrics.* Nov 2014;134(5):1013-23.
54. Costello JE. Commentary: 'Disease of the world': from epidemiology to etiology of child and adolescent psychopathology - a commentary on Polanczyk et al (2015). *J Child Psychhol Psychiatry* 2015. p. 366-369.
55. Fliers EA, de Hoog ML, Franke B, et al. Actual motor performance and self-perceived motor competence in children with attention-deficit hyperactivity disorder compared with healthy siblings and peers. *J Dev Behav Pediatr.* Jan 2010;31(1):35-40.
56. Kummeling I, Thijs C, Penders J, et al. Etiology of atopy in infancy: the KOALA Birth Cohort Study. *Pediatr Allergy Immunol.* Dec 2005;16(8):679-84.



CHAPTER 2

CHILDREN WITH ADHD SYMPTOMS: WHO CAN DO WITHOUT SPECIALIZED MENTAL HEALTH CARE?

Birgit Levelink
Frans Feron
Edward Dompeling
Dorothea van Zeben-van der Aa

Journal of Attention Disorders 2020; 24(1):104-112

ABSTRACT

Objective: A new Dutch child and youth act should reduce specialized mental health care for children with symptoms of ADHD. Characteristics of children referred to a specialized ADHD clinic are explored, to give direction to this intention.

Methods: Data of 261 children who underwent a multidisciplinary best practice evaluation (including rating scales, demographic, psychological and somatic findings) were analysed. Univariable and multivariable logistic regression models were used to find predictive variables for the need of specialized mental health care.

Results: Collected data were heterogeneous. (Sub)clinical total scores on the Teacher report form (TRF) and Child Behaviour Checklist (CBCL) were predictive variables for specialized mental health care. Also, children with divorced parents were more often referred to specialized care.

Conclusion: (Sub) clinical scores on the CBCL and TRF increase the need for specialized care but comprehensive assessment of every child with ADHD symptoms was necessary to differentiate between levels of care.

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a common childhood neurodevelopmental disorder with an estimated worldwide prevalence of 3.4 % [1]. It is a heterogeneous diagnosis, in which genetic, biological and environmental factors play an important role [2-4]. To meet DSM-5 classification criteria for ADHD, a child must display six out of nine symptoms from the inattention cluster and/or six out of nine symptoms from the hyperactivity/impulsivity cluster [5]. These symptoms depend on age and sex and may vary in different life stages [6-8]. In addition, ADHD has a high co-morbidity rate, and many symptoms of comorbid disorders show an overlap with ADHD symptoms [9]. Besides age, gender and comorbidity, psychosocial context may shape ADHD presentation [10, 11]. Diagnosing ADHD further requires symptoms to interfere with one's social life and development, presence of symptoms before the age of 12, and no alternative explanation of symptoms by another mental disorder [5]. This makes it a challenge for clinicians to make a distinction between ADHD symptoms due to an ADHD diagnosis or due to other causes.
In 2014, the Dutch Health Council (DHC) found a fourfold increase in methylphenidate use among children over the past decade and a thirty per cent increase in specialized health care facilities use for problems related to ADHD symptoms [12]. In order to halt this increase, the DHC proposed a prominent role for primary health care in differentiating between children with ADHD symptoms who only need supportive counselling, and children with serious impairment who need specialized mental health care. Therefore, the Dutch government introduced a new Child and Youth Act in 2015, which made local governments responsible for prevention, support and treatment of developmental and psychological problems and disorders. The premise of the Act is that care must match the needs of the child and family, which should not be dictated exclusively by the diagnosis of the child. The number of children in specialized care must be decreased by increasing preventive and early intervention support and the use of social networks within the direct environment of children [13]. Accurate evaluation of ADHD symptoms is one of the cornerstones of success of this new Act to prevent not only over diagnosis based only on symptoms but also under diagnosis with the risk of complications.
Prior to the introduction of the Child and Youth Act, a wide range of data from children seen at a specialized ADHD clinic was analysed to gain insight into characteristics of children sent to a specialized care facility. The data were analysed at the hand of the following research questions: first, is it possible to differentiate in an applicable manner between children with ADHD symptoms who need supportive counselling eventually combined with methylphenidate and children with serious impairment and/or comorbidity who need specialized mental health care? And second, which referral data, demographic variables, questionnaires and/or rating scales are helpful for this differentiation?

METHODS

Participants

The database was that of children attending the Medipsy ADHD clinic ('the ADHD clinic'). The ADHD clinic is collaboration between the Sint Jans Gasthuis hospital (SJG), Medipsy – a primary mental health care clinic – and Metggz – a specialized child psychiatry institute –, which started in 2010. It is an outpatient clinic for children between 6 - 18 years old, located at the SJG Weert, a small hospital in a southern province of the Netherlands. All children were referred by a general practitioner or youth health care physician (school doctor) because of symptoms related to attention deficit and / or hyperactivity and impulsivity. Fifteen children had seen a psychologist at another primary health care facility prior to their

visit and 14 children already used methylphenidate before referral. The ADHD clinic used only two triage criteria, namely age (>6 and <18 years) and a referral related to ADHD symptoms. There was no triage on the severity of DSM symptoms and cross-situational impairment. The dataset is based on files of children attending between September 2011 and November 2015, during the time in which there was consistent composition of, and practice by, the multidisciplinary team.

Procedure

The multidisciplinary team of the ADHD clinic consisted of a psychologist, a nurse specialist, a staff member from the child psychiatric centre and a paediatrician. Prior to the visit, all screening rating scales, an open questionnaire for the teacher and a demographic form were completed by both parents and teacher. During the clinical visit, the child and parents were extensively interviewed by the psychologist concerning different aspects of ADHD and comorbidities. Parents were always asked who took the initiative for referral to an ADHD clinic (e.g., parents, teacher, or both parents and teacher). Subsequently, a medical consultation took place. Besides medical history and complete physical examination, the paediatrician discussed the pre-filled demographic form, which also contained questions about early development of the child. The next step was for the ADHD multidisciplinary team to discuss the collected data. Diagnoses were made by team consensus, taking into account information from the interview, DSM-IV-TR criteria, developmental history and somatic comorbidity, thresholds on rating scales and information from the teacher open questionnaire [14]. Only children who met criteria for ADHD diagnosis without suspected comorbidity received a same day ADHD diagnosis. All others were either referred to a specialized child psychiatric centre for additional diagnostics or referred to adequate primary care, for example Youth Care or school counselling team.

Measures

CBCL, Child Behaviour Checklist; TRF, Teacher Report Form; YSR, Youth Self Report

The Child Behaviour Checklist (CBCL) is a component in the Achenbach System of Empirically Based Assessment (ASEBA) developed by Thomas M. Achenbach [15]. The ASEBA uses different checklists for teachers (Teacher report Form, TRF) and children older than 11 can fill in their own checklist (Youth Self report, YSR). We used the Dutch school age version from 2001 by Verhulst [16]. These sets of questionnaires offer a standardized way to quantify behavioural and emotional problems and skills in children. Both attention problem scores and total scores were used during the evaluation of the child; total scores were used to determine the need for specialized mental health care. T-scores between 65-70 were described as subclinical, above 70 as clinical scores. In 2013, the Dutch Committee on Test Affairs (COTAN) assessed the Dutch version as insufficient in terms of reliability but sufficient in terms of validity, what made this rating scale useful for our research question. In this study parents, the teacher and children older than 11 completed the form.

AVL, ADHD Vragen Lijst (ADHD-questionnaire)

AVL is a Dutch behavioural questionnaire for children aged 4 to 18 years that is based on the Conners Rating Scale for ADHD and developed by van der Ploeg and Scholte [17]. It determines whether there are behavioural symptoms of ADHD, and if so, to what extent symptoms of inattention, hyperactivity and impulsivity play a role. The AVL is based on the diagnostic criteria of the DSM IV and describes 18 behavioural symptoms. The COTAN assessed the test reliability as good and the validity as sufficient [18]. At the ADHD clinic, the teacher and both parents filled in the AVL.

Open questionnaire for the teacher

This open questionnaire for teachers was designed by the ADHD clinic based on the Conner's Rating Scale for ADHD. It consists of 13 general questions about functioning at school and psychosocial development, and 18 questions describing behaviour based on the DSM IV diagnostic criteria for ADHD.

Demographic form

This open questionnaire for parents was also designed by the ADHD clinic and consisted of questions concerning legal matters of parenthood, family situation, education level and employment of both parents, birth and early development of the child, prior interventions and family history.

Data analysis

All data used in this study was uploaded in SPSS version 22 for analysis [19]. To answer the research questions, the outcome at the end of the diagnostic process was divided into two groups; *group A* with ADHD and/or other psychiatric symptoms with special need due to serious impairment in need of specialized mental health care, *group B* with ADHD without comorbidity requiring supportive counselling eventually combined with methylphenidate at a primary care clinic or other problems requiring primary or supportive care.

First, the demographic characteristics of groups A and B were analysed; in group B (need for primary care) a distinction was made between those who were diagnosed with ADHD and those who did not receive a diagnosis. In addition, crosstabs were used to analyse if demographic variables and outcome of rating scales were associated with first initiative for referral. Logistic regression in a univariable model with group A and group B was used to identify significant factors differentiating between primary and specialized mental health care. In the logistic regression, positive family history for ADHD was combined with positive family history for other psychiatric diagnosis. Variables from this univariable logistic regression with a p value ≤ 0.01 were combined in a multivariable logistic regression to assess independence of each other on the outcome.

RESULTS

Sample Characteristics and study flow diagram (figure 1, table 1 and 2)

Files of 261 children were analysed. Mean age was 10.0 years (SD= 2.87), 72.8 % was male. In 258 cases, a clear answer on the question 'who took the first initiative for referral to an ADHD clinic for the inattention and/or hyperactive problems?' was present. Most children (50.8%) were referred by both parents and school. Initiative of referral was not significantly associated with the need for specialized care; the percentage of children in need of specialized mental health care was only slightly higher when both teacher and parents initiated the referral. 'ADHD and/or other psychiatric symptoms with special need due to serious impairment in need of specialized mental health care ' was the outcome in 82 children (31.4%). Besides marital status of the parents, there were no demographic differences between group A and B (table 1). Distribution of these demographic factors over the three-referral groups (i.e., referral by teacher, parents or both) only showed significantly more boys than girls in the school referral group (table 2). Scores on general symptom severity by mothers and teacher on the CBCL and TRF were higher in the group that was found to be in need of specialized health care. Scores on ADHD symptoms by both parents and teacher on ADHD rating scale (AVL) were the highest in group B, i.e., children diagnosed with ADHD in absence of comorbidity. Rating scales only partly reflected the initiative for referral by school or parents.

Figure 1 *| Study flow*

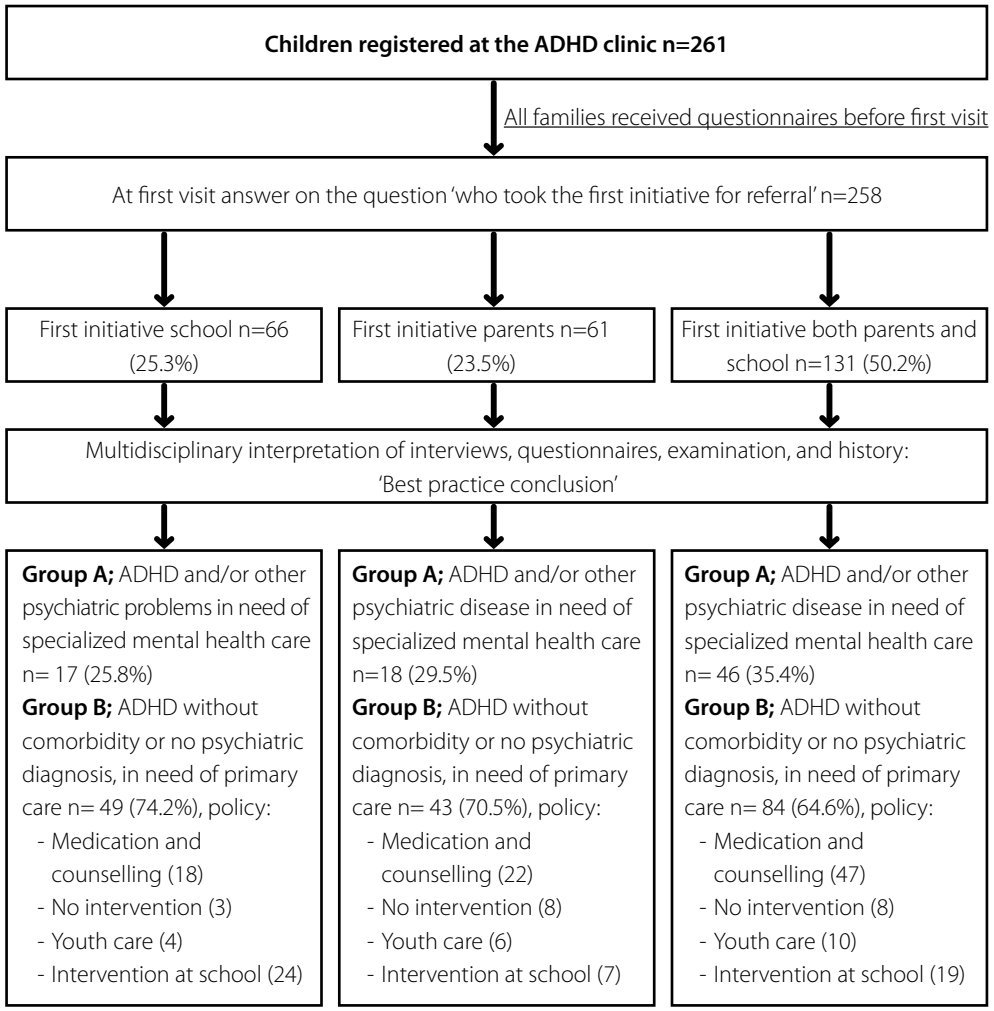


Table 1 *| Characteristics of children in need of specialized care (group A; 'ADHD and/or other psychiatric symptoms with serious impairment in need of specialized mental health care') and of children in need of primary care (group B; B1'ADHD without comorbidity requiring supportive counselling eventually combined with methylphenidate', B2 'Other problems requiring primary care').*

	Specialized care	**Primary care**	
Variable	Group A n=82 (31.4%) (n, %)	Group B1 n=87 (33.3%) (n, %)	Group B2 n=89 (34.1%) (n, %)
Gender; male	58 (70.7)	63 (72.4)	67 (75.3)
Age (years, mean, range)	10.2 (5-16)	9.4 (5-16)	10.6 (5-18)
Referral			
School	17 (21.0)	18 (20.7)	31 (34.8)
Parents	18 (22.2)	22 (25.3)	21 (23.6)
Both school and parents	46 (56.8)	21 (54.0)	37 (41.6)
Special program at school or special education	34 (41.5)	40 (46.0)	34 (38.6)
Education level mother			
Low	14 (19.2)	8 (10.5)	12 (14.8)
Middle	38 (52.0)	45 (59.2)	49 (60.5)
High	21 (28.8)	23 (30.3)	20 (24.7)
Education level father			
Low	12 (19.0)	14 (18.7)	10 (12.7)
Middle	29 (46.1)	33 (44.0)	42 (53.2)
High	22 (34.9)	28 (37.3)	27 (34.2)
Marital status			
Married	46 (57.5)	68 (82.9)	61 (70.1)
Divorced	25 (31.3)	9 (11.0)	17 (19.5)
Other	9 (11.3)	5 (6.1)	9 (10.3)
Family history			
ADHD	14 (17.1)	16 (18.4)	15 (16.9)
Psychiatry-no ADHD	45 (54.9)	38 (43.7)	40 (44.9)
Negative	23 (28.0)	33 (37.9)	34 (38.2)
AVL mother [a]			
Normal	27 (33.3)	22 (27.5)	50 (61.0)
High-clinical	54 (66.7)	58 (72.5)	32 (39.0)
AVL father [a]			
Normal	34 (48.6)	27 (36.5)	52 (74.3)
High-clinical	36 (51.4)	47 (63.5)	18 (25.7)
AVL teacher [a]			
Normal	35 (50.0)	29 (39.7)	53 (67.1)
High-clinical	35 (50.0)	44 (60.3)	26 (32.9)
CBCL total mother[a]			
Normal	33 (44.0)	43 (52.4)	61 (75.3)
Subclinical	13 (17.3)	16 (18.5)	12 (14.8)
Clinical	29 (38.7)	23 (28.1)	8 (9.9)
TRF [a]			
Normal	41 (54.7)	54 (66.7)	67 (83.8)
Subclinical	15 (20)	16 (19.8)	9 (11.3)
Clinical	19 (25.3)	11 (13.6)	4 (5.0)

Note. AVL = ADHD Vragen Lijst; CBCL = Child behavior Checklist; TRF = Teacher Report Form.
[a]Chi-square test, $p < .001$.

***Table 2** | Characteristics of children based on first initiative for referral (i.e., first initiative for referral taken by school, parents, or both parents and school.*

	Initiative school (n, %)	Initiative parents (n, %)	Initiative both school and parents (n, %)
Gender; male [a]	56 (84.8)	44 (72.1)	87 (66.4)
Age (years, mean)	9.6	10.7	9.9
Special program/education at school	39 (59.1)	33 (54.1)	78 (60.0)
Educational level mother			
Low	11 (18.7)	6 (10.7)	16 (13.9)
Middle	33 (55.9)	36 (64.3)	63 (54.8)
High	15 (25.4)	14 (25.0)	36 (31.1)
Educational level father			
Low	9 (15.8)	20 (30.8)	16 (15.2)
Middle	33(57.9)	26 (40.0)	45 (42.9)
High	15 (26.3)	19 (29.2)	44 (41.9)
Marital status			
Married	48 (73.8)	44 (74.6)	84 (67.2)
Divorced	10(15.4)	12 (20.3)	28 (22.4)
Other	7 (10.8)	3 (5.1)	13 (10.4)
Family history			
ADHD	9 (13.6)	13 (21.3)	24 (18.3)
Psychiatry-no ADHD	30 (45.5)	34 (55.7)	60 (45.8)
No psychiatry/ADHD	27 (40.5)	14 (23.0)	47 (35.9)
AVL mother			
Normal	30 (49.2)	24 (41.4)	46 (37.1)
High-clinical	31 (50.8)	34 (58.6)	78 (62.9)
AVL father			
Normal	35 (60.3)	32 (60.4)	47 (45.6)
High-clinical	23(39.7)	21(39.6)	56(54.5)
AVL teacher [b]			
Normal	21(36.2)	35 (68.6)	61 (54.0)
High-clinical	37 (63.8)	16 (31.4)	52 (46.0)
CBCL total mother			
Normal	40 (71.4)	32 (55.2)	66 (52.8)
Subclinical- clinical	16 (28.6)	26 (44.8)	59 (47.2)
TRF			
Normal	36 (64.3)	47 (79.7)	80 (65.6)
Subclinical - clinical	20 (35.7)	12 (20.3)	42 (34.4)

Note. AVL = ADHD Vragen Lijst; CBCL = Child behavior Checklist; TRF = Teacher Report Form.
[a] Chi-square test p < .05. [b] Chi-square test p < .01.

Characteristics of children associated with need of specialized care (table 3)

In the univariable analysis marital status of parents, the CBCL filled in by the mother and the TRF were associated with increased odds for the need of specialized mental health care. In the multivariable logistic regression analysis, all these three variables remained significant, with the TRF in particular (p=0.007, CBCL p=0.02, marital status p=0.02). The effect of the TRF and CBCL was even more obvious when analysis was done with clinical scores only.

***Table 3** | Univariable an multivariable logistic regression identifying risk factors for children with ADHD and/or other psychiatric symptoms with serious impairment in need of specialized mental health care (Group A).*

Univariable model	Odds ratio (95th CI)	*p value*
Gender	0.86 (0.48-1.53)	0.60
Age	1.03 (0.94-1.13)	0.50
Assistance at school	0.96 (0.57-1.65)	0.90
Marital status parents (divorced)	2.70 (1.42-5.13)	0.003
Level of education mother		
Low compared to high	1.21 (0.54-2.73)	0.64
Level of education father		
Low compared to high	1.10 (0.48-2.58)	0.80
Family history with psychiatric problems	0.83 (0.57-1.20)	0.31
First initiative referral parents compared to school	1.20 (0.55-2.63)	0.64
First initiative referral both parents and school compared to school	1.58 (0.81-3.01)	0.17
AVL		
Mother	1.60 (0.92-2.79)	0.10
Father	1.29 (0.73-2.28)	0.39
Teacher	1.17 (0.67-2.07)	0.58
CBCL mother	2.24 (1.29-3.91)	0.004
TRF	2.51 (1.41-4.47)	0.002
Multivariable model		
Marital status parents (divorced)	2.35 (1.15-4.80)	0.02
CBCL Mother	2.10 (1.14-3.80)	0.02
TRF	2.35 (1.26-4.38)	0.007

Note. AVL = ADHD Vragen Lijst; CBCL = Child behavior Checklist; TRF = Teacher Report Form.
CI= confidence Interval

DISCUSSION

The Committee on Psychosocial Aspects of Child and Family Health and Task Force on Mental Health (2009) wrote a policy statement in which they described mental health competencies for paediatric primary care [20]. The statement focused on treatment of children with mental problems in absence of a diagnosis by paediatric primary care. Until 2015, these children were treated by specialized mental and paediatric health care facilities in the Netherlands; the new Dutch Child and Youth Act must shift the care of these children to primary (health) care facilities [13]. This is also true for the support and treatment of children with ADHD without severe impairment and/or comorbidity. Primary health care for children in the Netherlands involves a diverse group including general practitioners, youth health care physicians, social workers, psychologists and coaches. In addition, the government wants to create a formal role for teachers and family members.

This study analysed data from children seen at a specialized ADHD clinic before introduction of the new Child and Youth act in order to identify characteristics that can be used to differentiate between children who require primary care and children with serious impairment in need of specialized mental health care. Of the children referred to this ADHD clinic 34.1% displayed ADHD symptoms but did not receive a specific mental diagnosis; they were referred to primary (health) care. In addition, 33.3% were diagnosed with ADHD in absence of comorbidity. The demographic characteristics of children both in need of primary and specialized care were heterogeneous and there were no demographic differences between the groups except for marital status of the parents, in the group of children referred to specialized care more parents were divorced. Recently Brown et al. concluded that 'there is a significant association between adverse childhood experiences (ACE) score and ADHD' and they advised routinely evaluating for ACE to improve ADHD management [21]. This study did not examine why more children from divorced parents were referred to specialized care (e.g., severity ADHD symptoms, family problems), but this result does fit with the advice to evaluate for ACE. No significance was found for a positive psychiatric family history to distinguish between levels of care, which may be explained by the fact that parents with mental health problems tend to use more services [22].

A striking observation was that almost half of the children referred only by school or only by the parents received a diagnosis of ADHD or was in need of specialized mental health care. Other studies have shown that concordance among teachers' and parents' perceptions of ADHD symptoms could differ due to reference framework, difference in salience, and/or variations in children's behaviour in different settings, which could be caused by differing situational demands [23]. A one-dimensional measurement of the initiative of referral can therefore not be used as screening criterion to differentiate between levels of care, as it does not adequately capture the presence of symptoms and/or impairment in different setting.

To objectivize presence of ADHD symptoms, rating scales can be used. Efron, Bryson, Lycett and Sciberras (2016) recently showed that rating scales of teachers are useful regarding ADHD symptoms, which was also reflected in this study [24]. Need for specialized mental health care was not reflected in ADHD rating scales, but in the total scores of the CBCL and TRF. This corresponds with the fact that these children suffer from serious impairment and/or comorbidities, which may give symptoms other than attention deficit and/or hyperactivity and impulsivity. Despite the fact that CBCL and TRF were statistically significant in differentiating between specialized or primary care, exclusive reliance on these questionnaires is a pitfall for clinical practice. Of the children in need of specialized care respectively 56% and 45% scored subclinical or clinical on the CBCL and TRF, and positive predictive value was low. Overall, there were few questionnaires with a symptom score in the clinical range. Like we know from literature, also in this study the cross-informant scores between teacher, father and mother on all rating scales varied [25]. To obtain a clear picture of symptoms and impairment, this study used contextual information during the interviews as a guide together with the questionnaires and the rating scales, as suggested in a meta-analysis concerning the multi informant [26, 27]. Studies by Gordon et al. (2006) and Gathje, Lewandowski and Gordon (2008) showed the impact of using the impairment criterion along with symptoms on clinical decision-making [28, 29]. Their studies found that impairment combined with symptoms can lower diagnoses. This study showed the same but also found the reverse; low symptom scores on questionnaires but impairment during the interview. This can have several causes; most noticeable was the difference between teacher's AVL and TRF questionnaires (low scores) and the open questionnaire for teachers, which did show impairment many times. This shows the importance of good cross-sectional analysis, not only through rating scales but also through interviews with, for example, teachers. Differentiation between levels of care was only possible through comprehensive interpretation of all data.

A key finding was that more than half of the children referred with attention problems received no additional support at school before referral. Regarding the goal of the Dutch government, this raises opportunities for early intervention by school-based programs.

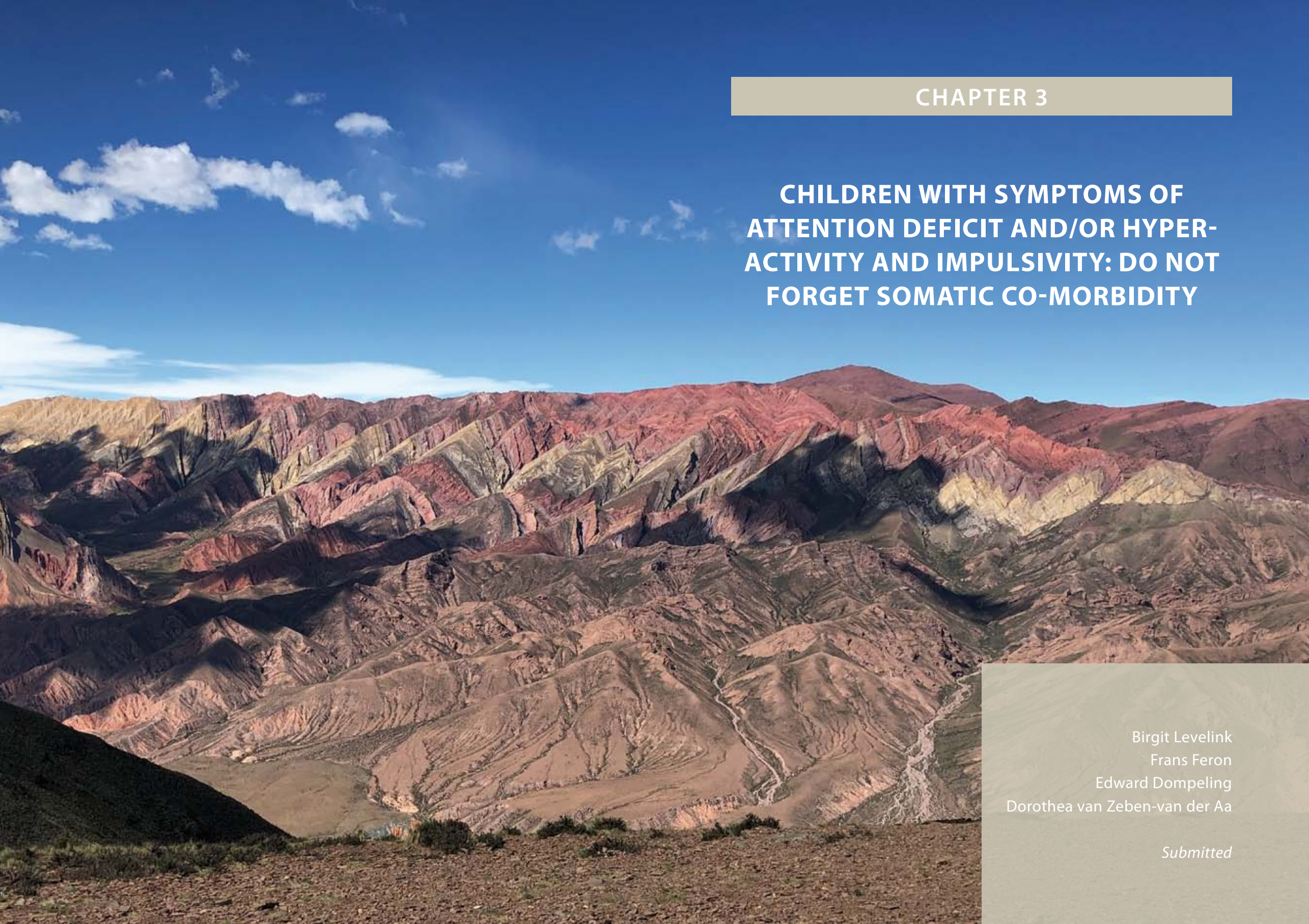
These results have several limitations. First, results are based on data collected from a group referred to a specialized ADHD clinic in a specific region in the Netherlands. Little is known about regional differences regarding ways of referral and use of different services for ADHD. Although the various subject characteristics like sex and age are in line with other populations and studies, we cannot assume that the demographics of patient populations seen by other clinics are identical or even similar. The clinic studied here is situated in a hospital; it is therefore possible that children with more comorbidity and social problems are directly referred to specialized mental health care. Second, it could be that some referred children did not register at the clinic, which may cause bias in the data set. Other studies find teacher referral rates of 30% to 38% [22, 30]. In this group, teacher referral rates were slightly lower (25.6%). This difference could be explained by the fact that some children, e.g., girls, referred by the teacher did not go to the ADHD clinic. Several factors can influence the likelihood of parents seeking help for attention deficit problems – and thereby influence referral outcome, such as parent education, unclearness of the referral route, or the availability of services in a region [31]. Third, ADHD diagnosis is a best practice diagnosis. There is no gold standard for a diagnosis of ADHD and it is difficult to discriminate between ADHD symptoms without mental diagnosis and a diagnosis of ADHD. There is no data on the uniformity of the diagnostic path in different centres. Due to inter-rater reliability, impairment can be weighed differently and change outcome [32]. Further research into ways of clinical decision-making is important for better interpretation and generalisation of data.

Clinical Implications and Conclusion

These findings shed light on the complexity of triaging children with ADHD symptoms – by implication, the viability of the Dutch government's goal to shift the care for children with ADHD symptoms to primary health care facilities. Children who seek help for their attention problems and/or hyperactivity form a heterogeneous group, and despite the fact that clinical scores on CBCL and TRF gave direction to the need of specialized care, only clinical decision making by the multidisciplinary team was decisive. Every child needs extensive comprehensive evaluation to gain insight in the origin of the symptoms, the presence of ACE's and to evaluate the degree of impairment. It is important to determine which options primary care has to evaluate symptoms of attention deficit and/or hyperactivity, to prevent under- and/or over diagnosis, and to make the new Dutch policy a success. By developing consultative structures and relationships between primary and specialized health care, proper critical assessment of every child can be done.

REFERENCES

1. Polanczyk G, Salum GA, Sugaya LS, Caye A, Rohde LA. Annual research review: A meta-analysis of the worldwide prevalence of mental disorders in children and adolescents. *J Child Psychol Psychiatry.* Mar 2015;56(3):345-65.
2. Larson K, Russ SA, Kahn RS, Halfon N. Patterns of comorbidity, functioning, and service use for US children with ADHD, 2007. *Pediatrics.* Mar 2011;127(3):462-70.
3. Pressman LJ, Loo SK, Carpenter EM, et al. Relationship of family environment and parental psychiatric diagnosis to impairment in ADHD. *J Am Acad Child Adolesc Psychiatry.* Mar 2006;45(3):346-354.
4. Thapar A, Cooper M. Attention deficit hyperactivity disorder. *Lancet.* Mar 2016;387(10024):1240-50.
5. American Psychiatric Association, APA. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Arlington, VA2013.
6. Barkley RA, Murphy KR. Attention-Deficit Hyperactivity Disorder: A Clinical Workbook. third edition ed: Guilford Press; 2006.
7. Biederman J, Kwon A, Aleardi M, et al. Absence of gender effects on attention deficit hyperactivity disorder: findings in nonreferred subjects. *Am J Psychiatry.* Jun 2005;162(6):1083-9.
8. Gershon J. A meta-analytic review of gender differences in ADHD. *J Atten Disord.* Jan 2002;5(3):143-54.
9. Jensen CM, Steinhausen HC. Comorbid mental disorders in children and adolescents with attention-deficit/hyperactivity disorder in a large nationwide study. *Atten Defic Hyperact Disord.* Mar 2015;7(1):27-38.
10. Rutter M. Achievements and challenges in the biology of environmental effects. *Proc Natl Acad Sci U S A.* Oct 2012;109 Suppl 2:17149-53.
11. Thapar A, Cooper M, Eyre O, Langley K. What have we learnt about the causes of ADHD? *J Child Psychol Psychiatry.* Jan 2013;54(1):3-16.
12. ADHD: medicatie en maatschappij. [ADHD: medication and society] (2014). Retrieved from https://www.gezondheidsraad.nl/documenten/adviezen/2014/07/03/adhd-medicatie-en-maatschappij
13. Ministerie Volksgezondheid WeSMoHaS. National Youth Law The Netherlands. https://eacea.ec.europa.eu/national-policies/en/content/youthwiki/12-national-youth-law-netherlands: EACEA National Policies Platform; European Commission; 2014.
14. American Psychiatric Association, APA. Diagnostic and Statistical Manual of Mental Disorders (DSM IV-TR). 4th edition, text revised ed. Washington, DC2000.
15. Achenbach, M. T, Rescorla L. *Manual for the ASEBA school-age forms & profiles. An integrated system of multi-informant assessment.* 2001.
16. F.C. V, J.M. K, G.W. A, J.W. V. *Praktische handleiding voor de CBCL* [Child Behavior Checklist) Practical guide for CBCL use]. van Gorcum and comp BV; 1990.
17. J.D. VdP, E.M. S. *ADHD-kinderen in ontwikkeling. Diagnostiek en effectieve behandeling in de jeugdzorg* [ADHD- children in development. Diagnostics and effective treatment in youth care]. Utrecht, The Netherlands: uitgeverij de Graaf; 2001.
18. Commissie Testaangelegenheden Nederland, COTAN (n.d.). [Dutch Committee on Tests and Testing]. https://www.cotandocumentatie.nl: Nederland's Instituut van Psychologen.
19. IBM SPSS Statistics for Windows version 22, IBM Corp. Armonk, N.Y., USA.
20. Committee on Psychosocial Aspects of Child and Family Health and Task Force on Mental Health - Policy statement - The future of pediatrics: mental health competencies for pediatric primary care. *Pediatrics.* Jul 2009;124(1):410-21.
21. Brown NM, Brown SN, Briggs RD, Germán M, Belamarich PF, Oyeku SO. Associations Between Adverse Childhood Experiences and ADHD Diagnosis and Severity. *Acad Pediatr.* 2017 May - Jun 2017;17(4):349-355.
22. Sayal K, Mills J, White K, Merrell C, Tymms P. Predictors of and barriers to service use for children at risk of ADHD: longitudinal study. *Eur Child Adolesc Psychiatry.* May 2015;24(5):545-52.
23. Efstratopoulou M, Simons J, Janssen R. Concordance among physical educators', teachers', and parents' perceptions of attention problems in children. *J Atten Disord.* Jul 2013;17(5):437-43.
24. Efron D, Bryson H, Lycett K, Sciberras E. Children referred for evaluation for ADHD: comorbidity profiles and characteristics associated with a positive diagnosis. *Child Care Health Dev.* 09 2016;42(5):718-24.
25. Rescorla LA, Bochicchio L, Achenbach TM, et al. Parent-teacher agreement on children's problems in 21 societies. *J Clin Child Adolesc Psychol.* 2014;43(4):627-42.
26. De Los Reyes A, Augenstein TM, Wang M, et al. The validity of the multi-informant approach to assessing child and adolescent mental health. *Psychol Bull.* Jul 2015;141(4):858-900.
27. Korsch F, Petermann F. Agreement between parents and teachers on preschool children's behavior in a clinical sample with externalizing behavioral problems. *Child Psychiatry Hum Dev.* Oct 2014;45(5):617-27.
28. Gordon M, Antshel K, Faraone S, et al. Symptoms versus impairment: the case for respecting DSM-IV's Criterion D. *J Atten Disord.* Feb 2006;9(3):465-75.
29. Gathje RA, Lewandowski LJ, Gordon M. The role of impairment in the diagnosis of ADHD. *J Atten Disord.* Mar 2008;11(5):529-37.
30. Visser SN, Zablotsky B, Holbrook JR, Danielson ML, Bitsko RH. Diagnostic Experiences of Children With Attention-Deficit/Hyperactivity Disorder. *Natl Health Stat Report.* Sep 2015;(81):1-7.
31. Yamauchi Y, Fujiwara T, Okuyama M. Factors Influencing Time Lag Between Initial Parental Concern and First Visit to Child Psychiatric Services Among ADHD Children in Japan. *Community Ment Health J.* Oct 2015;51(7):857-61.
32. Epstein JN, Kelleher KJ, Baum R, et al. Variability in ADHD care in community-based pediatrics. *Pediatrics.* Dec 2014;134(6):1136-43.



CHAPTER 3

CHILDREN WITH SYMPTOMS OF ATTENTION DEFICIT AND/OR HYPER-ACTIVITY AND IMPULSIVITY: DO NOT FORGET SOMATIC CO-MORBIDITY

Birgit Levelink
Frans Feron
Edward Dompeling
Dorothea van Zeben-van der Aa

Submitted

ABSTRACT

Objective: To describe the prevalence of somatic comorbidity in children referred to a specialized clinic, because of symptoms of attention deficit and/or hyperactivity and impulsivity, and to evaluate a possible relationship between an Attention-Deficit/Hyperactivity Disorder (ADHD) diagnosis and somatic conditions.

Methods: Data from 261 children (age 6-18 years) who underwent a multidisciplinary best practice evaluation at a specialized ADHD clinic were evaluated with special attention to medical history, early development and somatic comorbidity. A paediatrician rated somatic comorbidity.

Results: After evaluation, 33.7% children were diagnosed with ADHD, 31.8% with ADHD and psychiatric comorbidity and 34.5% had problems that did not match any psychiatric diagnosis. Delayed early development based on parent questionnaire and history taking was found in 31%, abnormalities at medical history taking in 34%, and abnormal physical examination in 26%. The clinical cohort was heterogeneous and somatic comorbidities were diverse. No significant differences in somatic conditions were found between children with ADHD (with or without psychiatric comorbidity), and children whose symptoms did not meet a psychiatric diagnosis.

Conclusion: Various somatic comorbidities were found in many children referred because of behavioural symptoms of ADHD. Therefore, we recommend an integral multidisciplinary approach, where both psychosocial and somatic problems are addressed.

INTRODUCTION

Attention-Deficit/Hyperactivity Disorder (ADHD) is a common childhood neurodevelopmental disorder with a multifactorial aetiology in which both genetic and environmental factors play a role [1,2]. With regard to the co-occurrence of medical illness and ADHD, the Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM-5) indicates that 'ADHD is not associated with specific physical characteristics, but there are several somatic abnormalities, which may affect ADHD symptoms' [3]. This statement of the DSM-5 is not very specific, probably due to the various findings in literature concerning ADHD and somatic comorbidity. Adults with psychiatric disorders have more somatic abnormalities in comparison with the normal population, and a recent systematic review concerning adult ADHD and comorbid somatic disease showed a consistent association between ADHD, and increased risk of obesity, sleep disorders and asthma [4,5]. In children these associations seem less clear. A recent meta-analysis found no association between ADHD and obesity, and there are several insights about the association between ADHD and childhood asthma 6-9. Many children with ADHD suffer from sleep problems, but sleep hygiene and parents' pedagogical approach to sleep difficulties are also important modifiable factors independently associated with sleep problems in children with ADHD [10,11]. It is known that ear problems, visual impairment, and epilepsy can mimic symptoms of attention deficit or hyperactivity, however in addition, children with epilepsy are also more likely to develop psychopathology [12-16]. A literature survey by Gontard and Equit (2015) showed co-occurrence of both daytime and nocturnal enuresis and encopresis with ADHD, and they suggested that all children with ADHD should be screened for these physical characteristics [17]. In addition to the association between ADHD and somatic symptoms, there are also children with underlying genetic syndromes like Neurofibromatosis type 1 and Fragile X, showing the behavioural characteristics of ADHD [18-20]. A systematic evaluation on somatic comorbidity of ADHD in a national sample of adolescents in the USA by Jameson et al. (2016) revealed significant increased odds for allergy, asthma, enuresis, headache and bowel problems, and they concluded that this finding 'highlights the complex interplay between physical and mental health' [21]. Their study showed in particular a relationship between ADHD and somatic comorbidities that have a multifactorial origin. Based on the wide variety of findings concerning ADHD and physical characteristics in the literature, it could be hypothesized that not the classification ADHD is associated with specific physical problems, but that the behavioural symptoms of inattention, hyperactivity and impulsivity are related with several somatic characteristics, due to a common origin and/or mutual influence. This raises the question whether all children with symptoms related to ADHD should receive a medical screening, independent of the underlying psychiatric diagnosis. A pilot study in 43 referred children with diverse psychiatric problems by Muskens et al. (2015) found that medical screening in a specialized mental health institute revealed many somatic comorbidities and had added value to treatment [22]. The current study focussed on children specifically referred to an ADHD clinic because of behavioural symptoms of inattention, hyperactivity and/or impulsivity. The aims of this study were:

1) To determine the type and prevalence of somatic comorbidity in this group of children after extensive history taking, physical examination and, if necessary, additional investigation;

2) To evaluate whether there are significant differences in somatic comorbidity between children who are diagnosed with ADHD and/or ADHD with psychiatric comorbidity, and those children in which ADHD symptoms appeared not to be based on a psychiatric diagnosis.

METHODS

Participants

Retrospective data of children attending the Medipsy ADHD clinic ('the ADHD clinic') were anonymously analysed. This specialized ADHD clinic is a collaboration between the Sint Jans Gasthuis hospital (SJG), Medipsy – a primary mental health care clinic, and Metggz – a specialized child psychiatry institute –, which started in 2010. It is an outpatient clinic for children between 6 - 18 years old, where only children with questions related to ADHD are examined. The ADHD clinic used only two triage criteria, namely age (> 6 and < 18 years), and referral related to ADHD symptoms. Data of all the children who visited the ADHD clinic were included in this observational study. The dataset is based on files of children attending between September 2011 and November 2015, during which period there was consistent composition of the multidisciplinary team. The dataset was used for previous research, in which the research question focussed on the ADHD diagnosis [23].

Procedure

The multidisciplinary team of the ADHD clinic consisted of a psychologist, a nurse specialist, a staff member from Metggz, and a paediatrician. The staff member of Metggz was a psychiatrist or other health care worker specialized in ADHD. Prior to the visit, both parents and the child's teacher completed an open questionnaire and several rating scales. During the clinical visit, the psychologist performed an extensive interview concerning different aspects of ADHD and psychiatric comorbidities, and discussed the results of the various questionnaires. Information of a third party was evaluated through the Teacher Report Form and an open questionnaire for teachers. Subsequently, a medical consultation by a paediatrician took place. A full medical history was taken in combination with a complete physical examination. Both the child and the parents were asked if the child had specific medical complaints and/or a medical diagnosis. The paediatrician also discussed answers of the parents on the open questionnaire concerning early development. The paediatrician determined somatic comorbidity by integrating medical history, the somatic conditions found during the physical examination and the demographic form. At a weekly team meeting the ADHD multidisciplinary team discussed all collected data, and diagnoses of ADHD were made by team consensus, taking into account information from the interviews, all DSM-IV-TR criteria, developmental history, somatic comorbidity, thresholds on rating scales and information from the teacher [24]. Three groups were distinguished; group A ' children with ADHD without psychiatric comorbidity', group B ' children with ADHD or ADHD symptoms with psychiatric comorbidity or other problems in need of specialized mental health care', and group C ' children with no psychiatric diagnosis, who had problems in need of primary (health) services'. Children in group B were all referred to specialized mental health care for further evaluation of the psychiatric comorbidity.

Measurements

Child Behavior Checklist; Teacher Report Form; Youth Self Report

The Child Behavior Checklist (CBCL) is a component in the Achenbach System of Empirically Based Assessment (ASEBA) developed by Thomas M. Achenbach [25]. The ASEBA uses different checklists for teachers (Teacher report Form, TRF) and children older than 11 can fill in their own checklist (Youth Self report, YSR). We used the Dutch school age version from 2001 by Verhulst [26]. In 2013, the Dutch Committee on Test Affairs (COTAN) assessed the Dutch version as insufficient in terms of reliability but sufficient in terms of validity [27]. Prior to the visit parents completed the CBCL. Children older than 11 years filled in the YSR and teachers the TRF. Both attention problem scores to evaluate ADHD symptoms and total scores were used during the evaluation of the child. T-scores between 65-70 were described as subclinical, above 70 as clinical scores.

ADHD-questionnaire (ADHD Vragen Lijst)

ADHD Vragen Lijst (AVL) is a Dutch behavioural screening questionnaire for children aged 4 to 18 years that is based on the Conners Rating Scale for ADHD and developed by van der Ploeg and Scholte [28]. The AVL is based on the diagnostic criteria of the DSM-IV and describes 18 behavioural symptoms. The COTAN assessed the test reliability as good and the validity as sufficient. By means of a Likert scale it was determined whether there are behavioural symptoms of ADHD, and if so, how severe these symptoms of inattention, hyperactivity were. The teacher and both parents completed the AVL.

Open questionnaire for the teacher

This open questionnaire for teachers was designed by the ADHD clinic based on the Conner's Rating Scale for ADHD. It consists of 13 general questions about functioning at school and psychosocial development, and 18 questions describing behaviour based on the DSM-IV diagnostic criteria for ADHD [29].

Demographic form

This open questionnaire for parents was designed by the ADHD clinic, and consists of questions about: family composition, level of education and employment of both parents, pregnancy, birth, developmental milestones (motor development, speech development, continence), the need for physiotherapy and/or speech therapy or the involvement of early intervention programs, medical history of the child and the family history. Developmental milestones were questioned by asking about the age at which a child achieved a certain development for the first time.

Physical examination

Physical examination started with assessment of height, weight, and blood pressure. Dutch growth charts were used to define abnormal height and/or body mass index (BMI) for age [30, 31]. Abnormal height depended on target height and growth curve. Blood pressure (BP) was defined as high, whenever it was ≥ P90, corrected for age and gender. Subsequently, general physical examination, and orientating neurological examination was performed. Specific case history on hearing, speech and vision problems was taken. All children with a cardiac murmur were screened by means of extensive cardiac anamnesis, and an electrocardiogram (ECG). An ultrasound of the heart, blood tests and other additional (physical) tests were only performed on indication.

Data Analysis

All data used in this study was uploaded in IBM SPSS Statistics version 22 for Mac for analysis [32]. To answer the research questions, the outcome at the end of the diagnostic process was divided into two groups; *group A and B*, children with ADHD without psychiatric comorbidity and children with ADHD or ADHD symptoms with psychiatric comorbidity or other problems in need of specialized mental health, and *group C*, children with no psychiatric diagnosis, who had problems in need of primary (health) services. Crosstabs were used to compare general characteristics of group A, B and C. Group A and B were compared to group C regarding specific comorbidities found during medical history taking and physical examination. Pearson's chi square test and Fisher's exact test was used for intergroup comparisons. Post-hoc power analysis was performed: with 80 children per group and a proportion of a specific patient characteristic in group A of 50%, and a difference in that patient feature of 23% or more in group B can be detected with a power of 80% and an alpha of 0.05. This was evaluated as sufficiently accurate for the purpose of this study.

RESULTS

Patient Characteristics

Files of 261 children were analysed. The mean age was 10.0 years (SD= 2.87), 72.8 % was male. After evaluation, ADHD was diagnosed in 87 children (33.7%), ADHD or ADHD symptoms with psychiatric comorbidity in 82 (31.8%), and 89 children (34.5%) received no psychiatric diagnosis; they had problems in need of primary (health) services. In 3 cases, no clear conclusion about the diagnosis was found in the data of the child, they were excluded. No significant differences in medical history, early development, general medical history taking and physical examination were found between children with ADHD, children with ADHD and psychiatric comorbidity, and children without a psychiatric diagnosis (table 1). Children who were diagnosed with ADHD used significantly more methylphenidate before the first consultation than children without a clear ADHD diagnosis *(p= 0.02)*. These children did not have an ADHD diagnosis before consultation, but a GP started medication while they were waiting for their appointment at the 'ADHD clinic'. Of the 14 children using methylphenidate before consultation, 3 had physical complaints (1 headache, 1 tiredness, 1 ear problems) and 3 had abnormalities on physical examination (2 cardiac murmurs, 1 high BMI). Hospital admission in the first year of life was mainly caused by assisted deliveries (including caesarean section and vacuum extraction) or neonatal problems, like hyperbilirubinemia or suspected postnatal infection. Hospitalisation after the first year of life was mainly due to ear-nose-throat (ENT) problems and surgical problems like inguinal hernia (respectively 61 and 16 children). These problems were equally divided over the tree outcome groups. Many parents reported a delayed early development of the child, in particular delayed speech (n=25, 9.6%), delayed continence (n=29, 11.1%), delayed motor development (n= 6, 2.3%), and delay in achieving milestones in general (n=21, 8%). No differences were found between the outcome groups.

Table 1 *| Demographic characteristics and characteristics of medical history taking per outcome group;* ***group A*** *'children with ADHD without psychiatric comorbidity',* ***group B*** *' children with ADHD or ADHD symptoms with psychiatric comorbidity or other problems in need of specialized mental health care',* ***group C*** *' children with no psychiatric diagnosis, who had problems in need of primary (health) services'*

Characteristic	Group A (n=87) n (%)	Group B (n=82) n (%)	Group C (n=89) n (%)
Mean age (years)	9.2	10.1	10.6
Male	63 (72.4)	58 (70.7)	67 (75.3)
Gestational age < 37 weeks	7 (8.5)	4 (5.1)	6 (7.1)
Child complications at birth	4 (4.7)	4 (4.9)	3 (3.4)
Hospital admission during first year of life	19 (21.8)	16 (19.5)	22 (24.7)
Hospital admission after first year of life	30 (34.5)	37 (45.1)	46 (51.7)
Abnormal early development (parents' opinion)	23 (26.4)	28 (35.4)	30 (33.7)
Non-pharmacological treatment before consultation [b]	45 (52.3)	39 (47.6)	42 (47.2)
Medication			
- Methylphenidate	10 (11.5)[a]	4 (4.9)	0 (0)
- Other (not ADHD) medication	11 (12.6)	9 (11.0)	9 (10.1)
Somatic comorbidity at medical history taking (table 2)	37 (44.6)	28 (35.0)	29 (33.3)
Physical examination with abnormalities (table 3)	24 (27.6)	24 (29.3)	22 (24.7)

[a] Pearson's chi square test p = 0.02
[b] Non pharmalogical treatment; i.e., physiotherapy, speech therapy, occupational therapy, youth care

Somatic comorbidity and physical abnormalities

Table 2 and 3 show details of somatic comorbidities that were found during medical history taking, and physical abnormalities that were identified during physical examination. Enuresis nocturna, asthma and headache were most prominent but none of them were found significantly more in children with ADHD than in children without a psychiatric diagnosis. Of the abnormalities found during physical examination, only cardiac murmurs were significantly higher in the ADHD group but only one cardiac murmur had clinical relevance. Additional investigation was done in 25 children; 3 children were referred to an ENT doctor, 4 were referred to a neurologist, 1 child got CT imaging of the brain, 1 genetic counselling, 2 children laboratory tests and 13 children got an ECG. All children referred to an ENT doctor were diagnosed with ear problems and 1 child with a murmur had a deviant ECG and was diagnosed with a significant congenital heart disease in need for cardiac intervention (hemodynamic significant atrial septal defect). All other additional investigations were normal.

***Table 2** | Somatic comorbidity found during medical history taking in **group A and B** (children with ADHD without psychiatric comorbidity and children with ADHD or ADHD symptoms with psychiatric comorbidity or other problems in need of specialized mental health) and **group C** (children with no psychiatric diagnosis, who had problems in need of primary (health) services)*

Somatic comorbidity	Group A and B N (%)	Group C N (%)
Nocturnal enuresis	14 (8.3)	3 (3.4)
Encopresis/constipation	5 (3.0)	6 (6.7)
Headache	19 (11.2)	10 (11.2)
Tiredness	9 (5.3)	5 (5.6)
Asthma	17 (10.1)	4 (3.4)
Epilepsy	1 (0.6)	1 (1.1)
Ear-nose throat (ENT) problem	3 (1.8)	1 (1.1)
Other medical condition	5 (3.1)	2 (2.3)

Note: 12 children had two or more somatic conditions.
Pearson Chi Square test or Fisher's Exact Test showed no significance for any of the variables.

***Table 3** | Physical abnormalities found during physical examination in **group A and B** (children with ADHD without psychiatric comorbidity and children with ADHD or ADHD symptoms with psychiatric comorbidity or other problems in need of specialized mental health) and **group C** (children with no psychiatric diagnosis, who had problems in need of primary (health) services)*

Physical characteristics	Group A and B N (%)	Group C N (%)
> 3 dysmorphic features	4 (2.4)	0 (0)
Eczema	1 (0,6)	2 (2.2)
"Clumsiness"	6 (3.6)	0 (0)
Cardiac murmur	12 (7.1) a	1 (1.1)
Blood pressure > P90	4 (2.4)	3 (3.4)
BMI high	5 (3.0)	3 (3.4)
BMI low	1 (0.6)	2 (2.2)
Deviant height	4 (2.4)	2 (2.2)
Current ENT problems	4 (2.4)	1 (1.1)
Early puberty symptoms	1 (0.6)	2 (2.2)
Other physical findings	6 (3.6)	6 (6.8)
Total	**48 (28.4)**	**22 (24.7)**

[a] Fisher's exact test p = 0.04
BMI = Body Mass Index, ENT = Ear Nose Throat

DISCUSSION

Of the children who were evaluated because of their ADHD symptoms, 36% showed somatic comorbidity at medical history taking, and 27% had an abnormal physical examination. The prevalence of medical comorbidity throughout the studied population showed no striking differences compared with prevalence rates of individual medical comorbidities among children in the general population studies [33-35]. In addition, abnormalities did not occur more frequently in children who met DSM-IV-TR criteria for ADHD or ADHD (symptoms) with psychiatric comorbidity (group A and B); delayed early development according to parents, and abnormalities during medical history taking and physical examination were equally divided among all children who presented at the ADHD clinic with behavioural symptoms of ADHD. Enuresis, asthma and cardiac murmurs were more prominent in group A and B, but only cardiac murmurs proved statistical significance. Cardiovascular issues are important when addressing ADHD, but mainly in relation to medication. Different guidelines, like the 2018 National Institute for Health and Care Excellence (NICE) guideline, provided specific recommendations concerning cardiac evaluation; heart rate (HR) and blood pressure should be routinely monitored at baseline and every six months after starting medication as well as before and after dose change [36]. In this study, 2 children with a cardiac murmur used methylphenidate. These children did not show abnormalities in HR and BP. A cardiac murmur does not necessarily imply a medical diagnosis. In this study all but one cardiac murmur had no clinical relevance; the child with a murmur due to a congenital heart disease did not meet the ADHD criteria.

Although not statistically significant, finding many children with nocturnal enuresis in group A and B coincides with other studies that demonstrate the co-occurrence of ADHD and enuresis, in particular nocturnal enuresis. The causal link is not known, but both nocturnal enuresis and ADHD are multifactorial disorders, where biological, social and psychosocial factors play an important role [17, 37]. Studies show different results regarding the association between childhood asthma and ADHD, but a meta-analysis by McQuaid in 2001 found that children with asthma should be considered at higher risk for behavioural difficulties [38]. There are studies suggesting a genetic link between the two, but most research exploring links between asthma and behaviour indicate that links are complex, reflecting the multifactorial determinants of both asthma and ADHD [39]. The number of children with asthma and/or enuresis in this clinical cohort seemed to underline the multifactorial origin of these problems and the importance of a multi-level approach where psychosocial and medical screening are combined to improve general well-being of the child.

The Dutch government introduced a new Child and Youth Act in 2015, which made local governments responsible for prevention, support and treatment of developmental, and psychological problems and disorders [40]. According to this act, children with ADHD without psychiatric comorbidities, who only need supportive counselling or methylphenidate should be treated by primary care providers. Current guidelines for primary care indicate that medical screening is not necessary when the following conditions are met: previously executed medical screening must reveal a good overall health and normal growth; medical history taking and development history must be blank; congenital abnormalities must be absent and hearing and vision should be normal [41]. A recent systematic review that investigated somatic comorbidities in children and adolescents with ADHD and autism spectrum disorder found that medical disorders in children with ADHD are widespread, and it was concluded that a multidisciplinary and integrated approach is necessary [42]. In addition, the current study showed a heterogeneous clinical cohort,

with somatic comorbidities not only found within the group diagnosed with ADHD or ADHD with co-morbidity, but in all children referred because of symptoms of attention deficit and/or hyperactivity and impulsivity. A medical problem like enuresis, asthma or headache, can have a major impact on the life of a child and/or his family. This study showed that, in order to improve well-being for these children, it is important to integrate psychosocial and medical care. Evaluation of these children in both primary and specialized care should include professionals addressing the psychosocial and biomedical problems. Training physicians who encounter children with ADHD symptoms, like a general practitioner, a youth health care physician (school doctor), paediatrician or child and youth psychiatrists, is important for an integral approach.

Some findings were remarkable, as they did not correspond with previous studies. First, no differences in preterm birth between the ADHD group and the group of children without an ADHD diagnosis were found. Prevalence of preterm birth in this cohort was the same as found in a systematic worldwide analysis [43]. Probably this finding is explained by the fact that all children had a gestational age of 31 weeks or more, and the odds ratio for ADHD is specifically raised in the very preterm, and very low birth weight group [44]. Second, although only found in the ADHD group, during physical examination fewer children than expected reported symptoms of Developmental Coordination Disorder (DCD) at medical history taking, or showed motor problems. Delayed motor development was also not prominent in the ADHD group. ADHD is known to be highly associated with DCD [45, 46]. Fliers et al. (2010) showed that children with ADHD tend to have a higher self-perceived motor competence [47]. This could explain the rare occurrence of this problem at medical history taking. In addition, it requires specific training to recognize these motor problems, and the paediatrician may have insufficiently identified these motor problems in some of the children. Due to the retrospective and observational character of this research, no standard Movement Assessment Battery for Children (Movement ABC) was performed. It would be interesting to know if a Movement ABC would have revealed more children with specific motor problems like DCD [48].

This study has several limitations. First, there is no (inter) national gold standard for diagnosing ADHD. Diagnosis was made on team consensus, taking into account all data collected during the diagnostic process, as proposed by recent literature [2]. Group characteristics showed that 70% of the referred children were male, which corresponded with other studies like the ADORE study in 2006, in which 84.3% of the referred children were male [49]. Only 65.5% was diagnosed with ADHD or ADHD with comorbidity. This could be due to the easy accessibility of the ADHD clinic, and because no screening on symptom severity, or presence of symptoms in at least two settings was done before the first visit. Another explanation could be the interpretation of symptoms by the team and evaluating data from this study may lead to different results. Possibly this would result in a different distribution of somatic comorbidities across the groups, but this would not change the fact that an integrated approach for all these children is necessary. Second, this was only a small group. Results showed many different somatic problems in a group of children referred to a specialized ADHD clinic. Due to heterogeneity of somatic comorbidity, the numbers were too small to draw general conclusions. Evaluation of larger clinical cohorts, with a control group of children visiting the hospital for a reason other than ADHD, is necessary to determine whether somatic comorbidities are more common in children referred with ADHD symptoms. It is also worthwhile to look at early developmental delay. Parents reported many and various problems during early development, but unfortunately these could not be objectively determined due to the study design. Third, various limitations are a consequence of the study design. Data were collected anonymously from a clinical cohort and was not collected for this study. Vision and/or hearing, and movement tests were

only done on indication, which could have underestimated the numbers of these problems. All children with psychiatric co-morbidities were referred to a specialized mental health care clinic for further evaluation or determination of these comorbidities. No data about the final diagnosis of the psychiatric comorbidities was included, because no permission was requested to have access to this information. However, somatic comorbidity between the ADHD group with and the ADHD group without psychiatric comorbidity was compared, and no differences were found between these groups.

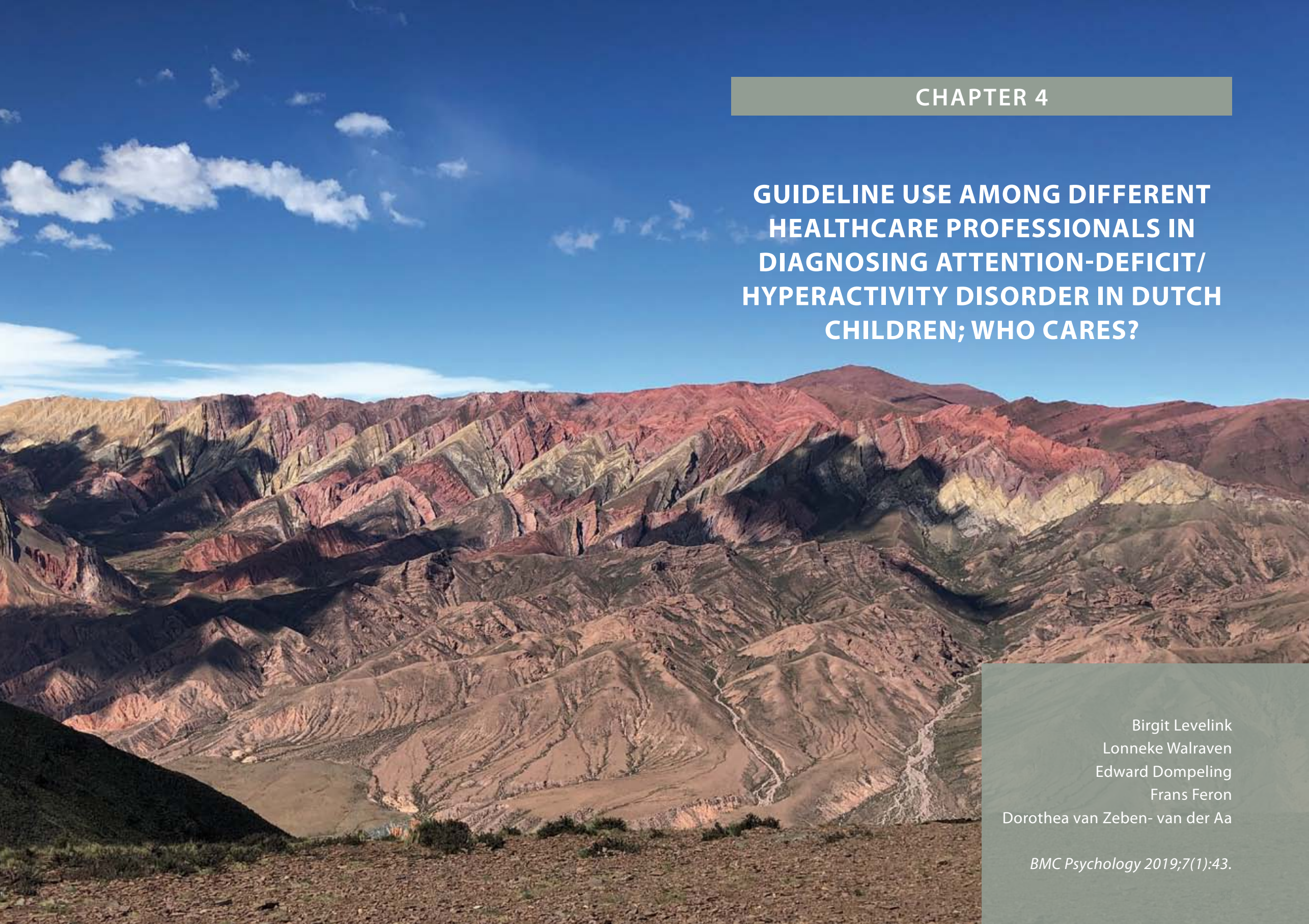
CLINICAL IMPLICATIONS AND CONCLUSION

Different somatic comorbidities were found in children referred with ADHD symptoms. It is important to address both psychosocial and physical problems in these children. Problems like nocturnal enuresis and asthma seemed to be more common when a diagnosis of ADHD or ADHD with psychiatric comorbidity was made, which may be the result of the multifactorial origin of both ADHD and problems like enuresis and asthma. However, both children with an ADHD diagnosis and children with ADHD symptoms but without a psychiatric diagnosis, showed somatic comorbidities. Abnormalities during medical history taking or development history taking and abnormalities during physical examination were found among many children. These problems were diverse, and correct interpretation required training. In general, integrating psychosocial and medical care for all children with symptoms of inattention, hyperactivity and impulsivity will improve their general well-being. Development of multidisciplinary consultative networks can contribute to this goal for this heterogeneous population of children.

REFERENCES

1. Biederman J, Faraone SV. Attention-deficit hyperactivity disorder. *Lancet.* 2005 Jul 16-22 2005;366(9481):237-48.
2. Thapar A, Cooper M. Attention deficit hyperactivity disorder. *Lancet.* Mar 2016;387(10024):1240-50.
3. American Psychiatric Association, APA.. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Arlington, VA2013.
4. Felker B, Yazel JJ, Short D. Mortality and medical comorbidity among psychiatric patients: a review. *Psychiatr Serv.* Dec 1996;47(12):1356-63.
5. Instanes JT, Klungsøyr K, Halmøy A, Fasmer OB, Haavik J. Adult ADHD and Comorbid Somatic Disease: A Systematic Literature Review. *J Atten Disord.* 02 2018;22(3):203-228.
6. Biederman J, Milberger S, Faraone SV, Guite J, Warburton R. Associations between childhood asthma and ADHD: issues of psychiatric comorbidity and familiality. *J Am Acad Child Adolesc Psychiatry.* 1994 Jul-Aug 1994;33(6):842-8.
7. Fasmer OB, Riise T, Eagan TM, et al. Comorbidity of asthma with ADHD. *J Atten Disord.* Oct 2011;15(7):564-71.
8. Kwon HJ, Lee MY, Ha M, et al. The associations between ADHD and asthma in Korean children. *BMC Psychiatry.* Mar 2014;14:70.
9. Nigg JT, Johnstone JM, Musser ED, Long HG, Willoughby MT, Shannon J. Attention-deficit/hyperactivity disorder (ADHD) and being overweight/obesity: New data and meta-analysis. *Clin Psychol Rev.* Feb 2016;43:67-79
10. Sciberras E, Song JC, Mulraney M, Schuster T, Hiscock H. Sleep problems in children with attention-deficit hyperactivity disorder: associations with parenting style and sleep hygiene. *Eur Child Adolesc Psychiatry.* Sep 2017;26(9):1129-1139.
11. Sung V, Hiscock H, Sciberras E, Efron D. Sleep problems in children with attention-deficit/hyperactivity disorder: prevalence and the effect on the child and family. *Arch Pediatr Adolesc Med.* Apr 2008;162(4):336-42.
12. Adesman AR, Altshuler LA, Lipkin PH, Walco GA. Otitis media in children with learning disabilities and in children with attention deficit disorder with hyperactivity. *Pediatrics.* Mar 1990;85(3 Pt 2):442-6.
13. Brikell I, Ghirardi L, D'Onofrio BM, et al. Familial Liability to Epilepsy and Attention-Deficit/Hyperactivity Disorder: A Nationwide Cohort Study. *Biol Psychiatry.* Jan 2018;83(2):173-180.
14. Neto FK, Noschang R, Nunes ML. The relationship between epilepsy, sleep disorders, and attention deficit hyperactivity disorder (ADHD) in children: A review of the literature. *Sleep Sci.* 2016 Jul-Sep 2016;9(3):158-163.
15. Okur M, Ruzgar H, Erbey F, Kaya A. The evaluation of children with monosymptomatic nocturnal enuresis for attention deficit and hyperactivity disorder. *Int J Psychiatry Clin Pract.* 2012. p. 229-262.
16. Soylu E, Soylu N, Yıldırım YS, Sakallıoğlu Ö, Polat C, Orhan I. Psychiatric disorders and symptoms severity in patients with adenotonsillar hypertrophy before and after adenotonsillectomy. *Int J Pediatr Otorhinolaryngol.* Oct 2013;77(10):1775-81.
17. von Gontard A, Equit M. Comorbidity of ADHD and incontinence in children. *Eur Child Adolesc Psychiatry.* Feb 2015;24(2):127-40.
18. Kayl AE, Moore BD. Behavioral phenotype of neurofibromatosis, type 1. *Ment Retard Dev Disabil Res Rev.* 2000;6(2):117-24.
19. Lo-Castro A, D'Agati E, Curatolo P. ADHD and genetic syndromes. *Brain Dev.* Jun 2011;33(6):456-61.
20. Sullivan K, Hatton D, Hammer J, et al. ADHD symptoms in children with FXS. *Am J Med Genet A.* Nov 2006;140(21):2275-88.
21. Jameson ND, Sheppard BK, Lateef TM, Vande Voort JL, He JP, Merikangas KR. Medical Comorbidity of Attention-Deficit/Hyperactivity Disorder in US Adolescents. *J Child Neurol.* 10 2016;31(11):1282-9.
22. Muskens JB, Vermeulen K, van Deurzen PA, et al. [Somatic screening in child and adolescent psychiatry: a descriptive pilot study]. *Tijdschr Psychiatr.* 2015;57(10):710-8.
23. Levelink B, Feron FJM, Dompeling E, van Zeben-van de Aa DMCB. Children With ADHD Symptoms: Who Can Do Without Specialized Mental Health Care? *J Atten Disord.* 01 2020;24(1):104-112.
24. Association AP. Diagnostic and Statistical Manual of Mental Disorders (DSM IV-TR). 4th edition, text revised ed. Washington, DC2000.
25. Achenbach, M. T, Rescorla L. *Manual for the ASEBA school-age forms & profiles. An integrated system of multi-informant assessment.* 2001. University of Vermont, Research Centre for Children, Youth and Families.
26. F.C. V, J.M. K, G.W. A, J.W. V. *Praktische handleiding voor de CBCL* [(Child Behavior Cecklist) Practical guide for CBCL use]. van Gorcum and comp BV; 1990.
27. Commissie Testaangelegenheden Nederland, COTAN (n.d.). [Dutch Committee on Tests and Testing]. https://www.cotandocumentatie.nl: Nederland's Instituut van Psychologen.
28. J.D. VdP, E.M. S. ADHD-kinderen in ontwikkeling. Diagnostiek en effectieve behandeling in de jeugdzorg [ADHD- children in development. Diagnostics and effective treatment in youth care]. Utrecht, The Netherlands: uitgeverij de Graaf; 2001.
29. American Psychiatric Association, APA. DSM-IV: Diagnostic and Statistical Manual of Mental Disorders. American Psychiatric Press; 1994.
30. Cole TJ, Flegal KM, Nicholls D, Jackson AA. Body mass index cut offs to define thinness in children and adolescents: international survey. *BMJ.* Jul 2007;335(7612):194.
31. Dutch Organization for Applied Scientific Research, TNO, Vijfde landelijke groeistudie [fifth national growth study]. http://www.tno.nl/groei.
32. IBM SPSS Statistics for Windows v, version 22, IBM Corp. Armonk, N.Y., USA.
33. Wijga AH, Kerkhof M, Gehring U, et al. Cohort profile: the prevention and incidence of asthma and mite allergy (PIAMA) birth cohort. *Int J Epidemiol.* Apr 2014;43(2):527-35.
34. Abu-Arafeh I, Razak S, Sivaraman B, Graham C. Prevalence of headache and migraine in children and adolescents: a systematic review of population-based studies. *Dev Med Child Neurol.* Dec 2010;52(12):1088-97.
35. Butler RJ, Golding J, Northstone K, Team AS. Nocturnal enuresis at 7.5 years old: prevalence and analysis of clinical signs. *BJU Int.* Aug 2005;96(3):404-10.
36. Attention Deficit Hyperactivity Disorder, guidance and guidelines, NICE 2019 https://www.nice.org.uk/guidance/ng87/chapter/Recommendations#maintenance-and-monitoring2019.
37. Okur M, Ruzgar H, Erbey F, Kaya A. The evaluation of children with monosymptomatic nocturnal enuresis for attention deficit and hyperactivity disorder. *Int J Psychiatry Clin Pract.* Sep 2012;16(3):229-32.
38. McQuaid EL, Kopel SJ, Nassau JH. Behavioral adjustment in children with asthma: a meta-analysis. *J Dev Behav Pediatr.* Dec 2001;22(6):430-9.
39. Mogensen N, Larsson H, Lundholm C, Almqvist C. Association between childhood asthma and ADHD symptoms in adolescence--a prospective population-based twin study. *Allergy.* Sep 2011;66(9):1224-30.

40. Ministerie Volksgezondheid WeSMoHaS. National Youth Law The Netherlands. https://eacea.ec.europa.eu/national-policies/en/content/youthwiki/12-national-youth-law-netherlands: EACEA National Policies Platform; European Commission; 2014.
41. Richtlijnontwikkeling LSM. *Multidisciplinaire Richtlijn voor diagnostiek en behandeling van ADHD bij kinderen en jeugdigen* [Multidisciplinar Guideline for diagnosis and management of ADHD in children and adolescents]. Trimbos instituut. Utrecht2005.
42. Muskens JB, Velders FP, Staal WG. Medical comorbidities in children and adolescents with autism spectrum disorders and attention deficit hyperactivity disorders: a systematic review. *Eur Child Adolesc Psychiatry.* Sep 2017;26(9):1093-1103.
43. Blencowe H, Cousens S, Oestergaard MZ, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. *Lancet.* Jun 2012;379(9832):2162-72.
44. Franz AP, Bolat GU, Bolat H, et al. Attention-Deficit/Hyperactivity Disorder and Very Preterm/Very Low Birth Weight: A Meta-analysis. *Pediatrics.* 01 2018;141(1)
45. Fliers EA, Franke B, Buitelaar JK. Motorische problemen bij kinderen met ADHD [Motor problems in children with ADHD]. *Nederlands tijdschrift voor Geneeeskunde.* p. A3559.
46. Piek JP, Dyck MJ, Nieman A, et al. The relationship between motor coordination, executive functioning and attention in school aged children. *Arch Clin Neuropsychol.* Dec 2004;19(8):1063-76.
47. Fliers EA, de Hoog ML, Franke B, et al. Actual motor performance and self-perceived motor competence in children with attention-deficit hyperactivity disorder compared with healthy siblings and peers. *J Dev Behav Pediatr.* Jan 2010;31(1):35-40.
48. Damme TV, Simons J, Sabbe B, van West D. Motor abilities of children and adolescents with a psychiatric condition: A systematic literature review. *World J Psychiatry.* Sep 2015;5(3):315-29.
49. Nøvik TS, Hervas A, Ralston SJ, et al. Influence of gender on attention-deficit/hyperactivity disorder in Europe--ADORE. *Eur Child Adolesc Psychiatry.* Dec 2006;15 Suppl 1:I15-24.



CHAPTER 4

GUIDELINE USE AMONG DIFFERENT HEALTHCARE PROFESSIONALS IN DIAGNOSING ATTENTION-DEFICIT/ HYPERACTIVITY DISORDER IN DUTCH CHILDREN; WHO CARES?

Birgit Levelink
Lonneke Walraven
Edward Dompeling
Frans Feron
Dorothea van Zeben- van der Aa

BMC Psychology 2019;7(1):43.

ABSTRACT

Objective: Current data about Attention Deficit Hyperactivity Deficiency (ADHD) guideline use in the Netherlands are absent. This study analysed ADHD guideline use among different healthcare workers, and the use of key elements from these guidelines to diagnose ADHD.

Method: A survey assessing ADHD guideline use was distributed throughout the Netherlands to various health care professionals. Only professionals involved during the diagnostic process were included.

Results: Response rate among GPs was low (111/1450), but high among other health care professionals (251/287). A total of 362 surveys were analysed, 186 responders (51%) were involved during the diagnostic process. Overall guideline use was 64.5%; the national multidisciplinary guideline or a guideline made by a professional's own institution were most used. Psychiatrists, psychologists and paediatricians reported compliance with key elements of the guidelines such as gathering information from a third party (>90%) and carrying out a developmental history (>88%). Use of a standardized interview (<52% often use) was low. Only paediatricians performed a physical examination regularly (88%).

Conclusion: Despite low general use of guidelines, psychiatrists, psychologists and paediatricians use similar key elements of ADHD guidelines. This study provides opportunities to improve care through increasing familiarity with ADHD guidelines and the use of standardized interviews.

INTRODUCTION

Attention-Deficit Hyperactive Disorder (ADHD) is a neurodevelopmental disorder, affecting people of all ages with an onset in childhood. According to the most recent meta-analyses, worldwide prevalence in children and adolescents is estimated between 3.4% and 7.2% [1-3]. Although no increase in the worldwide prevalence of ADHD was found in the past ten years, in 2014 the need for (health) care in relation to symptoms of attention deficit and/or hyperactivity and impulsivity in the Netherlands showed a thirty per cent increase over the previous decade [4-7]. Recent studies provided several explanations, such as increased awareness of ADHD among health care professionals, parents and teachers, increased academic research on the disorder, and better accessibility to (health) care [6, 8, 9]. Little is known about the care pathways of Dutch children with problems of attention deficit and/or hyperactivity, and the use of, and compliance with ADHD guidelines by different healthcare professionals. It is important to know how an ADHD diagnosis ADHD is made, as deviation from recommendations may lead to undetected comorbid conditions, misdiagnosis and unnecessary use of tests. ADHD is a complex diagnosis in which both genetic and environmental factors play an important role [10]. During the diagnostic process it is important to assess that, due to symptoms of attention deficit and / or hyperactivity and impulsivity, the child experiences limitations in his or her functioning [11]. Correct interpretation of behavioral characteristics requires sufficient knowledge about the disorder. Worldwide research between 1995 and 2016 showed a lack of knowledge about ADHD and a shortage of enthusiasm among GPs to get involved in ADHD care [12-18]. Epstein and colleagues (2014) concluded that part of community-based American paediatricians did not act according to evidence-based guidelines [19]. As in many other countries, ADHD is diagnosed in the Netherlands by various healthcare professionals, such as general practitioners (GPs), psychologists, child & youth psychiatrists and pediatricians [20-23]. Over time, several Dutch ADHD guidelines were published to standardize and improve diagnosis and treatment. In 2005, a multidisciplinary guideline was published which has many similarities with the guideline commissioned by the British National Institute for Health and Clinical Excellence [24, 25]. Since 2014 guidelines for GPs, youth care and primary youth health care have been issued, which gave the opportunity to diagnose and treat symptoms of ADHD in consultation with specialists [26, 27].

To gain more insight into the increase of (health) care use in the Netherlands due to ADHD symptoms, it is important to know whether important elements of an ADHD diagnosis are sufficiently taken into account by (health) care professionals to avoid misdiagnosis. For example, consideration should be given to the presence of ADHD behavior in different settings. In addition, it is useful to know if problems are adequately detected in primary health care. The first step is to gain insight into the use of the existing guidelines by different (health) care professionals, and to evaluate if these guidelines are applied correctly. The objective of this study was therefore 1) to describe the use of different ADHD guidelines among healthcare professionals for children in the Netherlands and 2) to determine whether diagnosing ADHD is in accordance with key elements of these guidelines.

METHODS

Study design and setting

This cross-sectional study was conducted between March 2017 and August 2017 at the paediatric department of the Maastricht University Medical Centre. A survey was designed using the online questionnaire platform Qualtrics [28]. A wide variety of healthcare professionals may be involved in ADHD care, but exact data were not available. Therefore, all known institutions for ADHD care in the Netherlands were identified through searches on the Internet, to then evaluate whether they were involved in ADHD diagnostics. The targeted professional groups included paediatricians, child and youth psychiatrists, psychologists, GPs, general practice-based nurse specialists and youth health care physicians (school doctors). The Dutch ADHD Network distributed the survey directly to health care professionals affiliated with the network. In total 36 psychologists, 27 child and youth psychiatrists, 48 paediatricians and 13 youth health care physicians were directly addressed by the ADHD network, and 128 institutions for child mental health, 10 hospitals and 25 primary health services were approached. Among individual general practitioners it was difficult to determine if ADHD care was provided. GPs are organized per province in groups, and email addresses for individual GPs were requested from the presidents of these GP groups. Two provinces released this data, and therefore a sample of 1450 GPs was addressed.

Measurement

A 27-question survey based on the different Dutch guidelines was developed for this study, focusing on elements used during the diagnostic process. The first part of the survey consisted of 4 questions assessing involvement of the individual healthcare professional during the diagnostic phase of ADHD. Respondents not belonging to the target group were excluded after finishing this part. The following 16 questions related to the use of guidelines in general and evaluated the practice patterns with regard to an ADHD diagnosis. Survey items assessed adherence to five diagnostic key elements specified in the Dutch multidisciplinary guideline, the Dutch guideline for GPs and the youth healthcare guideline (figure 1).

***Figure 1** | Dutch guideline recommendations; diagnostic key elements from the guidelines, which are asked for in the survey.*

Evaluation of attention deficit, hyperactivity and impulsivity symptoms Advised by all guidelines. Specifically asked were the use of semi-structured interviews, options: semi-structured interview with parents (Anxiety Disorders in Interview Schedule for DSM-IV (ADIS), Children's Aggression Scale (CAS), Kiddie Schedule for Affective Disorders and Schizophrenia for school aged children (K-SADS), Kiddie Disruptive Behavior Disorders Schedule (K-DBDS), Parental Account of Children's Symptoms (PACS), Parent Interview for Child Symptoms (PICS-4-dutch version), Semi-structured Clinical Interview for Children and Adolescents (SCICA)).
Gathering information from somebody else than the parents and/or child Advised by all guidelines. Specifically asked how information is gathered; questionnaires, semi-structured interview or direct observation.
Use of questionnaires Advised by the Dutch multidisciplinary guideline: Child Behavior Checklist (CBCL), Youth Self Report (YSR) and Teacher report Form (TRF). Advised by youth health care: Strengths and Difficulties Questionnaire (SDQ), ADHD Questionnaire (ADHD vragenlijst AVL). Other possibilities; CRS, Conner's Rating Scale, Questionnaire for behavioural problems in children (Vragenlijst voor Gedragsproblemen bij Kinderen, VvGK)
Knowledge of developmental history, family history and physical condition Advised by all guidelines
Additional examination only advised on indication Only advised on indication by all guidelines Specifically asked: Complete neuropsychological testing, Intelligent Quotient test (IQ), didactic test, Electrocardiogram (ECG), laboratory tests.

Questions about diagnostic instruments and (re) screening tools were tailored to the Dutch situation. Questionnaires advised by different guidelines and askes for in the survey were: 1. 'ADHD Vragenlijst' [AVL, The Dutch ADHD Questionnaire], a Dutch behavioural questionnaire for children aged 4 to 18 years that is based on the Conners' Rating Scale for ADHD [29]. 2. The Child Behavior Checklist (CBCL) and the Teacher's Report Form (TRF), both components of the Achenbach System of Empirically Based Assessment (ASEBA) [30]. 3. The Strengths and Difficulties Questionnaire (SDQ), a brief behavioural screening instrument [31]. Use of The Conners' Rating Scale (CRS), a behavioural questionnaire designed to assess symptoms of ADHD, originally developed by C. Keith Conners in 1969 and revised in 1997, was added as an extra option. To gather the intended information multiple choice questions and 3-point and 5-point Likert-type scale measured responses were mainly used. For some questions an open text field was included automatically when the answer "otherwise" was chosen. A paediatrician, a research worker and a GP from the University of Maastricht were asked to pilot test the questionnaire, whereupon its applicability was improved for primary as well as secondary health care professionals.
The last 7 questions assessed the characteristics of the health care professionals, like gender, age, work experience and experience with diagnosing ADHD in children. A question about the location of the institution was included to determine geographic diversity.

Analysis

Responses were converted to IBM SPSS Statistics version 22 for Mac for further analysis [32]. First, univariate descriptive statistics were used to assess frequencies of responses by demographic variables. To determine guideline use in general, and per profession Pearson chi square tests was used. This test was also applied to analyse the use of important guideline elements. For each guideline component, reported response 'often' or 'always' was contrasted with reported response 'never', 'rarely' or 'sometimes'. Because numbers of respondents per professional were low, and varied between subgroups, subgroup analyses were not possible. Finally, univariate logistic regression was used to analyse if the use of a standardised approved national guideline led to more adherence to key elements of the guidelines than the use of a protocol of the own institution or any other protocol. Professionals who responded to having used the approved Dutch multidisciplinary guideline, the GP guideline or the youth health care guideline were marked as using a standardised guideline. They were compared with professionals who responded to having used a protocol from their own institute or a protocol made by themselves.

RESULTS

Characteristics of respondents

Response rate of GPs was low; 111 of the 1450 surveys returned. In contrast, the response rate of other health care professionals was high; 251 of 287 surveys were returned. In total 362 questionnaires were returned (figure 2). Only 186 professionals responded that they were actually involved during the diagnostic process of ADHD, 176 professionals referred children with symptoms of ADHD to another care professional. In particular youth health care physicians (45/50), GPs (98/111) and paediatricians (22/40) were excluded in the first part of the survey because they referred children when they suspected ADHD, and evaluated that additional diagnostics were necessary. 166 professionals completed the whole survey. Characteristics of professionals involved during the diagnostic process are shown in table 1. The majority was female (84.3%). Most of the respondents evaluated less than 25 new patients per year (57.8%); especially pediatricians indicated that they had more than 100 consultations per year because of problems related to ADHD (41.2%). With the exception of GPs, respondents were equally distributed over the Netherlands.

Figure 2 | *Response rate and included professionals.*

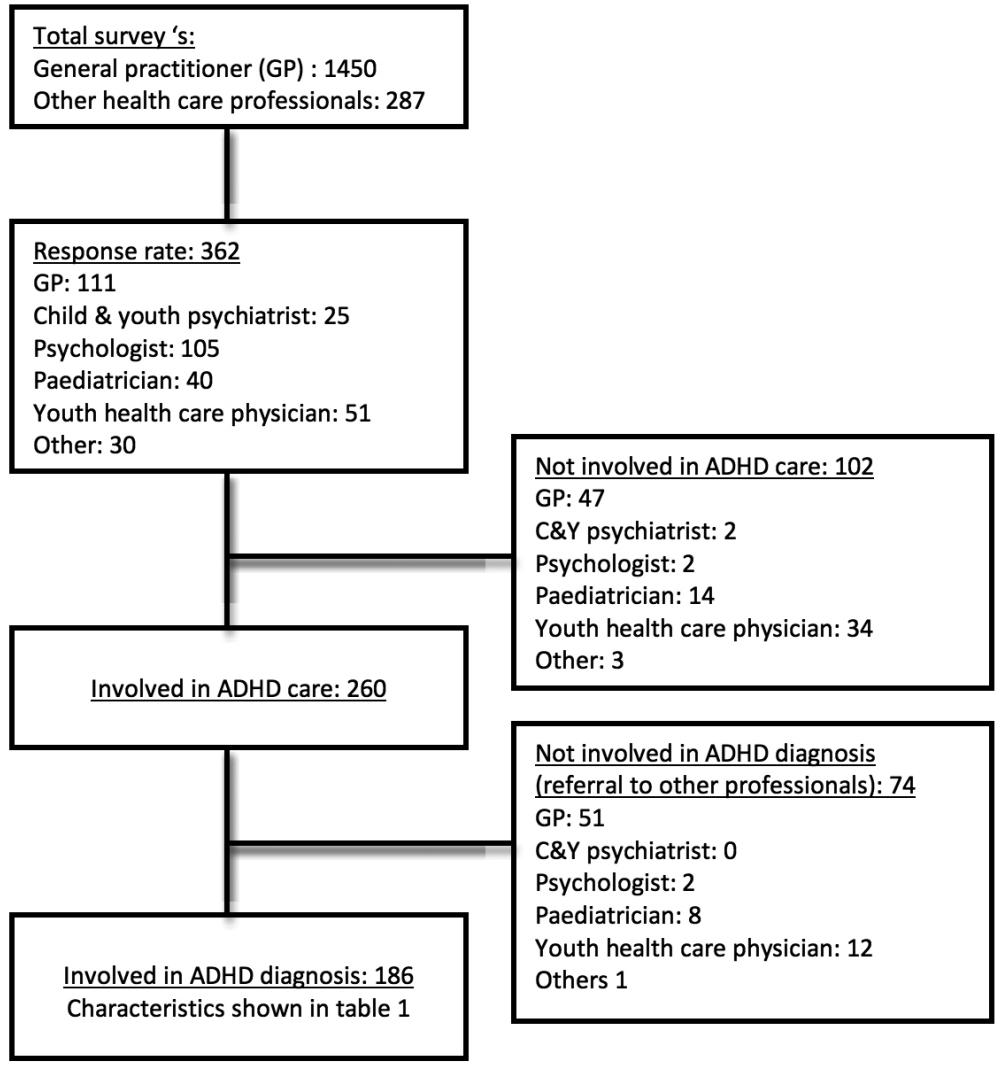


***Table 1** | Characteristics of health care professionals involved during the diagnostic process.*

	Number of respondents N (%)
Profession (n=186)	
Child & youth psychiatrist	23 (12)
Psychologist	101 (54)
Paediatrician	18 (10)
General practitioner	13 (7)
Youth health care physician	5 (3)
Remedial teacher	17 (9)
Other	9 (5)
Sex (n=166)	
Female	140 (84)
Age in years (n=166)	
20-35	65 (39)
36-55	74 (45)
56>	27 (16)
Number of new patients per year (n=166)	
0-25	96 (58)
25-100	53 (32)
>100	17 (10)

Guideline use

The majority of professionals used some kind of guideline (64.4%). Of respondents who indicated that they did not use a guideline, 18.3% used their own protocol, and 17.2% used no protocol at all. Table 2 shows the use of guidelines by the four major response groups, i.e., child & youth psychiatrists, psychologists, paediatricians and GPs and the use of key elements from these guidelines. Psychiatrists used guidelines most frequently (81.8%). Standardized interviews, recommended in the official guidelines, were used by less than 52 % of all professionals. Most used interviews were the Anxiety Disorders in Interview Schedule for DSM-IV (ADIS) and the Parent Interview for Child Symptoms (PICS-4-NL). Gathering information from a third party (e.g., school) was done by all disciplines. Information from a third party was gathered by observation (40%), standardized interviews (23%) and by questionnaires (34%). Although only recommended on indication in all guidelines, the majority of respondents performed an IQ test (70.5%). Only paediatricians performed physical examination regularly (88.3%). Comparison of the group using an approved standardized Dutch guideline with the group using a protocol from the own institute or made by the (health) care professional showed two significant differences (Table 3). Professionals who used an official Dutch guideline more often used a semi-structured interview (OR 2.1; 95% CI 1.1-3.7), and they were more likely to perform a physical examination (OR 2.6; 95% CI 1.1-5.9).

***Table 2** | Use of Dutch guidelines and diagnostic key elements from guidelines per healthcare professional*

Dutch diagnostic guideline recommendations	Overall adherence (%; N= 169)	C&Y psychiatrists (%; N= 19)	Psycho-logists (%; N=93)	Paedia-tricians (%; N=17)	GPs (%; N=13)	*p* value
General Guideline use	64.4	81.8	60.8	73.7	50.0	0.05
Guidelines used:						
Multidisciplinary guideline	38.6	72.2	33.3	50.0	14.3	
Youth healthcare guideline	11.4	0	14.0	14.3	0	
GP guideline	6.1	0	0	0	71.4	
Protocol own institution	39.5	27.8	49.1	21.4	0	
Not specified			3.6	14.3	14.3	
Evaluation of ADHD symptoms*						
Use of semi structured interview	51.7	68.2	49.5	63.2	50.0	0.09
Gathering information from third party *	92,8	94.7	97.8	94.1	50.0	<0.001
Use of questionnaires *						
CBCL [τ]	40.8	63.2	39.8	41.7	11.8	
TRF [τ]	53.8	73.7	59.1	64.7	23.1	
SDQ*	49,1	42,1	51.6	41.7		0.001
AVL*	66.3	73.7	71.0	70.6	16.7	0.04
CR-scale [τ]	5.3	21.1	4.3	0	25,0	
Additional knowledge*						
Developmental history	89.2	100	96.7	88.2	91.7	<0.001
Perform physical examination	19.2	10.5	7.6	88.3	100	<0.001
Additional examination**						
neuropsychological tests	62.7	73.3	56.5	70.6	100	0.25
IQ tests	29,5	10,5	19.6	41.2	100	<0.001
Electrocardiogram	100	100	100	100		
Laboratory tests	100	100	100	100		

** use often or always*
*** use never or rarely on occasion*
[τ] Use of this instrument was not asked in version of questionnaire for GPs and youth health care physicians.
C&Y psychiatrist = Child and Youth psychiatrist; GPs = General Practitioners; AVL= ADHD Vragenlijst (Dutch ADHD Questionnaire); CBCL = Child Behavior Checklist; TRF = Teacher's Report Form; SDQ = Strengths and Difficulties Questionnaire; CRS = Connor's Rating Scale; IQ = Intelligence Quotient.

***Table 3** | Likelihood of using key elements when using a Dutch national approved ADHD guideline (instead of a protocol made by the own institution or a protocol made by the healthcare professional)*

	Odds ratio	95% CI
Use of semi structured interview	2.1	1.1 - 3.7
Gathering information from a third party	1.7	0.5 - 5.7
Use of questionnaires		
CBCL	0.9	0.5 - 1.8
SDQ	1.6	0.9 - 2.9
AVL	0.6	0.3 - 1.2
Use of developmental history	1.6	0.6 - 4.2
Perform physical examination	2.6	1.1 - 5.9
Use of additional examination		
Neuropsychological tests	0.8	0.5 - 1.6
IQ tests	0.7	0.4 - 1.5

CI = Confidence Interval; CBCL = Child Behavior Checklist; SDQ = Strengths and Difficulties Questionnaire; AVL = ADHD Vragenlijst (Dutch ADHD Questionnaire); IQ = Intelligence Quotient

DISCUSSION

As data about ADHD guideline use in the Netherlands were lacking, this study analysed ADHD guideline use among different healthcare workers, and the use of key elements from these guidelines to diagnose ADHD. The use of national approved Dutch guidelines was low, but was in accordance with the results of studies in other countries [33-35]. Many of the responding professionals commented to have a protocol of their own institute based on the national guidelines. These institution protocols probably have many similarities with the national approved guidelines; the overall use of important diagnostic key elements, like gathering information from a third party and performing a developmental history was high, both in accordance with the different national guidelines. The only significant difference between the group using an approved national guideline and the group using an institution protocol was the use of a semi-structured interview and performing a physical examination. The more positive response on the question concerning physical examination in the group using a national approved guideline was not simply explained by the use of this approved guideline. Paediatricians were the only professionals who responded to perform regular physical examinations. All other professionals hardly used a physical examination as part of the diagnostic process. Physical problems, like visual and hearing impairment may mimic ADHD, and ADHD can also be part of a physical disease like neurofibromatosis. Children with ADHD often have somatic comorbidities like enuresis, making physical examination an important part of the diagnostic process [36-39]. It seems necessary to reaffirm the importance of the physical examination to several professionals.

There were some striking features. Overall use of semi-structured interviews was low. ADHD is a best practice diagnosis, but diagnostic clinical structured interviews showed high values for sensitivity and specificity in relation to the comprehensive best practice diagnosis [40]. Low use of structured interviews

may either lead to inaccurate diagnosis or undetected comorbidities. The heterogeneity of obtaining information regarding symptoms of inattention and hyperactivity from third parties and the high use of IQ tests and neuropsychological tests, by psychologists, C&Y psychiatrists and paediatricians was also remarkable. It is possible that our respondents evaluated a selected patient population with high comorbidity rates, requiring a tailored child-focused program, with more need for additional tests. However, part of these additional IQ and neurological tests may have been unnecessary, and therefore increased costs for ADHD care.

Currently various healthcare professionals in the Netherlands diagnose ADHD. Despite the introduction of several ADHD guidelines for primary healthcare workers, the majority of GPs and youth health care workers indicated to refer children with ADHD symptoms to other professionals. The National Health Statistics Report of the United States of America showed a high involvement of paediatricians; in their study almost 40% of the parents were told by a paediatrician that their child had ADHD [20, 41]. Many paediatricians in the Netherlands indicated not to be involved when it comes to diagnosing ADHD. Mental health care workers, in particular child psychologists and psychiatrists, were most involved during the diagnostic process. This study was conducted after the transformation of youth care in 2015 in The Netherlands, which might explain low involvement of paediatricians [42]. The transformation changed the financing system; municipalities instead of healthcare insurances became responsible for ADHD care both in terms of contents and finance. After the transformation, only hospitals with an arrangement with the municipalities were allowed to deliver ADHD care, and many paediatricians decided not to provide care to children with problems related to ADHD any longer. In this study, 50% of the responding paediatricians indicated themselves to be specialized in ADHD care, which corresponded with the large number of children they said to evaluate every year. An explanation for this could be that municipalities particularly contracted paediatricians with large practices after the transformation of youth care. This could also explain the relatively high use of additional tests; these large practices are often highly specialized and therefore see children with complex problems.

This transformation of youth care was part of the new Child and Youth Act, which formed the basics of a plan of action made by all professionals involved in the care for children with (symptoms of) ADHD in 2015 [42]. The three major principles of this Child and Youth Act were: to make more use of 'own strength' and the social network of children and their parents; to allow children to participate as much as possible by normalizing, unburdening and not unnecessarily medicalize, and: to reduce specialized health care by using more primary care [43]. The number of included GPs in the study was low, maybe because they were only involved in ADHD care for children since 2014. Most GPs referred children directly after presenting with symptoms of ADHD or when they suspected co-morbidity. Due to the low number of GPs, no conclusions could be drawn for this group. It is important to do more research on the involvement of GPs in the care for children with ADHD, as making use of primary care professionals is an important principle of the new Child and Youth Act.

This study has several limitations. It was impossible to include professionals randomly by inviting the targeted group, because no exact data of professionals involved in ADHD care in the Netherlands was available. This has created various risks for selection bias. First, it is not clear whether a good reflection of care providers has received the questionnaire. Second, respondent bias was possible due to self-selection of the respondents; most likely professionals who felt involved in ADHD care completed the survey. Another limitation was the low number of some professionals. Response rate in the GP group was

extremely low and the number of GPs involved in ADHD care even lower. As a result, no conclusions could be made concerning ADHD care by GPs. As opposed to all other professionals who were located all over the Netherlands, GPs from only two provinces could be approached. These provinces were representative for a part of the Netherlands, but not for provinces where the major cities are located. Finally, the survey focussed on the diagnostic process and did not include treatment (both pharmacological and non-pharmacological). It was a deliberate choice to exclude professionals who were not involved in the diagnostic process at the beginning of the survey. This was to prevent people who were not involved in ADHD diagnostics from completing the questionnaire and thus influencing the results negatively. Retrospectively, it would have been interesting to know whether the group that was excluded at the beginning of the questionnaire was involved in the treatment of ADHD. According to the guidelines, ADHD symptoms must be regularly evaluated during treatment, to determine to what extent ADHD symptoms still lead to dysfunction. In order to evaluate ADHD symptoms properly, sufficient knowledge about the disorder is essential; the question is whether this knowledge is sufficient if you do not participate in diagnosing ADHD. Further research is necessary to gain insight in the knowledge of professionals who only treat children with ADHD.

Clinical Implications

ADHD is a best-practice diagnosis. This was a quantitative study and no statements can be made about the quality of the ADHD diagnosis made by individual health care professionals or the possible impact on the increased demand for ADHD care. However, practice variations were identified which generated new hypotheses. Involvement of (relatively cheap) primary care was low. Response rate from the GPs was very low. The Dutch government wants a prominent role for GPs in the diagnostic process of ADHD so it is important to conduct more research on the involvement and knowledge of ADHD in this group. Use of (expensive) additional testing was high, which may be linked to easy access to these resources, different demands of the referred patient group or low use of nationwide guidelines. Implications of these patterns cannot be derived from this study but are of interest for further investigation, especially directed to proper use of additional (neuro) psychological testing. Finally, more attention should be paid to the use of standardized interviews, for example by incorporating them in new guidelines.

CONCLUSION

Various health care professionals, working in primary, secondary and tertiary care, diagnose ADHD in children in the Netherlands differently. In particular mental health care workers and specialized pediatricians are involved in the diagnostic process. A slight majority is using a nationwide guideline or a protocol of the professional's own institution based on national approved guidelines. Adherence to guidelines differs per health care profession, but the use of diagnostic key elements, like use of information from a third party and a developmental history, is high among professionals with the highest response rate. Use of semi-structured interviews and physical examination is low, raising opportunities for improvement.

REFERENCES

1. Polanczyk G, Salum GA, Sugaya LS, Caye A, Rohde LA. Annual research review: A meta-analysis of the worldwide prevalence of mental disorders in children and adolescents. *J Child Psychol Psychiatry.* Mar 2015;56(3):345-65.
2. Thomas R, Sanders S, Doust J, Beller E, Glasziou P. Prevalence of attention-deficit/hyperactivity disorder: a systematic review and meta-analysis. *Pediatrics.* Apr 2015;135(4):e994-1001.
3. Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA. The worldwide prevalence of ADHD: a systematic review and metaregression analysis. *Am J Psychiatry.* Jun 2007;164(6):942-8.
4. Sayal K, Prasad V, Daley D, Ford T, Coghill D. ADHD in children and young people: prevalence, care pathways, and service provision. *Lancet Psychiatry.* Feb 2018;5(2):175-186.
5. Health Council The Netherlands (2000). Diagnostiek en behandeling van ADHD [Diagnosis and treatment of ADHD]. https://www.gezondheidsraad.nl/documenten/adviezen/2000/11/13/diagnostiek-en-behandeling-van-adhd2000.
6. ADHD: medicatie en maatschappij. [ADHD: medication and society] (2014). https://www.gezondheidsraad.nl/documenten/adviezen/2014/07/03/adhd-medicatie-en-maatschappij
7. Gijssen R, Nugteren R. Jaarprevalentie van ADHD-achtige symptomen in de huisartsenregistratie, 2014 [Year prevalence of ADHD-like symptoms in general practice registration, 2014]. In: Milieu RvVe, editor. Bilthoven, the Netherlands, retrieved from: https://www.volksgezondheidenzorg.info/onderwerp/adhd/cijfers-context/trends#node-trend-prevalentie-adhd-achtige-symptomen-huisartsenpraktijk2016.
8. Buitelaar JK. Discussies over aandacht tekort-hyperactiviteitstoornis (ADHD): feiten, meningen en emoties [Discussion about attention deficit hyperactive disorder (ADHD): facts, opinions and emotions]. *Nederlands tijdschrift voor geneeskunde* 2001. p. 1485-1489.
9. Graaf de R, Ten Have MM, van Dorsselaer S. De psychische gezondheid van de Nederlandse bevolking. NEMESIS-2: Opzet en eerste resultaten [The mental health of the Dutch population. NEMESIS-2: Design and first results]. Utrecht, The Netherlands: Trimbos-instituut 2010.
10. Thapar A, Cooper M. Attention deficit hyperactivity disorder. *Lancet.* Mar 2016;387(10024):1240-50.
11. American Psychiatric Association, APA. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Arlington, VA2013.
12. Ghanizadeh A, Zarei N. Are GPs adequately equipped with the knowledge for educating and counseling of families with ADHD children? *BMC Fam Pract.* Jan 2010;11:5.
13. Jawaid A, Zafar AM, Naveed A, et al. Knowledge of primary paediatric care providers regarding attention deficit hyperactivity disorder and learning disorder: a study from Pakistan. *Singapore Med J.* Dec 2008;49(12):985-93.
14. Shaw K, Wagner I, Eastwood H, Mitchell G. A qualitative study of Australian GPs' attitudes and practices in the diagnosis and management of attention-deficit/hyperactivity disorder (ADHD). *Fam Pract.* Apr 2003;20(2):129-34.
15. Tatlow-Golden M, Prihodova L, Gavin B, Cullen W, McNicholas F. What do general practitioners know about ADHD? Attitudes and knowledge among first-contact gatekeepers: systematic narrative review. *BMC Fam Pract.* 09 2016;17(1):129.
16. Kwasman A, Tinsley BJ, Lepper HS. Pediatricians' knowledge and attitudes concerning diagnosis and treatment of attention deficit and hyperactivity disorders. A national survey approach. *Arch Pediatr Adolesc Med.* Nov 1995;149(11):1211-6.

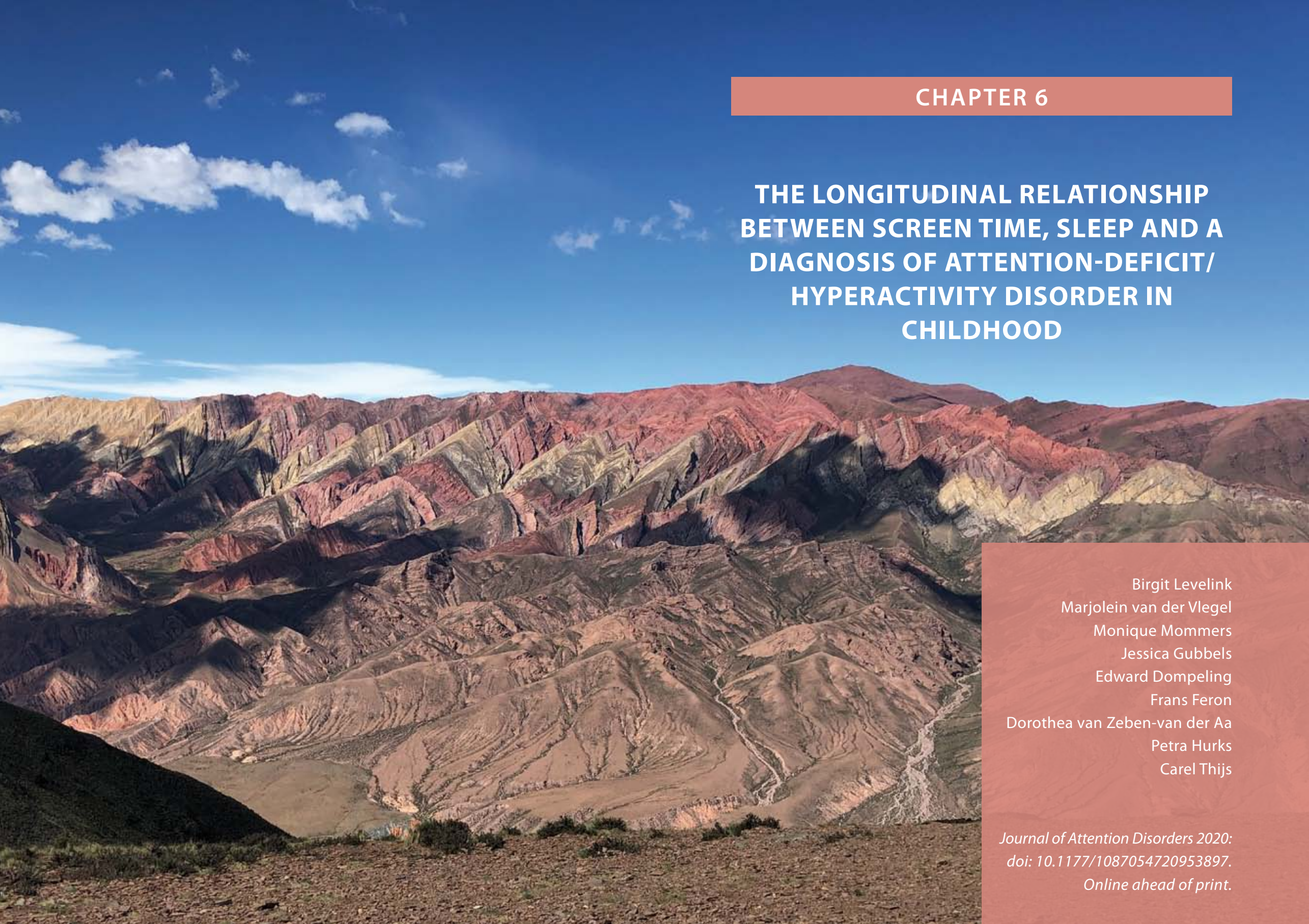
17. Stein RE, Storfer-Isser A, Kerker BD, et al. Beyond ADHD: How Well Are We Doing? *Acad Pediatr.* Mar 2016;16(2):115-21.
18. Hirfanoğlu T, Soysal AS, Gücüyener K, Cansu A, Serdaroğlu A. A study of perceptions, attitudes, and level of knowledge among paediatricians towards attention-deficit/hyperactivity disorder. *Turkisch J Pediatr*2008. p. 160-166.
19. Epstein JN, Kelleher KJ, Baum R, et al. Variability in ADHD care in community-based pediatrics. *Pediatrics.* Dec 2014;134(6):1136-43.
20. Visser SN, Zablotsky B, Holbrook JR, Danielson ML, Bitsko RH. Diagnostic Experiences of Children With Attention-Deficit/Hyperactivity Disorder. *Natl Health Stat Report.* Sep 2015;(81):1-7.
21. Canadian Attention Deficit Hyperactivity Disorder Resource Alliance. (2010). *Canadian ADHD practice guidelines (CAP-Guidelines)* – Third edition. Toronto: CADDRA.
22. Wolraich M, Brown L, Brown RT, et al. ADHD: clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. *Pediatrics.* Nov 2011;128(5):1007-22.
23. The Royal Australasian College of Physicians. (2009). Australian guidelines on Attention Deficit Hyperactivity Disorder (ADHD). Sydney: RACP. Retrieved from https://www.racp.edu.au/docs/default-source/advocacy-library/pa-australian-guidelines-on-adhd-draft.pdf.
24. Richtlijnontwikkeling LSM. Multidisciplinaire Richtlijn voor diagnostiek en behandeling van ADHD bij kinderen en jeugdigen [Multidisciplinar Guideline for diagnosis and management of ADHD in children and adolescents]. Trimbos instituut. Utrecht 2005.
25. National Collaborating Centre for Mental Health, National Institute for Health and Clinical Excellence. Diagnosis and management of ADHD in children, young people and adults – National Clinical Practice Guideline Number 72. Leicester and London: The British Psychological Society and The Royal College of Psychiatrists 2009.
26. Boer F, Glind vdG. JGZ-richtlijn ADHD; Signalering, begeleiding en toeleiding naar diagnostiek [Youth Health Care guideline ADHD: signalling, guiding and leading towards diagnosis]. https://www.ncj.nl/richtlijnen/alle-richtlijnen/richtlijn/?richtlijn=24: Trimbos Institute; 2015.
27. van Avendonk MJ, Hassink-Franke LJ, Stijntjes F, Wiersma T, Burgers JS. Summary of the Dutch College of General Practitioners' (NHG) practice guideline 'ADHD in children'. *Ned Tijdschr Geneeskd.* 2015;159:A8395.
28. Qualtrics. Retrieved from https://library.maastrichtuniversity.nl/support/qualtrics/.
29. Ploeg J.D, Scholte E.M.. ADHD-kinderen in ontwikkeling. Diagnostiek en effectieve behandeling in de jeugdzorg [ADHD- children in development. Diagnostics and effective treatment in youth care.] Utrecht, The Netherlands: uitgeverij de Graaf; 2001.
30. Achenbach, M. T, Rescorla L. *Manual for the ASEBA school-age forms & profiles. An integrated system of multi-informant assessment.* 2001.
31. Goodman R. The strengths and difficulties questionnaire; A research note. *Journal of child psychology and psychiatry* 1997. p. 581-586.
32. IBM SPSS Statistics for Windows v 22, IBM Corp. Armonk, N.Y., USA.
33. Chan E, Hopkins MR, Perrin JM, Herrerias C, Homer CJ. Diagnostic practices for attention deficit hyperactivity disorder: a national survey of primary care physicians. *Ambul Pediatr.* 2005 Jul-Aug 2005;5(4):201-8.
34. Rushton JL, Fant KE, Clark SJ. Use of practice guidelines in the primary care of children with attention-deficit/hyperactivity disorder. *Pediatrics.* Jul 2004;114(1):e23-8.
35. Wolraich ML, Bard DE, Stein MT, Rushton JL, O'Connor KG. Pediatricians' attitudes and practices on ADHD before and after the development of ADHD pediatric practice guidelines. *J Atten Disord.* May 2010;13(6):563-72.
36. Adesman AR, Altshuler LA, Lipkin PH, Walco GA. Otitis media in children with learning disabilities and in children with attention deficit disorder with hyperactivity. *Pediatrics.* Mar 1990;85(3 Pt 2):442-6.
37. von Gontard A, Equit M. Comorbidity of ADHD and incontinence in children. *Eur Child Adolesc Psychiatry.* Feb 2015;24(2):127-40.
38. van den Heuvel E, Starreveld JS, de Ru M, Krauwer V, Versteegh FG. Somatic and psychiatric co-morbidity in children with attention deficit hyperactivity disorder. *Acta Paediatr.* Mar 2007;96(3):454-6.
39. Muskens JB, Velders FP, Staal WG. Medical comorbidities in children and adolescents with autism spectrum disorders and attention deficit hyperactivity disorders: a systematic review. *Eur Child Adolesc Psychiatry.* Sep 2017;26(9):1093-1103.
40. Parker A, Corkum P. ADHD Diagnosis: As Simple As Administering a Questionnaire or a Complex Diagnostic Process? *J Atten Disord.* 06 2016;20(6):478-86.
41. McElligott JT, Lemay JR, O'Brien ES, Roland VA, Basco WT, Roberts JR. Practice patterns and guideline adherence in the management of attention deficit/hyperactivity disorder. *Clin Pediatr (Phila).* Sep 2014;53(10):960-6.
42. Ministerie Volksgezondheid WeSMoHaS. National Youth Law The Netherlands. https://eacea.ec.europa.eu/national-policies/en/content/youthwiki/12-national-youth-law-netherlands: EACEA National Policies Platform; European Commission; 2014.
43. Werkgroep 'gepaste zorg voor kinderen met aandachttekort en/of hyperactiviteit en impulsiviteit' [Taskforce 'appropriate care for children with inattention and/or hyperactivity and impulsivity] 2015. https://www.poraad.nl/nieuws-en-achtergronden/plan-van-aanpak-gepaste-zorg-bij-kenmerken-van-adhd-gelanceerd.

CHAPTER 5

FROM PRE- AND PERINATAL TO EARLY POSTNATAL RISK FACTORS FOR ATTENTION-DEFICIT/ HYPERACTIVITY DISORDER: DUTCH KOALA BIRTH COHORT STUDY

Birgit Levelink
Marjolein van der Vlegel
Monique Mommers
Edward Dompeling
Petra Hurks
Carel Thijs

Submitted



CHAPTER 6

THE LONGITUDINAL RELATIONSHIP BETWEEN SCREEN TIME, SLEEP AND A DIAGNOSIS OF ATTENTION-DEFICIT/ HYPERACTIVITY DISORDER IN CHILDHOOD

Birgit Levelink
Marjolein van der Vlegel
Monique Mommers
Jessica Gubbels
Edward Dompeling
Frans Feron
Dorothea van Zeben-van der Aa
Petra Hurks
Carel Thijs

Journal of Attention Disorders 2020: doi: 10.1177/1087054720953897. Online ahead of print.

ABSTRACT

Objective: To evaluate longitudinal associations between recreational screen time and sleep in early childhood, and attention-deficit/hyperactivity disorder (ADHD) at age 8-10 years.

Method: Questionnaires from 2768 mother-child pairs from the Dutch KOALA Birth Cohort Study were used. General estimating equation logistic regression analyses examined associations between screen time and sleep at age 2, 4 and 6, and ADHD at age 8-10. Linear regression analysis examined associations between television time, sleep and CBCL/2-3 scores at age 2.

Results: Longitudinally, neither screen time nor sleep were associated with ADHD. Cross-sectionally, CBCL/2-3 externalizing symptom scores increased by 0.03 with every hour television time (95%CI 0.002 to 0.05) and increased by 0.02 per hour of less sleep (95%CI -0.03 to -0.01).

Conclusion: Despite an association with externalizing symptoms at age 2, screen time and sleep in early childhood were not associated with ADHD. Carefulness is warranted when extrapolating cross-sectional associations at early age to an ADHD diagnosis.

INTRODUCTION

Since the introduction of the television (TV) in the 1950s, the use of digital media has become an integral part of the lives of children and adolescents. Although a recent American study by Loprinzi and Davis showed a slow decline in parent reported television use among preschool and primary school children over the past 2 decades, most parents still reported that their children watched TV, on average, for 2 hours/day [1]. This decrease in watching TV may be explained by a rapid increase in other digital media use, like (game) computers and touch screen telephones and tablets [2]. Worldwide, both parents and health care workers have concerns about the possible negative effects of screen use, whether TV screens or other digital media use, on the physical and psychological health of children and adolescents. One health-related concern is the potential impact screen use has on attention-deficit/hyperactivity disorder (ADHD) or ADHD-like symptoms [3, 4]. Several cross-sectional studies showed a positive association between ADHD-like symptoms and different types of screen use [5-7]. A longitudinal cohort study by Ra et al. (2018), indicated e.g., that high-frequency digital media use by high school students was associated with significantly higher odds for ADHD-like symptoms, and emphasized the importance of longitudinal research of the development of ADHD [8]. As most studies regarding digital media use so far are cross-sectional, and only focus on behavioural symptoms of ADHD, it is extremely difficult to determine whether children who are often exposed to digital media are more prone to actually develop ADHD, or if children with ADHD for example tend to use more digital media [9, 10].

When evaluating a possible relationship between hours of screen time and ADHD, sleep is also an important factor to consider. Sleep can be a confounder, mediator or independent variable. A systematic literature review concerning screen time and sleep among healthy school-aged children found that screen time was adversely associated with sleep outcomes (primarily shortened duration and delayed timing) [11]. Besides that, less sleep duration can cause an increase in ADHD symptoms, and various studies also showed an association between ADHD and sleep problems [12-14].

To date, no longitudinal studies were reported, in which both screen time and total sleep duration were monitored early in life, and in addition data concerning a possible ADHD diagnoses were collected in childhood, considering potential pre, peri- and postnatal confounding factors. The main research question of this study was the longitudinal association between the amount of recreational screen time and sleep duration from age 2 until the age of 6-8 years, and an ADHD diagnosis at age 8-10 years. In addition, at the age of 2, associations between television time, the total amount of sleep and specific behavioural characteristics (i.e., overactive and externalizing behaviour) were analysed.

METHOD

Participant population

Data originated from the prospective KOALA Birth Cohort Study in the Netherlands [15]. Healthy pregnant women were recruited between October 2000 and December 2002 from the general population, by approaching women who participated in an existing study on pregnancy-related pelvic girdle pain (N = 2,343, referred to as conventional recruitment group). In addition, healthy pregnant women with an 'alternative lifestyle' with regard to dietary habits (e.g., preferring organic food), vaccination programs and/or antibiotic use were recruited through posters in organic shops, or anthroposophical physician offices and midwives, Steiner schools and magazines (N = 491, referred to as the alternative recruitment group). Mother-infant pairs were excluded from analysis for the current study when the mother

had a twin or a multiple pregnancy, when the infant died, or in case the child had a severe congenital disorder leading to intellectual disability, such as Down's syndrome. All parents signed informed consent, and ethical approval was obtained from the medical ethics committee of the Maastricht University/ University Hospital of Maastricht.

Data collection

Questionnaires especially designed for the KOALA study were completed by parents during pregnancy and at set moments in the child's life. Information on pre- peri- and postnatal factors, and various lifestyle characteristics were collected. The current study used data from the questionnaires at 14 and 34 weeks of gestation, and at child ages of 2 weeks, 3 months, 2 years, 4-5 years, 6-8 years and 8-10 years. Questionnaires at age 2 were retrieved throughout the year, at age 4-5 and 6-8 they were distributed and retrieved during the schoolyear.

Dependent variables

Data regarding an ADHD diagnosis was obtained by questionnaire, filled out by the parents at child's age 8-10 years in 2011. Parents were asked through an open question: 'Did a doctor, psychologist, or remedial educationalist diagnose your child with ADHD?'. The answer to this question was used as outcome measure of professional based parent-reported ADHD, simply referred to as 'parent reported ADHD'. In addition, parents were asked informed consent to approach their general practitioner (GP) for retrieval of medical data. These GPs were mailed in 2014 with a short questionnaire including: 'Has the above-named patient ever been diagnosed with ADHD?' Because the diagnosis from GPs was retrieved in a subgroup of the cohort, these data were only used to validate whether results with parent reported ADHD as outcome were confirmed by GP reported ADHD.

At the age of two, questions from the Child Behavior Checklist/2-3 (CBCL/2-3) for children aged 2 to 3 years, were included in the KOALA questionnaire. The CBCL is a component of the Achenbach System of Empirically Based Assessment (ASEBA), developed by Thomas M. Achenbach [16]. For this study, the factor structure of the CBCL/2-3 based on the article of Koot et al. (1997) was used, who adapted the structure of the American CBCL/2-3 to the Dutch situation [17]. This Dutch version of the CBCL/2-3 addressed behavioral problems at a young age, which were subdivided into externalizing problems (overactive, aggressive, and oppositional scale) and internalizing problems (anxious, depressed, and sleep problems scale). Psychometric properties of this Dutch CBCL/2-3 were comparable to those obtained from American samples [17]. For the current study, only the externalizing scale which included the overactive subscale was selected, as symptoms linked to attention deficit at pre-school age are part of the externalizing scale of the CBCL/2-3. Parents were asked to rate items that described the child's behavior at that moment or within the past two months as 2 if the item was true or often true, 1 if the item was somewhat or sometimes true, and 0 if the item was not true. Mean scale scores were computed by summing the raw scores of 0, 1 and 2 on each CBCL/ 2-3 item belonging to the Dutch oppositional behavior (17 items), aggression (9 items) and overactive behavior scale (5 items), and dividing total raw scores by the number of items in the specific scale.

Exposure variables and potential confounders

Questions regarding recreational screen time included questions about daily hours of watching television and playing computer games outside school hours, and were asked at the age of 2, 4-5 and 6-8 years. The sum of TV time and computer time will hereinafter be referred to simply as screen time. At age 2, both for TV time and computer time, parents could choose between five standardised answers

concerning minutes of TV and computer time per day. At ages 4-5 and 6-8, first parents were asked about the number of days per week, and then about the minutes per day of TV and computer use, using standardised answers. Averages were calculated from these two variables. Data regarding sleep were collected using open ended questions, which asked about average hours sleep. Total sleep duration was measured by adding hours of day- and night-time sleep at ages 2 and 4-5. At 6-8 years, general sleep duration over 24 hours was asked. Maternal social demographic data were collected at 14 gestational weeks. Data on maternal prenatal smoking and alcohol use came from the questionnaires completed by 14- and 34-weeks' gestation. Perinatal data, including gestational age, gender of the child and birth weight were collected two weeks after birth. Data on marital discord came from the questionnaire 3 months postpartum. Questions on daily family routine were asked in the questionnaire taken at the age of 2 years. Data concerning hours of playing outside were asked at the age of 2, 4-5 and 6-8 years and analysed as a possible confounder; results are only shown if significant.

Some determinants had missing values. For education, mode of birth, marital discord and daily family routine the missing values were placed in an 'other/unknown' group in the baseline characteristics table, missing values are presented in a separate 'unknown' category. For pre-pregnancy BMI the median was imputed and the GHQ missing values were placed in the 'GHQ score <3' category. For TV time, computer time and sleep missing values were not replaced.

Data analysis

All statistical analyses were performed using SPSS software [18]. General estimating equation (GEE) logistic regression analyses with an independent correlation structure were performed to examine the longitudinal associations between total screen time (television watching plus playing computer games outside school hours), and total sleep duration (daytime plus nighttime sleep) at ages 2, 4-5, 6-8 as the repeated exposure variables, and parent reported ADHD at age 8-10 as the outcome variable. The same analysis was done with GP reported ADHD as the outcome variable, these results are only presented if different from the results with parent reported ADHD as outcome variable. Persistence of associations over time of follow-up was evaluated by testing for interaction with time (age when the questionnaires of the exposure variables were taken) in the GEE models, which is reported if the p-value for interaction was less than 0.05. Deviation from linearity was tested by adding quadratic terms to the GEE model for both screen time and sleep and checking for significance ($p<0.05$). To assess whether the longitudinal association were modified by gender or were different between the recruitment groups, results were stratified and only presented if significant ($p<0.05$).

After examining the univariate characteristics of the independent variables, multiple linear regression analysis was used to assess the cross-sectional analysis of the association between the continuous variable's hours of TV time and total sleep duration at the age of 2 years as independent exposure variables, and mean CBCL/2-3 scores on the overactive scale and externalizing scale as outcome variables, correcting for potential confounding covariates. Television time was used as a separate variable, due to the low amount of computer time and large standard deviations at age 2. Testing for effect modification by gender was performed by adding interaction variables for both gender and television time and gender and sleep. Finally, uni- and multiple logistic regression analysis was performed to examine the longitudinal association between the externalizing and overactive scale of the CBCL/2-3, television time and sleep at age 2 as the exposure variables and an ADHD diagnosis at age 8-10 as the outcome variable.

RESULTS

Baseline characteristics

Of the available 2,834 children from the original KOALA Birth Cohort, 66 were excluded based on exclusion criteria for this study, leaving a total number of 2,768 children. The study flow in Figure 1 shows the available data for the various analyses at the different ages. Baseline characteristics of the total cohort and the subgroups with complete follow-up on parent- and GP reported outcomes are shown in Table 1. Follow-up rates were slightly higher among the families with higher maternal education, non-smoking in pregnancy, and without marital discord, as can be seen from the slight shift between the total cohort and those at follow-up in Table 1. Values for TV time, computer time and total sleep duration were not different in the parent reported ADHD group and the group that was lost to follow-up.

Figure 1 | *Study flow*

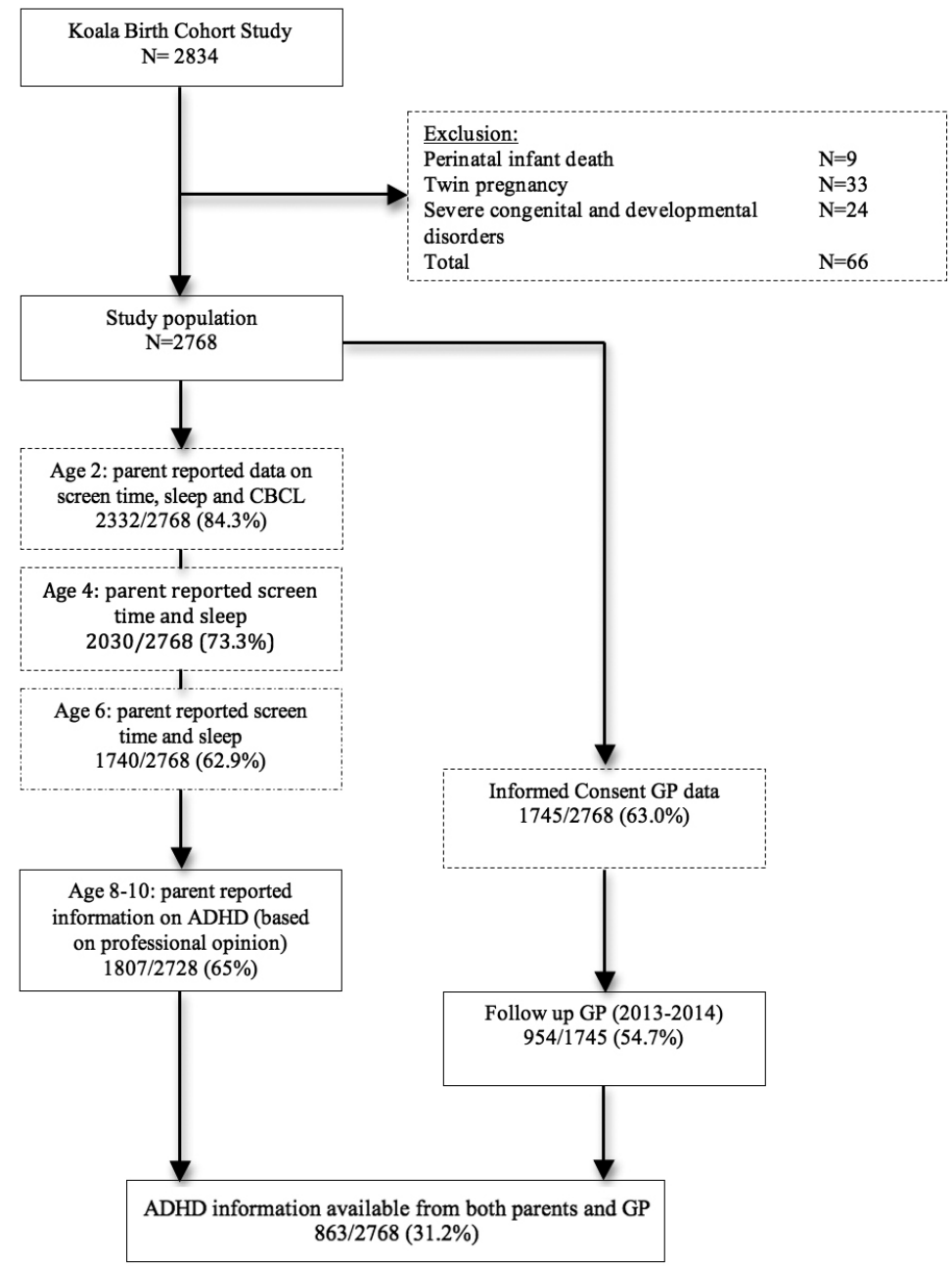


***Table 1** | Baseline characteristics of maternal, pre- peri- and postnatal characteristics of the total cohort and follow-up subgroups.*

Variable	Total cohort	Follow up parents (8-10 years)	Study cohort with informed consent GP data	Follow up GP (11-13 years)
Participants, N (%)	2768 (100)	1807 (64)	1745 (62)	954 (34)
Recruitment group				
(conventional) N (%)	2295 (83)	1470 (81.4)	1423 (81.5)	770 (80.7)
Maternal Education				
low	283 (10.2)	152 (8.4)	143 (8.2)	76 (8.0)
middle	1040 (37.6)	665 (36.8)	672 (35.9)	328 (34.4)
high	1301 (47.0)	904 (50)	898 (51.5)	512 (53.7)
unknown	144 (5.2)	86 (4.8)	77 (4.4)	38 (4)
Maternal smoking in pregnancy, N (%)	213 (7.7)	95 (5.3)	90 (5.2)	45 (4.7)
Maternal alcohol use in pregnancy, N (%)	513 (18.5)	346 (19.1)	327 (18.7)	187 (19.6)
Gender of child, male N (%)	1414 (51.1)	920 (50.9)	864 (49.5)	467 (49.0)
Gestational age > 37 weeks, N (%)	2688 (97.1)	1755 (97.1)	1699 (97.4)	929 (97.4)
Birth weight > 2500 gram, N (%)	2688 (97.7)	1762 (97.5)	1707 (97.8)	932 (97.7)
Marital discord, N (%)				
No	2363 (85.4)	1621 (89.7)	1549 (88.8)	849 (89)
Yes	220 (7.9)	135 (7.5)	142 (8.1)	76 (8)
No partner/unknown	185 (6.7)	51 (2.8)	54 (3.1)	29 (3)
Daily routine of the family 2 years, N (%)				
(almost) always	2265(81.8)	1618 (89.5)	1566 (89.7)	857 (89.8)
seldom or never	263 (9.5)	175 (9.7)	161 (9.2)	89 (9.3)
missing	240 (8.7)	14 (0.8)	18 (1.0)	8 (0.8)
Television watching, mean minutes/day (SD)*				
2 years	29.4 (25.3)	28.2 (24.9)	28.4 (25.1)	29.1 (25.6)
Percentage children who watch TV (age 2)	92%	92%	92%	92%
4-5 years	58.3 (33.1)	57.6 (32.8)	58.0 (32.8)	58.3 (32.9)
6-8 years	67.9 (34.6)	67.8 (34.5)	67.9 (34.6)	68.9 (34.4)
Computer games, mean minutes/day (SD)*				
2 years	0.51 (3.4)	0.51 (3.5)	0.45 (3.3)	0.47 (3.3)
Percentage children who play computer				
games (age2)	4%	5%	4%	5%
4-5 years	18.8 (24.7)	18.2 (24.1)	18.2 (24.1)	18.1 (24.0)
6-8 years	37.1 (27.3)	36.7 (26.8)	36.9 (27.1)	36.7 (27.2)
Total sleep duration, mean hours/day (SD)				
2 years	13.3 (1.2)	13.3 (1.2)	13.3 (1.2)	13.3 (1.2)
4-5 years	11.2 (0.8)	11.2 (0.8)	11.2 (0.8)	11.2 (0.7)
6-8 years	10.4 (1.5)	10.4 (1.5)	10.5 (1.5)	10.5 (1.6)

Variable	Total cohort	Follow up parents (8-10 years)	Study cohort with informed consent GP data	Follow up GP (11-13 years)
Playing outside, mean minutes/day (SD)				
2 years	67.6 (39.3)	66.8 (39)	66.9 (39.0)	65.7 (38.4)
4-5 years	100.4 (42.9)	100.6 (43.1)	100.1 (43.0)	99.6 (41.8)
6-8 years	107.1 (40.7)	107.7 (40.7)	106.8 (40.5)	107.7 (40.7)
CBCL/2-3, mean score overactive scale (SD) †	0.50 (0.39)	0.50 (0.38)	0.50 (0.38)	0.49 (0.36)
CBCL/2-3, mean score externalizing				
scale (SD) †	0.44 (0.26)	0.44 (0.26)	0.45 (0.25)	0.44 (0.24)
Parent reported ADHD 8-10 years n (%)	98 (5.4)	81 (5.3)	48 (5.6)	
GP reported ADHD 9-11 years n (%)				82 (8.6)

SD= standard deviation, CBCL= Child Behavior Checklist, ADHD= attention-deficit/hyperactivity disorder, GP= general practitioner
** Television watching and computer time measured outside school hours † total range of scale is 0 to 2, scales based on items of the Dutch version of the CBCL/2-3 (Koot et al. 1997)*

Longitudinal association between screen time, sleep duration, and parent reported ADHD

Unadjusted GEE analysis showed a significant association between screen time at the ages of 2, 4-5 and 6-8 years and parent reported ADHD, which disappeared after adjustment for potential confounders (Table 2). Total sleep duration was unrelated to ADHD in both the unadjusted and the adjusted model. No statistical significance was found when testing for deviation from linearity. Stratification for both recruitment group and gender did not influence the results (conventional group $p = 0.5$ for screen time and $p = 0.9$ for sleep; gender only male $p = 0.1$ for screen time $p = 0.8$ for sleep). Testing on time interaction was also not significant, indicating no increasing or decreasing trend with age of the strength of the association between screen time or sleep duration with ADHD.
Multiple logistic regression analysis with parent reported ADHD as outcome variable showed no independent association with the score on the externalizing scale of the CBCL/ 2-3 (table 3). By contrast, a 1-point higher score on the overactive scale of the CBCL/2-3 was associated with a meaningfully higher risk of ADHD at age 8-10 (OR 1.8, 95% CI 1.0-3.2); results for screen time and sleep duration were similar as in the GEE model.
In the GP reported group, both unadjusted and adjusted GEE analysis showed no associations between either screen time or total sleep duration and ADHD.

***Table 2** | Longitudinal association between screen time* and sleep duration as repeated measurements at age 2, 4 and 6, and parent reported ADHD at age 8-9 as the outcome.*

Variable	Unadjusted		Adjusted†	
	OR (95% CI)	p-value	OR (95% CI)	*p*-value
Screen time (hours/day; age 2, 4, 6)	1.4 (1.1-1.7)	0.004	1.1 (0.9-1.4)	0.33
Sleep duration (hours/day; age 2, 4, 6)	0.9 (0.8-1.1)	0.22	1.0 (0.8-1.1)	0.73

Odds ratios (OR) with 95% confidence interval (95%CI) from General Estimation Equations logistic regression analysis.
** Screen time consists of the sum of TV time and computer time outside school hours. † Adjusted for recruitment group, education level of the mother, smoking during pregnancy, alcohol use during pregnancy, gender, gestational age, marital discord 3 months postpartum, and both factors in the table.*
Number of subjects with complete data on screen time and sleep duration at age 2, N=1784, age 4 N=1647, and age 6 N=1603.

Cross-sectional association between watching television, sleep and the CBCL/2-3 at age 2

Multiple linear regression analysis showed a significant association between hours of watching TV and the externalizing behavior scale of the CBCL/2-3, but no association with the overactive subscale, as shown in table 4. A similar result was found for sleep: fewer hours of sleep were only associated with higher scores on the externalizing scale of the CBCL 2/3, but not specifically with the overactive scale. Although statistically significant, effect sizes were small for both screen time and sleep: e.g., an increment of 1h/d of TV watching was associated with a 0.03 higher score on the externalizing scale (scale 0-2, mean 0.44, SD 0.26; effect size = standardized mean difference = 0.03/0.26 = 0.12), and an increment of 1h/d sleep was associated with 0.02 lower score on the externalizing scale (effect size = 0.08). Furthermore, being male, low education of the mother, no rhythm in family life at age two and marital discord showed a significant association with both the externalizing scale and the overactive scale of the CBCL/2-3. No effect modification by the variable gender on watching TV or sleep was found (test for interaction).

***Table 3** | Longitudinal association between scores on the CBCL/2-3, screen time* and sleep duration at age 2 (and other exposures), and parent reported ADHD at age 8-10 as the outcome.*

Variable	Unadjusted	Adjusted†	Adjusted£
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Recruitment group (conventional)	**2.7 (1.3-5.6)**	1.9 (0.9-4.0)	1.8 (0.8-3.7)
Education mother (low)	**5.1 (2.9-8.9)**	**3.8 (2.1-7.2)**	**3.6 (1.9-6.9)**
Smoking during pregnancy (yes)	**2.7 (1.4-5.2)**	1.8 (0.9-3.8)	1.7 (0.8-3.5)
Gender (male)	**3.1 (1.9-5.0)**	**3.3 (2.0-5.5)**	**3.3 (2.0-5.5)**
Gestational age	0.9 (0.8-1.0)	0.9 (0.8-1.1)	0.9 (0.8-1.1)
Marital discord	**1.8 (1.0-3.0)**	1.8 (0.9-3.3)	1.8 (0.9-3.2)
Rhythm in family at age 2	**0.6 (0.3-0.9)**	0.6 (0.3-1.0)	0.6 (0.3-1.1)
CBCL/2-3 externalizing scale	**3.1 (1.5-6.6)**	1.4 (0.6-3.3)	
CBCL/2-3 overactive scale	**2.7 (1.6-4.4)**		**1.8 (1.0-3.2)**
Screen time (hours/day; age 2)	**1.4 (1.1-1.7)**	1.2 (0.9-1.6)	1.2 (0.9-1.6)
Sleep (hours/day; age 2)	1.0 (0.8-1.2)	1.0 (0.8-1.2)	1.0 (0.8-1.2)

Odds ratios (OR) and 95% Confidence Intervals (CI) from logistic regression. CBCL Child Behavioral Check List
** Screen time consists of the sum of TV time and computer time outside school hours. † adjusted for all variables in the model, except for CBCL/2-3 overactive scale; £ adjusted for all variables in the model, except for CBCL/2-3 externalizing scale.*

***Table 4** | Cross-sectional association between TV time and sleep duration (and other exposures), and the mean CBCL/2-3† score of the externalizing behaviour scale and overactive subscale at age 2 as the outcome.*

Variable	CBCL/2-3 externalizing behaviour scale		CBCL/2-3 overactive subscale	
	Unstandardized B (95% CI)	*p*	Unstandardized B (95% CI)	*p*
Watching TV (hours/day)	0.03 (0.002 to 0.05)	0.04	0.02 (-0.02 to 0.06)	0.3
Sleep (hours/day)	-0.02 (-0.03 to -0.01)	<0.001	-0.01 (-0.23 to 0.002)	0.1
Recruitment group (conventional)	0.01 (-0.02 to 0.04)	0.4	0.09 (0.04 to 0.13)	<0.001
Maternal education				
low	0.07 (0.03 to 0.1)	0.001	0.13 (0.07 to 0.19)	< 0.001
middle	0.05 (0.02 to 0.07)	<0.001	0.08 (0.05-0.12)	<0.001
Smoking during pregnancy	0.06 (0.02 to 0.1)	0.006	0.05 (-0.02 to 0.11)	0.1
Alcohol use during pregnancy	-0.02 (-0.05 to 0.004)	0.09	-0.03 (-0.07 to 0.01)	0.1
Gender (male)	0.06 (0.04 to 0.08)	<0.001	0.05 (0.02 to 0.08)	0.005
Gestational age	0.002 (-0.005 to 0.01)	0.6	-0.02 (-0.01 to 0.01)	0.7
Marital discord	0.07 (0.04 to 0.10)	<0.001	0.05 (0.001 to 0.1)	0.05
Rhythm in family (yes, age 2)	-0.08 (-0.12 to -0.05)	<0.001	-0.08 (-0.14 to -0.03)	0.002
Playing outside (hours/day)	-0.01 (-0.03 to 0.01)	0.3	-0.01 (-0.03 to 0.02)	0.5

N = 2332; 1189 males. CBCL = Child Behaviour Checklist
Regression coefficients (B) and 95% confidence intervals (95%CI) from multiple linear regression analysis.
† The factor structure of the CBCL/2-3 is based on the article of Koot (Koot, Van Den Oord, Verhulst, & Boomsma, 1997). This Dutch version of the CBCL 2/3 subdivides behavioural problems at young age in 6 scales (overactive, aggressive, oppositional, anxious, depressed, sleep problems) and two problem scales (externalizing and internalizing).
The externalizing behaviour scale consists of the overactive, aggressive and oppositional scales.
Adjusted for all the factors in the table. Constant externalizing scale is 0.6, and for overactive scale 0.67.

DISCUSSION

The current study aimed to examine the longitudinal association between recreational screen time and total sleep duration in early childhood and an ADHD diagnosis at age 8-10 years. After correction for possible confounders, no relation between both the amount screen time and total sleep duration at age 2, 4-5 and 6-8 and a parent reported ADHD diagnosis was found. The absence of this longitudinal association was confirmed in the GP reported ADHD group. By contrast, at the age of 2, both watching television and sleep duration were found to be associated with a higher score of the externalizing scale of the CBCL/2-3.

Screen time and ADHD

Multiple cross-sectional and longitudinal studies have evaluated the association between TV time, computer time or screen time in general, and symptoms of hyperactivity, inattention, or externalizing behaviour [5, 7, 8, 19-22]. Different from these studies, the current study used an actual ADHD diagnoses instead of ADHD symptoms as outcome variable. In order to diagnose ADHD, a child must meet, in addition to a high score on inattention, hyperactivity and impulsivity symptoms, also other diagnostic criteria based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Most important, the child must experience serious impairment due to the behavioural symptoms [23]. These behavioural symptoms can differ in life due to age, gender or environment [24, 25]. Most previous studies showed that the environmental factor screen time was associated with increased symptoms of externalizing behaviour, hyperactivity or inattention in healthy preschool and school-aged children [5, 7, 8, 19-21, 26]. Our study showed a comparable cross-sectional association between externalizing behaviour and time watching TV at the age of two, but there was no longitudinal relationship between the amount of screen time at a young age and an actual ADHD diagnosis at the age of 8 to 10 years. Finding no association between screen time at age 2, 4-5 and 6-8 and a professional based parent reported ADHD diagnosis, underlined the importance not to confuse the presence of behavioural symptoms of ADHD with an actual ADHD diagnosis. It showed that the influence of environmental factors like screen time should be considered, when a young child is evaluated because of these ADHD-like symptoms, and stressed the importance of applying all DSM-5 criteria for ADHD when a child is evaluated because of inattention, hyperactivity or impulsivity symptoms. Multiple explanations for this association between externalizing symptoms and screen time could be thought of. Parents may put young children with an overactive temperament in front of the television to get a little bit of rest, as Stevens and colleagues suggested, who also found no meaningful relationship between television exposure at a young age and later symptoms of ADHD [22]. Another explanation may be that watching screens only has a direct effect on behaviour; more hours behind screens may result in immediate externalizing behaviour or inattention, without long-lasting effects. The positive association at age two between more TV time and a higher score on the externalizing scale, could be a result of both of the above explanations. The lack of association between TV time and the overactive subscale of the CBCL/2-3 at age 2 seemed to support this. The 5 items of the overactive subscale are part of the total of 31 items of the externalizing scale of the CBCL/2-3, and overlap with the DSM-5 symptom score for ADHD APA, [17, 23]. This explained the positive association between the overactive subscale of the CBCL/2-3 and an ADHD diagnosis. The externalizing behavioural scale on the other hand, showed no association with an ADHD diagnosis at the age of 8-9 years, making it less likely that the externalizing behavioural characteristics were another expression of ADHD.

A recent study of Tanana et al. (2019) showed that in particular a prolonged amount of screen time (including the use of TV, computer, tablet and mobile phone) was associated with clinically relevant externalizing morbidity and inattention problems [19]. Our study did not reveal such a dose effect between hours of screen time early in life and an ADHD diagnosis at the age of 8. The reported amount of screen time in the current study at age 4-5 appeared to be only slightly lower than in the study of Tamana et al. (1.3 vs 1.4 hours/day). However, the total amount of screen time at age 2 was only 30 minutes in this study, which was much lower than the amount of screen time found in other studies, where screen time or TV time varied between 1.5 and 3.6 hours/day at age 3 [19, 27, 28]. Data collection concerning hours of screen time for the current study took place from 2000 to 2009. In 2010 the first touch screen devices were introduced, which could have accounted for an increase in screen time in studies in which data were collected after 2010. Despite the fact that touch screen devices were not yet released when data were collected for this study, the results were useful. Dutch studies showed an enormous increase in medication use for ADHD between 2000 and 2010, the years that data for the KOALA birth cohort were collected [29]. If this increase in ADHD was linked to an increase in screen time, a positive association would have been found in the current study.

Sleep and ADHD

Total sleep duration also showed no longitudinal association with ADHD. As with screen time, an association between sleep duration and externalizing behavior was found in the analysis at age two. Cause and effect could not be separated, however. In other words, it was not possible to determine if a child became rebellious due to little sleep, or if externalizing behavior caused decreased sleep time and therefore less sleep duration.

A meta-analysis of subjective and objective studies concerning sleep and ADHD by Cortese (2009), showed many associations between various sleep disturbances and ADHD, but the item 'sleep duration' was also not significantly associated with ADHD [12]. The authors of this meta-analysis gave as a possible explanation the different interpretation of sleep duration by the parents (e.g., from lights off to wake up time versus the time a child actually sleeps). Parental perceptions could also have influenced the findings of our study. However, one would expect that if children sleep shorter due to their ADHD problems, parents would notice this over the years (for example because children get out of bed), which would become clear with repeated measurements.

Strengths and Limitations

This study has several limitations. Concerning information bias, first, questionnaires that were used measuring both screen time, and sleep were developed specifically for the KOALA study. Screen time and sleep were not measured, but were only parent reported. Especially, the amount of screen time at age 2 was low compared with most other studies [19, 28]. Only few studies which were conducted at the same period as this study, reported on both type and hours of media use. A difference between results shown in this article and other studies, is the country where data were collected, which may be an explanation for the difference in TV time, in addition to the possibility of information bias. Unfortunately, precise data to verify this are missing. Maybe more screen time particularly at this very young age, is associated with ADHD symptoms later in life, as other studies showed [30]. In addition, the content of the television and computer programs was not asked. This could have affected study results, as Zimmerman and Christakis (2007) showed that only violent content was associated with attention problems at age 0-3 [6]. It was likely that screen time in our study included violent as well as non-violent content. Second, the ADHD diagnosis was parent reported. Parents where asked whether a doctor, psychologist, or remedial educationalist had ever diagnosed their child with ADHD, but they were not asked in what way this diagnosis was made, and whether this diagnosis fully met DSM-IV-TR criteria American Psychiatric Association,

2000 [31]. Despite the fact that the percentage of children with ADHD and other known relevant factors (like male gender of the child) corresponded with the estimates from the literature, the parent reported group could have given an over- or under estimation of the diagnosis ADHD [32]. However, using GP reported ADHD as outcome variable, did not yield differences compared with the results of the analysis with parent reported ADHD as outcome. Only the magnitude of the estimates of the different risk factors was slightly higher in the parent reported group, but also in the GP group no longitudinal association was found between screen time or sleep and ADHD, which supported the results of this study. Selection bias may have occurred due to selective loss-to-follow-up, but the follow-up rates differed only slightly according to baseline characteristics, indicating a limited potential for selection bias.

Finally, a family history of ADHD was not assessed, which might have caused effect modification or confounding. ADHD is both caused by the combined effects of genetic vulnerability and environmental exposures [33, 34]. It is often difficult to separate environmental factors from genetic factors, as genetic studies show that some phenotypes are caused by the same genetic behavioural pathways common to risk-taking propensity, like ADHD and smoking [35]. Besides that, recent genome-wide-association meta-analysis found genetic correlations between ADHD and phenotypes like education and smoking [36]. Known environmental factors that are partly correlated with genetic pathways of ADHD, such as smoking during pregnancy and education level of the mother, were included as confounders in the current study [37-40]. These factors were indeed associated with both overactive and externalizing symptoms on the CBCL-2/3 at age 2. Only the education level of the mother was associated with an ADHD diagnosis later in the child's life. Although these factors did not eliminate potential modification of the outcome due to missing data on family history, it is likely that by adjusting for the variables with a known strong correlation with a positive family history, the lack of adjustment for family history was partly corrected for in the analyses.

CONCLUSION

This birth cohort study showed no longitudinal association between recreational screen time or sleep duration in early childhood and an ADHD diagnosis at age 8. It did find a weak cross-sectional association between time spent watching television, hours of sleep, and higher scores for externalizing behavioural symptoms at the age of two. Yet, these externalizing behavioural symptoms were not associated with an ADHD diagnosis later in life. The results of the current study showed that it is important to include questions about hours of screen time and sleep when evaluating externalizing, overactive or inattention symptoms and to include environmental factors into a differential diagnosis before diagnosing ADHD. Furthermore, the study underlines the importance of longitudinal research when examining environmental risk factors for ADHD and other disorders.

REFERENCE

1. Loprinzi PD, Davis RE. Secular trends in parent-reported television viewing among children in the United States, 2001-2012. *Child Care Health Dev.* Mar 2016;42(2):288-91.
2. The Lancet Child Adolescent Health. Growing up in a digital world: benefits and risks. *Lancet Child Adolesc Health.* 02 2018;2(2):79.
3. Ceranoglu TA. Inattention to Problematic Media Use Habits: Interaction Between Digital Media Use and Attention-Deficit/Hyperactivity Disorder. *Child Adolesc Psychiatr Clin N Am.* Apr 2018;27(2):183-191.
4. Reid Chassiakos YL, Radesky J, Christakis D, Moreno MA, Cross C, MEDIA COCA. Children and Adolescents and Digital Media. *Pediatrics.* 11 2016;138(5)
5. van Egmond-Fröhlich AW, Weghuber D, de Zwaan M. Association of symptoms of attention-deficit/hyperactivity disorder with physical activity, media time, and food intake in children and adolescents. *PLoS One.* 2012;7(11):e49781.
6. Zimmerman FJ, Christakis DA. Associations between content types of early media exposure and subsequent attentional problems. *Pediatrics.* Nov 2007;120(5):986-92.
7. Lingineni RK, Biswas S, Ahmad N, Jackson BE, Bae S, Singh KP. Factors associated with attention deficit/hyperactivity disorder among US children: results from a national survey. *BMC Pediatr.* May 2012;12:50.
8. Ra CK, Cho J, Stone MD, et al. Association of Digital Media Use With Subsequent Symptoms of Attention-Deficit/Hyperactivity Disorder Among Adolescents. *JAMA.* 07 2018;320(3):255-263.
9. Ioannidis K, Hook R, Goudriaan AE, et al. Cognitive deficits in problematic internet use: meta-analysis of 40 studies. *Br J Psychiatry.* Feb 2019:1-8.
10. Starcevic V, Khazaal Y. Relationships between Behavioural Addictions and Psychiatric Disorders: What Is Known and What Is Yet to Be Learned? *Front Psychiatry.* 2017;8:53.
11. Hale L, Guan S. Screen time and sleep among school-aged children and adolescents: a systematic literature review. *Sleep Med Rev.* Jun 2015;21:50-8.
12. Cortese S, Faraone SV, Konofal E, Lecendreux M. Sleep in children with attention-deficit/hyperactivity disorder: meta-analysis of subjective and objective studies. *J Am Acad Child Adolesc Psychiatry.* Sep 2009;48(9):894-908.
13. van der Heijden KB, Stoffelsen RJ, Popma A, Swaab H. Sleep, chronotype, and sleep hygiene in children with attention-deficit/hyperactivity disorder, autism spectrum disorder, and controls. *Eur Child Adolesc Psychiatry.* Jan 2018;27(1):99-111.
14. Owens JA, Maxim R, Nobile C, McGuinn M, Msall M. Parental and self-report of sleep in children with attention-deficit/hyperactivity disorder. *Arch Pediatr Adolesc Med.* Jun 2000;154(6):549-55.
15. Kummeling I, Thijs C, Penders J, et al. Etiology of atopy in infancy: the KOALA Birth Cohort Study. *Pediatric allergy and immunology.* 2005;16(8):679-684.
16. Achenbach, M. T, Rescorla L. *Manual for the ASEBA school-age forms & profiles. An integrated system of multi-informant assessment.* 2001.
17. Koot HM, Van Den Oord EJ, Verhulst FC, Boomsma DI. Behavioral and emotional problems in young preschoolers: cross-cultural testing of the validity of the Child Behavior Checklist/2-3. *J Abnorm Child Psychol.* Jun 1997;25(3):183-96.
18. IBM SPSS Statistics for Windows v 24, IBM Corp. Armonk, N.Y., USA.
19. Tamana SK, Ezeugwu V, Chikuma J, et al. Screen-time is associated with inattention problems in preschoolers: Results from the CHILD birth cohort study. *PLoS One.* 2019;14(4):e0213995.

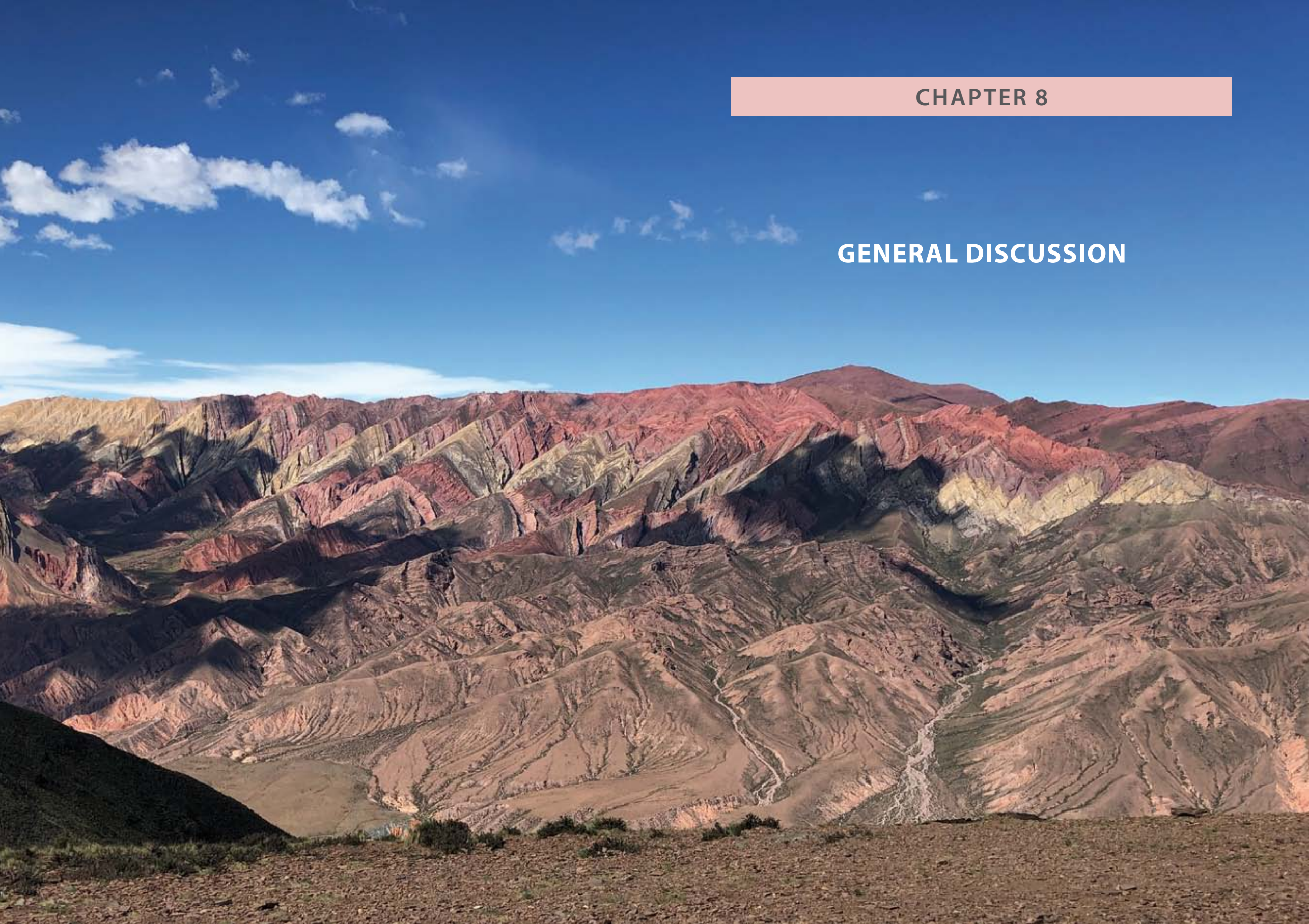
20. Zimmerman FJ, Christakis DA, Meltzoff AN. Associations between media viewing and language development in children under age 2 years. *J Pediatr.* Oct 2007;151(4):364-8.
21. Miller CJ, Marks DJ, Miller SR, et al. Brief report: Television viewing and risk for attention problems in preschool children. *J Pediatr Psychol.* May 2007;32(4):448-52.
22. Stevens T, Mulsow M. There is no meaningful relationship between television exposure and symptoms of attention-deficit/hyperactivity disorder. *Pediatrics.* Mar 2006;117(3):665-72.
23. American Psychiatric Association, (APA) PA. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). 2013. Wahington DC.
24. Thapar A, Cooper M. Attention deficit hyperactivity disorder. *Lancet.* Mar 2016;387(10024):1240-50.
25. Barkley RA, Murphy KR. Attention-Deficit Hyperactivity Disorder: A Clinical Workbook. third edition ed: Guilford Press; 2006.
26. Xie G, Deng Q, Cao J, Chang Q. Digital screen time and its effect on preschoolers' behavior in China: results from a cross-sectional study. *Ital J Pediatr.* Jan 2020;46(1):9.
27. Chaput JP, Colley RC, Aubert S, et al. Proportion of preschool-aged children meeting the Canadian 24-Hour Movement Guidelines and associations with adiposity: results from the Canadian Health Measures Survey. *BMC Public Health.* Nov 2017;17(Suppl 5):829.
28. Christakis DA, Zimmerman FJ, DiGiuseppe DL, McCarty CA. Early television exposure and subsequent attentional problems in children. *Pediatrics.* Apr 2004;113(4):708-13.
29. ADHD: medicatie en maatschappij . [ADHD: medication and society] (2014). Retrieved from https://www.gezondheidsraad.nl/documenten/adviezen/2014/07/03/adhd-medicatie-en-maatschappij
30. Christakis DA, Ebel BE, Rivara FP, Zimmerman FJ. Television, video, and computer game usage in children under 11 years of age. *J Pediatr.* Nov 2004;145(5):652-6. doi:10.1016/j.jpeds.2004.06.078
31. American Psychiatric Association (APA). Diagnostic and Statistical Manual of Mental Disorders 4th edition, text revised ed. 2000. Washington DC.
32. Sayal K, Prasad V, Daley D, Ford T, Coghill D. ADHD in children and young people: prevalence, care pathways, and service provision. *Lancet Psychiatry.* Feb 2018;5(2):175-186.
33. Faraone SV, Asherson P, Banaschewski T, et al. Attention-deficit/hyperactivity disorder. *Nat Rev Dis Primers.* 08 2015;1:15020.
34. Mill J, Petronis A. Pre- and peri-natal environmental risks for attention-deficit hyperactivity disorder (ADHD): the potential role of epigenetic processes in mediating susceptibility. *J Child Psychol Psychiatry.* Oct 2008;49(10):1020-30.
35. Strawbridge RJ, Ward J, Cullen B, et al. Genome-wide analysis of self-reported risk-taking behaviour and cross-disorder genetic correlations in the UK Biobank cohort. *Transl Psychiatry.* 02 2018;8(1):39.
36. Demontis D, Walters RK, Martin J, et al. Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. *Nat Genet.* 01 2019;51(1):63-75.
37. Faraone SV, Ghirardi L, Kuja-Halkola R, Lichtenstein P, Larsson H. The Familial Co-Aggregation of Attention-Deficit/Hyperactivity Disorder and Intellectual Disability: A Register-Based Family Study. *J Am Acad Child Adolesc Psychiatry.* Feb 2017;56(2):167-174.e1.
38. Sciberras E, Mulraney M, Silva D, Coghill D. Prenatal Risk Factors and the Etiology of ADHD-Review of Existing Evidence. *Curr Psychiatry Rep.* Jan 2017;19(1):1.
39. He Y, Chen J, Zhu LH, Hua LL, Ke FF. Maternal Smoking During Pregnancy and ADHD: Results From a Systematic Review and Meta-Analysis of Prospective Cohort Studies. *J Atten Disord.* Mar 2017:1087054717696766.
40. Zhu JL, Olsen J, Liew Z, Li J, Niclasen J, Obel C. Parental smoking during pregnancy and ADHD in children: the Danish national birth cohort. *Pediatrics.* Aug 2014;134(2):e382-8.

CHAPTER 7

GENERAL PARENTING IN A BIRTH COHORT: EVALUATING PARENTING SUB CONSTRUCTS FOR BOYS AND GIRLS WITH ADHD

Birgit Levelink
Ester van der Borgh-Sleddens
Petra Hurks
Jessica Gubbels
Frans Feron
Carel Thijs

Submitted



CHAPTER 8

GENERAL DISCUSSION

1. OVERVIEW

Over the last thirty years, the way in which symptoms of inattention, hyperactivity and impulsivity and attention-deficit/hyperactivity disorder (ADHD) are dealt with has changed dramatically. Whereas until the nineties the main focus was on the behavioural characteristics of ADHD, and the disruptive effect of this behaviour on the environment, it is now widely accepted that ADHD is a heterogeneous neurodevelopmental disorder [1-3]. The genetic predisposition of a child interacts both with the environment and the social context, creating a wide variety in ADHD phenotypes [4]. Simply put, this ***heterogeneity*** can be due to three causes, which may also interact with one another, creating numerous possible presentations of ADHD. First, heterogeneity in appearance is related to the aetiology of ADHD, whereby genes and environment interact with each other, both intrauterine and after birth [4]. Hereby it is important to consider the homogeneity of environmental factors and the moment of interaction [5]. Appearance of ADHD can also differ in terms of the age or gender of the child [6]. Second, heterogeneity may result from the interpretation of behavioural characteristics. Especially in relation to younger children, this largely depends on the interpretation of the behavioural characteristics of the child by the parents and teacher [7]. Finally, heterogeneity can be attributed to the health care system, as referrals are made to different health care institutions, and behavioural characteristics are therefore examined and interpreted by various health care workers. Whenever evaluating a child with symptoms of inattention and/ or hyperactivity and impulsivity, it is important not only to evaluate on a microlevel (e.g., genes, behaviour) but also from a macrolevel perspective (considering the interaction with environmental factors) [8].

Paediatricians, among other health care professionals, have traditionally been involved in the care of children with ADHD (due to a shortage of professionals in mental health care). However, as a result of the transition and transformation of youth care in 2015, care pathways for children with symptoms related to ADHD have changed. Local municipalities became fully responsible for the funding of ADHD care, and often they did not contract-out hospitals. Due to this change in funding, paediatricians have become less involved in the care for children with (symptoms related to) ADHD. However, they still encounter children with behavioural symptoms related to ADHD. For example, when physical problems accompany ADHD, or when a child has developmental problems with no known cause. It is unclear whether paediatricians should always be involved when a child is first evaluated because of ADHD symptoms, and whether there is a role for social paediatricians in particular.

The ***first objective*** of this thesis was to discuss the role of (social) paediatricians with regard to the complexity of ADHD, following the transition and transformation of youth care. The research questions presented in this thesis arose both out of experience in clinical practice and in response to turbulent policy changes that have greatly affected children with ADHD (symptoms) and their parents. While the scope of the thesis is of course limited, these studies provide a solid foundation for future research. The aims of the studies were: a) to identify bio-psycho-social characteristics of children, referred to a hospital because of ADHD symptoms, which could be used as indicator for whether the child needed specialized health care or primary care, b) to gain insight into the kinds of (health care) professionals involved in diagnosing ADHD in the Netherlands and the diagnostics guidelines they use. The ***second objective*** was to further explore the influence of environmental factors associated with ADHD. For this purpose, a longitudinal birth cohort was used, in order to evaluate important environmental factors which may be associated with ADHD, and identify opportunities for prevention and/or intervention.

2. ADHD; BIO-PSYCHO-SOCIAL CHARACTERISTICS AND THE HEALTH CARE SYSTEM

2.1 Health care system

In 2014, a report from the Dutch health council entitled 'ADHD: medication and society' was published [9]. In this report, much attention was paid to the rapid increase in the use of methylphenidate to treat ADHD in children in the Netherlands between 2003 and 2013. It was concluded that the increase in demand for (health) care for symptoms of inattention and/or hyperactivity was greater than would be expected, considering the fact that worldwide prevalence of ADHD remained the same [10, 11]. At the same time, some researchers discussed the issue of 'subthreshold ADHD', while others emphasized the significance of the impairment criterion when diagnosing ADHD, and the risk of overdiagnosis, all in light of the introduction of the new Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)[2], [12-18]. Controversy surrounding the idea that ADHD was over diagnosed or overtreated was rife in the Netherlands at that time. Illustrating the point, in 2012, a book was published entitled, 'How to prevent ADHD? By not making the diagnosis', in which it was emphasized that ADHD is merely a classification, and that ADHD behaviour should be viewed as more of a social problem [19]. Overdiagnosis occurs when a true abnormality is discovered, but detection of that abnormality does not benefit the patient, and should not be confused with misdiagnosis which relates to an inaccurate diagnosis [18]. Whilst there is a scarcity of research concerning overdiagnosis and ADHD, it has been found, for example, that children born in the months of August to December (and therefore younger than the other children in their school class) were more likely to be diagnosed with ADHD or prescribed medication [20-22]. Overdiagnosis of ADHD can have a stigmatizing effect, entail the risk of overmedication, and can lead to specific problems not being sufficiently addressed (e.g., concentration problems or hyperactive behaviour due to child abuse [23]). However, the risk of overdiagnosis is offset by the fact that ADHD is a risk factor for a wide range of other (medical) health problems, including defiant, disruptive and antisocial behaviour, emotional problems and substance misuse, as well as broader negative outcomes such as educational underachievement, difficulties with employment and relationships, and criminality [24-27]. This highlights the need for an accurate interpretation of the behavioural characteristics of a child - and the importance of accurate triage and referral so that the child follows an appropriate diagnostic trajectory before being classified as 'having ADHD'. In the Netherlands, the increase in demand for health care services to treat ADHD has been attributed to various factors, such as increased awareness of ADHD among health care professionals, parents and teachers, increased academic research on the disorder, and better accessibility to (health) care [28, 29]. One of the goals of the transition and transformation of youth care, as specified in the Youth Act (2015), was to ensure that children are not immediately referred to (expensive) second- or third-line care. Children with 'mild' ADHD, children with subthreshold ADHD, and children with inattention or hyperactivity not due to ADHD are to be cared for first by primary care or community care. This raises the question of whether the various biological and psychosocial aspects of a complex classification such as ADHD can be sufficiently addressed in this new system.

2.2 Characteristics of children referred because of inattention and/or hyperactivity

Data for Chapters 2 and 3 were collected during this rather complicated period just before the introduction of the new Youth Act. The transformative aim of this act – amongst others to provide more support for children in primary care - was applied retrospectively on a group of children referred to an ADHD-clinic because of ADHD symptoms. By mapping pre-existing known bio-, psycho-, and social characteristics of the referred children, we evaluated whether a decision about whether to refer or not could have

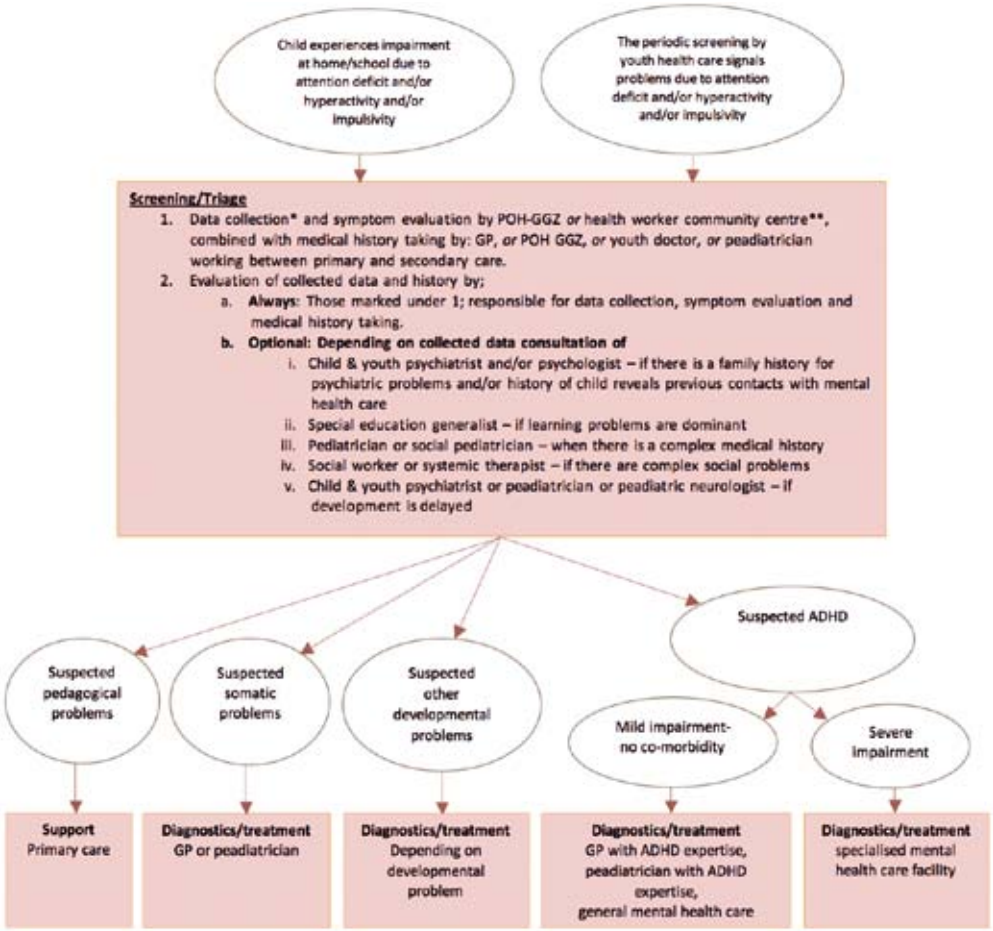
been made based on specific characteristics. Not entirely surprisingly, no simple variable was found to differentiate between different levels of care, and characteristics of the studied group of children were heterogeneous [30]. Interestingly, children who did end up receiving specialized care were found to have significantly higher scores on the Child Behaviour Check List (CBCL) and the Teacher's Report Form (TRF), indicating the occurrence of co-morbidities [31]. In addition, the parents of these children were more often divorced. However, although statistically significant, these characteristics cannot be used as tool to decide upon the appropriate level of care, as heterogeneity was considerable.

One hypothesis that we tested was that, in cases where an agreement had not been reached between parents and teachers regarding the necessity of a referral, support and treatment could initially be provided by primary care. This assumption was rejected; necessity of specialized health care did not depend on whether the school, parents - or both school and parents - saw reasons for referral. This can be due to several causes, and one can be due to the study design, and the fact that the question 'first initiative for referral' was used, instead of the question 'was impairment due to symptoms experienced by parents, school, or both'. Besides, referral due to symptoms of inattention and hyperactivity is known to be a complex process, and therefore sensitive to bias. First, previous research has demonstrated that variance in the interpretation of symptom severity between parents and teachers can lead to different opinions regarding the need for referral [32-34]. Second, the knowledge that primary health care providers and/or parents have about ADHD and the services available has been shown to play a role [35]. This is important, as several studies have reported that general practitioners' (GP) knowledge about ADHD is often still limited [36-38]. Third, referral depends in part on parental mental health, and the effect of child behaviour on the parent [39]. Lastly, the referral process may be different for boys and girls, partly accounting for the difference in prevalence between boys and girls [40]. In the Netherlands, referral pathways for children with inattention/hyperactivity symptoms (but also other developmental problems) are still poorly understood. Studying these pathways and the reasons behind choices for referral can provide information which can be used to improve triage processes.

Unexpectedly, more than 50% of the children studied had ADHD without comorbidity, or only inattention/hyperactivity symptoms that did not fulfil the criteria for a diagnosis, and thus according to the new Youth Act, did not meet the criteria of children needing specialized mental health care. However, our study did not reveal clinically relevant variables useful for triage between primary or specialized care. One dimensional measurement could not be used to differentiate between the need for different care levels, and cross-sectional analysis using screening tools, information from a third party, and interviews, followed by a comprehensive interpretation of all data, were (almost) always necessary. This raises the question of whether the premise of the Dutch transformation of youth care can be realised in relation to ADHD, when assuming a stepped care model with primary care, municipalities and community teams playing an important role. It seems likely that referral to specialized care will only decrease if the professionals responsible for the triage of children with symptoms of inattention and/or hyperactivity are equipped to evaluate behavioural problems adequately. A recent Dutch study evaluating youth care for children with behavioural problems after the transition showed that employees of municipalities, youth care regions, centres for youth and family (CJG), and community teams rated their knowledge of behavioural problems and the treatment of these problems as 'insufficient' [41]. In addition, ADHD guidelines were only used by some of these professionals. Although no firm conclusions can be drawn as to whether children are being referred correctly at this moment, it is clear that training to increase knowledge among those working in the community is important. This should lead to a better

understanding of the psychological, biomedical, and social aspects of inattention and/or hyperactivity symptoms, and facilitate the interpretation of information provided by parents, children and teachers. Moreover, this could contribute to the prevention of 'growing into deficit', as it will lead to early treatment of those children with serious impairment. The use of structured evaluations might also prevent unnecessary referral or overdiagnosis. In addition to increasing education opportunities for employees of municipalities, youth care regions, centres for youth and family (CJG), and community teams, it may also be worthwhile to explore the ways in which different (health) care professionals could share existing knowledge about ADHD between themselves. For example, triage could be carried out by a multidisciplinary team, consisting of a wide variety of (health care) professionals who are able to address psychological, social and physical factors. However, this might be a very expensive option, and therefore not a realistic one. One solution that may be more feasible would be to use a flexible consultative multidisciplinary network, operating in a primary care setting, as shown in Figure 1. Within these flexible networks, community workers and primary health care workers remain responsible for completing the first problem inventory in relation to the child and the family. Depending on the needs and impairments of the child and his or her family, professionals with specific knowledge should be consulted and asked to give their opinion about the right choice for referral. Ideally, a triage team would be composed of permanent members working in primary care and the community, as well as consultative experts. The advantage of such a flexible consultative multidisciplinary network is that it has self-learning capacity, and will also result in increased knowledge among professionals in primary care and those operating within the community. In general, the role of a social paediatrician is to consider the influence of health and disease on a child's development, taking information about professional and social networks into account. A (social) paediatrician should therefore be consulted whenever there is a combination of medical and developmental problems interacting with the social environment besides symptoms of inattention and/or hyperactivity.

***Figure 1** | Modification of the quality standard for screening, diagnosing and treatment of ADHD in the Netherlands.*



** Data collection, consisting of: medical history of the child, family history, developmental information from youth health care, information from school, optional screening lists from school and/or youth health care.*
*** health care worker community centre; professional depending on municipality.*

The research in this thesis also revealed that it was not only children in need of specialized health care, but also children with inattention and/or hyperactivity symptoms without an ADHD diagnosis, who had a variety of somatic symptoms. Problems like enuresis and asthma were common when a child had symptoms of inattention and/or hyperactivity, independent of an ADHD diagnosis, probably due to the multifactorial aetiology of both. These results are consistent with previous research, showing associations with various physical complaints, underlining the importance of somatic history taking and physical examination [42-47]. It is well known that children with symptoms of inattention/hyperactivity should always be tested on vision and hearing [4, 48]. This research underlines the importance of paying attention to other possible physical complaints, and suggests that these children should also be evaluated at an early stage by a medical doctor. Given the nature of the physical problems, this does not necessarily have to be a paediatrician.

2.3 ADHD guideline use of different professionals in the Netherlands

In order to classify symptoms of inattention, hyperactivity and impulsivity, a diagnostic process takes place following screening and referral. Children can be referred to various professionals, and there are several guidelines for different (health) care workers available in the Netherlands [49, 50]. Use of - and adherence to - ADHD guidelines among different care providers in the Netherlands is important, as deviation from the recommendations may lead to undetected comorbidities, mis- or overdiagnosis, or the unnecessary use of (expensive) tests. Due to the fact that there was no available data on this in the Netherlands, we conducted a survey after the Dutch transition of youth care, to identify which professionals were involved during the diagnostic process, and which particular guidelines they used. Analysis of these surveys revealed that only a small majority adhered to guidelines, in accordance with the results of studies in other countries [51-54]. However, the use of diagnostic key elements, for example the use of information from a third party or taking a developmental history, was more prevalent among professionals with the highest response rate. This suggests that diagnostic processes were actually based upon national guidelines. Due to the quantitative nature of the study, no further assumptions about the quality of evaluation of ADHD symptoms could be made, but this would be an interesting topic for further research, as interpretation of symptoms is a very important part of the diagnostic process. Although not a standard test for diagnosing ADHD, intelligent quotient (IQ) tests were frequently used. However, this data may not be representative, as IQ tests were mainly performed by professionals with the highest response rate, or working in specialized health care. It is possible that these professionals see more children with complex problems, justifying the high use of IQ tests. However, the overuse of IQ tests cannot be completely ruled out. Qualitative research into the reasons for this extensive use would be worthwhile, in order to evaluate the value of using IQ tests in relation to making an ADHD diagnoses.

Many paediatricians indicated that they were not involved during the diagnostic process. This may be a result of the transition and transformation of youth care. Due to the transition, municipalities (rather than health insurers) became responsible for financing ADHD-related issues. In response to this, many hospitals decided to stop care for children with ADHD, as agreeing financial contracts with the municipalities proved complicated. Therefore, it is most likely that only paediatricians who treated large populations of children with ADHD continued providing this care. Those paediatricians who remained involved showed many similarities in the use of guidelines when compared to the psychologists and psychiatrists. However, only the paediatricians performed regular physical examinations. It is important to provide good alternatives for medical history taking and physical examination, given that fewer and fewer children are seen by a paediatrician. However, bearing in mind the type of medical problems that often occur with ADHD, these assessments do not necessarily have to be carried out by a paediatrician.

A GP or youth doctor can also a provide much of this care adequately. However, for children with a complex medical history or serious illnesses, it is important to involve a paediatrician, in order to relate ADHD symptoms to the underlying disease, and the developmental level of the child, and to integrate treatment.

It is worthwhile to briefly consider the role of the GP. GPs are assigned a prominent role, both according to the 'ADHD standard of care', and in the context of the transformation of youth care. The response rate of GPs in the survey we conducted was very low, so no firm conclusions could be drawn about the way GPs evaluated children with symptoms of inattention and hyperactivity. Of those who did respond, 88% indicated that they immediately referred children if they thought that more information about the symptoms related to ADHD was needed. In addition, of those who indicated that they were involved during the diagnostic process, only a few used diagnostic key elements. If we want GPs to play a role in the triage, diagnosis and treatment of (mild) ADHD, additional training is probably needed. GPs are already heavily burdened with a great diversity of problems they have to take care of. It may be a better option for children with symptoms of inattention, hyperactivity and impulsivity to be seen by a nurse practitioner specializing in child mental health within the GP practice, and to concentrate the care for these children.

3. ADHD: ENVIRONMENTAL FACTORS

3.1 What do we know?

Multiple family and twin studies have shown that ADHD is a highly heritable disorder, with heritability estimates of around 0.7 [55-57]. In addition, ADHD often occurs with many different psychiatric and physical co-morbidities, and these relationships are partly based on common genetic pathways [58, 59]. Adoption studies seem to support the heritability effect [60]. Data from the English and Romanian Adoptees study showed that long-term early deprivation in particular is associated with persistently higher inattention and hyperactivity scores, and has deleterious long-term effects on well-being that seem insusceptible to years of nurturing and support in adoptive families [61]. ADHD has its onset in childhood, a period in which children develop rapidly [62]. For a long time, explanations of behavioural symptoms of ADHD have been based around simple causal models of single, common core dysfunctions. Nowadays, the notion that there are multiple neurodevelopmental pathways - influenced by environmental factors - is commonly accepted [63]. Various research findings have indicated that almost all environmental insults associated with physical or psychiatric illness occur in utero or during the immediate neonatal period [64]. Many factors have been associated with ADHD, such as smoking and alcohol use during pregnancy, prematurity and low gestational birth weight, maternal stress and obesity, socioeconomic disadvantage, breastfeeding, early deprivation, and family environment/parenting [60, 65-75]. However, although several epidemiological and data linkage studies have made substantial contributions to a better understanding of the associations between, for example, prematurity and ADHD, it is still not possible to infer causality from these findings [76].

3.2 Pre-, peri and postnatal risk factors

We used The KOALA Birth Cohort Study to investigate early risk factors for ADHD. Although other cohort studies have been conducted in recent years, so far, most studies on early risk factors have been based on a retrospective assessment of these variables, which is very sensitive to recall bias. In addition, the longitudinal studies carried out often did not take confounding variables into account. The great advantage of the KOALA Birth Cohort Study is that the questionnaires were already sent to the mothers in early pregnancy. Many parent- and family characteristics were assessed at baseline level, and the child and family were followed from delivery to the present date. The risk of recall bias in this prospective study was therefore much lower. The results of the KOALA study showed associations between ADHD and several factors: prenatal maternal overweight and obesity, prenatal maternal smoking, low maternal education, and marital discord. Unfortunately, due to the study design, the psychopathology of the parents was not assessed. Therefore, the argument that these associations are partly due to the genetic preposition of the mother cannot be ruled out [57, 59, 77, 78].

It is well known that the human embryo is sensitive to cues from the environment, and its developmental plasticity has great implications for later health and well-being [79]. In addition, the risk factors maternal smoking, and maternal overweight, identified in this study, have also been shown to be related to peri- and postnatal morbidity and mortality [80, 81]. In the Netherlands, thanks to the efforts of many researchers, the government is becoming more aware that a child's brain is highly sensitive during the first 1000 days of life, counting from conception[82]. Therefore, several preventive programmes aimed at reducing pre-, peri- and postnatal morbidity and mortality, and increasing well-being later in life, have been rolled out. For example, campaigns and individual programmes aimed at smoking cessation and reducing obesity in pregnant women [83, 84]. The effect of these programmes may be even broader, as this study and other studies have demonstrated that these risk factors may also affect child behaviour. The continuation and expansion of government and preventive programmes aimed at combating the tobacco industry and supporting individuals to quit smoking remains crucial. For maternal obesity and overweight, preventative health programmes are increasingly being set up, often in collaboration with municipalities. However, there are still many opportunities for the Dutch government to prevent overweight, for example through introducing a sugar tax, lowering the costs of healthy food, and combating poverty. With regard to the association between ADHD and marital discord, or a low educational level of the mother, solutions must be found regarding the early identification of - and provision of support to - these mothers and families. The Netherlands has a strong preventive healthcare system, and youth health care already plays an important role. In addition, other health professionals such as midwives, gynaecologists, paediatricians and GPs must take responsibility, and look beyond just physical illness and health. In South Limburg, midwives, gynaecologists, maternity care, youth health care, and paediatricians already collaborate to identify vulnerable families during pregnancy, in order to offer the appropriate support. It is important to involve the families concerned to offer tailor-made solutions.

3.3 Screen time and sleep

Many cross-sectional studies have found a relationship between recreational screen time and (symptoms related to) ADHD, and between total sleep duration and ADHD. However, the question remains as to whether these relationships are causal, and there is a need for more longitudinal data. Therefore, we examined the longitudinal association between recreational screen time and total sleep duration at the ages of 2, 4 and 6 years, and ADHD at the age of 8 years in the KOALA Birth Cohort Study. In contrast to many cross-sectional studies, no association was found between both recreational screen time and ADHD, or between total sleep duration and ADHD [85-88]. These results provide important new insights. Although no longitudinal associations were found between these factors and ADHD, both screen time and sleep duration were associated with externalizing behavioural characteristics at the age of 2 in the cross-sectional analysis. This is in accordance with other studies with cross sectional study designs, using symptoms related to ADHD instead of an ADHD diagnosis as outcome variable [86-89]. However, in our longitudinal study, the associations found between both screen time and sleep duration and

externalizing symptoms at the age of 2 years were not followed by and confirmed with an actual ADHD diagnosis at 8 years of age. These results show that it is important to include questions about hours of screen time and sleep when evaluating externalizing, overactive or inattention symptoms, and to integrate environmental factors into a differential diagnosis before diagnosing ADHD. Questions about total sleep duration sleep and recreational screen time should be a standard part of history taking, and must be part of a differential diagnosis.

3.4 General parenting

Lastly, we analysed the cross-sectional association between general parenting and ADHD at the age of 8 years in the Koala Birth Cohort Study. Parents with a child with ADHD scored significantly lower on the higher-order construct Nurturance/Structure. This construct shows much similarity with an authoritative or warm parenting style, which has also been found to be negatively associated with ADHD in previous studies [90-92]. This association may be related to genetic preposition of the parent, a mutual influence of parental- and child behaviour, or a combination of both. In contrast to our predictions, no differences were found between boys and girls, which may partly be due to the fact that we studied a group who had already been diagnosed with ADHD. Addressing parenting practices will be challenging, as these practices influence child ADHD via within child mechanisms and are influenced by many other social factors as well as the pheno/genotype of the parents. Despite the fact that this study was only descriptive in nature, demonstrating an association between ADHD and lower parental scores on the construct Nurturance/Structure suggests that parent training and support may be a helpful part of treatment for childhood ADHD [93].

4. INTERPRETATION OF AHDH SYMPTOMS

Although this thesis does not include a study that focused on the professional interpretation of ADHD symptoms, this is an important aspect of the diagnostic process to consider. Many of the studies in this thesis used clinically assessed, or parent-reported ADHD as an outcome measure. Of course, this has limitations. However, research using an ADHD diagnosis as the outcome variable rather than scores from questionnaires is an attempt to integrate the impairment criterion of the DSM-IV and 5 [1-3]. Application of the impairment criterion can have enormous consequences for research into risk factors associated with ADHD [14, 15]. Almost all longitudinal research into the relationship between screen time and ADHD has been done using behavioural characteristics (measured using screening lists) as the primary outcome [94, 95]. As mentioned earlier, although the higher scores on the overactive subscale of the CBCL/2-3 at age 2 were associated with ADHD at age 8, screen time and sleep at age 2 were only associated with higher externalizing scores. This externalizing scale was not associated with ADHD. Having more screen time and less sleep only seemed to have a direct behavioural effect. This emphasizes how important it is not to draw conclusions based only on questionnaire results.

Chapter two showed that there were significant discrepancies between fathers, mothers and teachers with respect to the scores on several questionnaires, a finding which is consistent with large studies on this topic [33]. Variation in questionnaire scores may also be due to various other causes. For example, sometimes the same ADHD screening lists are used for boys and girls, even though it is well known that gender affects symptom presentation [40, 96, 97]. It is also important to realize that ADHD is very often associated with co-morbidity, and some questionnaires do not differentiate between the origin of symptoms. It is appropriate to comment here on two important limitations in some of the research

presented in this thesis. As a result of the use of an existing birth cohort, some important data were missing; some chapters did not measure psychiatric co-morbidity, which may have affected our results. In addition, the lack of family history taking may also have influenced results, given the high degree of inheritance of ADHD.

5. CHALLENGES, OPPORTUNITIES AND FUTURE PERSPECTIVE

5.1 Challenges and opportunities

Before a child is classified as having attention-deficit/hyperactivity disorder, there are many potential pitfalls; symptoms may be misinterpreted by the family of the child, teachers, and/or the (health) care system. Like any other chronic disease, ADHD has more than one cause, and most risk factors have more than one pathological effect [98]. Assessing a child with symptoms related to ADHD therefore always requires more than knowledge of the behavioural characteristics alone.

The premise of the transformation, as included in the new Youth Act, is that care must match the needs of the child and family, and not be determined solely by the diagnosis of the child. In addition, care must be centred around the child and the family as much as possible, and preferably executed by primary care or community care workers. Since the transformation, paediatricians seem less involved when the developmental problems of a child are related to inattention and / or hyperactivity (expert opinion). This poses three potential risks. First, evaluation of children with diverse developmental problems is often performed by paediatricians. Due to the fact that ADHD care is no longer provided by hospitals, diagnosis may be delayed, causing a delay in appropriate care and missed opportunities for early intervention. Second, when children are only seen by psychologists, psychiatrists and other (health) care workers, attention given to somatic symptoms may be too limited. Third, if paediatricians are only involved in the treatment of ADHD with medication, and no longer involved during the diagnostic process, there is a risk of misinterpretation of symptoms and over-medication. Both the first and third problem can be addressed by training paediatricians, and by paediatricians working in multidisciplinary teams together with, amongst others, child and youth psychiatrists and psychologists in- and outside hospitals. Furthermore, (mandatory) internships in youth care, or child & youth psychiatry, could become part of the paediatric traineeship. Participation in exchanges with trainees in child & youth psychiatry will help to stimulate interdisciplinary thinking and, as an additional benefit, child & youth psychiatrists may also become more comfortable with physical examination. The second risk (limited attention for somatic problems) can be reduced by always involving a doctor in the evaluation of a child with ADHD symptoms. Fortunately, the Netherlands has a well-functioning preventive youth healthcare system, and all children are tested for hearing or visual problems, growth, health, and development. However, other physical problems that are known to be associated with ADHD should also be assessed by, for example, a GP, or a paediatrician working between primary and secondary care.

It is worthwhile to briefly zoom in on schools. Before the introduction of the Youth Act in 2015, it was hypothesized that children might be diagnosed with ADHD in order to receive extra support at school. Before 2014, support as school was funded by a so called 'backpack' (called in Dutch: rugzakje), which was only awarded to schools if a child had an ADHD diagnosis, confirmed by healthcare professionals. The findings presented in this thesis underline these thoughts, as less than half of the children in Chapter 2 received special support at school before referral. Slightly prior to the introduction of the Youth Act (2015), a new act for children in need of extra support at school was introduced in 2014 (the Inclusive Education Act) [99-100]. According to this act, schools can also claim extra funding for a child, even

when the child has no diagnosis, and use this money for early intervention to prevent growing into deficit. However, going down this route could also cause a delay in referral. Training teachers about the multivariable origin of inattention and/or hyperactivity symptoms, and the various ways in which these children can be supported, remains necessary. One way of offering teachers extra support would be to make it easier for them to consult with various professionals (depending on the problems the child is experiencing).

Re-establishing the association between several early risk factors and ADHD reiterates the importance of existing Dutch preventative programmes. These include programmes such as Smoke Free Start (called in Dutch: Rookvrije Start and Rook Vrije Generatie), whose aim is to make sure that no child is exposed to cigarette smoke from conception onwards, Top Mums (in Dutch: Top Mama), focusing on healthy motherhood, and Solid Start: the action programme (in Dutch; Kansrijke start: het actieprogramma), aimed, among other things, at the early detection of psychosocial risk factors [83, 84]. The effects of these programmes may be even more extensive, as they may provide secondary health benefits for children with disorders like ADHD. Solid start, in particular, offers possibilities for early intervention. This is an action programme in which the government, municipalities, professionals involved in maternity and youth health care services, and other (health) care professionals from both the medical and social domains join forces to offer children an equal chance. This provides an opportunity to mediate the reciprocal influence of the child's early (social) environment and behaviour.

Several studies presented in this thesis showed an association between factors such as low maternal education, marital problems or divorce and ADHD. Children with ADHD often grow up with more adverse childhood experiences (ACE), but it is unknown whether addressing these ACEs as early as possible will yield health benefits with regard to ADHD [101]. However, it is in the best interest of every child, and therefore an obligation not only for social paediatricians but for every professional, to be attentive to potential ACEs when a child presents with inattention and/or hyperactivity.

5.2 Future perspective

Although ADHD is a neurodevelopmental disorder, both its assessment and treatment are linked to environmental, behavioural and social factors and their interactions. Individual behaviour reciprocally changes both biological and social circumstances. Therefore, it is still a major challenge to determine whether symptoms of inattention and/or hyperactivity warrant an ADHD diagnosis, are caused by something else like too much screen time, or represent a variation within the normal range. Knowledge of the normal development of a child is essential for the early recognition of possible neurodevelopmental disorders. It is therefore necessary that different (health) care domains, schools and parents work together. Care for children with ADHD should be multidisciplinary, personalized, and slide over the following domains; control, especially for difficult behavioural problems in highly specialized clinics; cure, if necessary through the use of medication by GPs, child & youth psychiatrists, paediatricians, and treatment of somatic problems by GPs or paediatricians; care, provided by community teams, youth care, schools and other professionals in primary care; prevention, through the use of proper education programmes for teachers, screening of vision and hearing, early intervention by youth health care and youth care services, and secondary prevention through programmes like Solid Start, and for example by creating flexible multidisciplinary consultative networks.

Despite the initial scepticism regarding the transition and transformation of youth care among many health care workers, there have been positive developments, and the control-cure-care-prevent principle as outlined above seems to be increasingly applied. However, ignorance of the opportunities available and a wish to 'stick with what you known', financially conflicting interests, and certain laws

and regulations often interfere with extensive collaboration. The increase in demand for youth care will probably not decrease simply by supporting and treating more children in primary care, but rather by careful triage, early detection of potential risk factors and (secondary) prevention. By deploying professionals who are used to interdisciplinary care, and aware of variation in the development of children, more personalized care can be offered, and growing into deficit can perhaps be delayed or prevented.

Before real solutions can be implemented in clinical practice, more research is necessary. First, qualitative research into referral pathways, and the reasons behind choices concerning referral to different levels of care, is important. The same applies to the diagnostic process after referral; qualitative research into the use of questionnaires, diagnostic interviews and expensive tests can provide opportunities for improvement. Additionally, it is important to assess the level of knowledge and consider the role of GPs and primary care teams in relation to ADHD. Finally, new cohort studies must be carried out, starting during pregnancy. These should take into account the new programmes aimed at preventing environmental insults, in order to evaluate the many different possible direct and indirect effects of these programmes on both physical and psychosocial problems. These cohort studies could also evaluate associations between (early) childhood behaviour and the longitudinal effects on general parenting, perhaps in combination with an intervention study aimed at supporting parents. It is also important to evaluate whether the healthcare professionals involved during pregnancy are able to recognize environmental vulnerabilities, and to identify any potential barriers to discussing these vulnerabilities.

Finally, it is important to integrate biomedical, psychological and social care for children and their families. As a result of the transition and transformation of youth care, a (partial) separation of youth care and healthcare has arisen. Subsequently, biomedical factors might be overlooked, and multidimensional thinking reduced. By investing resources to allow a wide variety of (healthcare) professionals and community workers to talk and collaborate with each other, professionals from different disciplines can learn to understand each other - and their capabilities and limitations - better. In this way, expertise can be shared across various institutions with a mutual focus on the well-being and optimal care of children.

REFERENCES

1. American psychiatric Association, APA. Diagnostic and Statistical Manual of Mental Disorders (DSM IV-TR). 4th edition, text revised ed. Washington, DC2000.
2. American psychiatric Association, APA. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Arlington, VA2013.
3. American psychiatric Association, APA. DSM-IV: Diagnostic and Statistical Manual of Mental Disorders. American Psychiatric Press; 1994.
4. Thapar A, Cooper M. Attention deficit hyperactivity disorder. *Lancet.* Mar 2016;387(10024):1240-50.
5. Rutter M. Achievements and challenges in the biology of environmental effects. *Proc Natl Acad Sci U S A.* Oct 2012;109 Suppl 2:17149-53.
6. Barkley RA, Murphy KR. Attention-Deficit Hyperactivity Disorder: A Clinical Workbook. third edition ed: Guilford Press; 2006.
7. De Los Reyes A, Augenstein TM, Wang M, et al. The validity of the multi-informant approach to assessing child and adolescent mental health. *Psychol Bull.* Jul 2015;141(4):858-900.
8. Weissenberger S, Ptacek R, Klicperova-Baker M, et al. ADHD, Lifestyles and Comorbidities: A Call for an Holistic Perspective - from Medical to Societal Intervening Factors. *Front Psychol.* 2017;8:454.
9. ADHD: medicatie en maatschappij . [ADHD: medication and society] (2014). Retrieved from: https://www.gezondheidsraad.nl/documenten/adviezen/2014/07/03/adhd-medicatie-en-maatschappij
10. Faraone SV, Sergeant J, Gillberg C, Biederman J. The worldwide prevalence of ADHD: is it an American condition? *World Psychiatry.* Jun 2003;2(2):104-13.
11. Rescorla L, Ivanova MY, Achenbach TM, et al. International epidemiology of child and adolescent psychopathology ii: integration and applications of dimensional findings from 44 societies. *J Am Acad Child Adolesc Psychiatry.* Dec 2012;51(12):1273-1283.e8.
12. Coghill D, Seth S. Do the diagnostic criteria for ADHD need to change? Comments on the preliminary proposals of the DSM-5 ADHD and Disruptive Behavior Disorders Committee. *Eur Child Adolesc Psychiatry.* Feb 2011;20(2):75-81.
13. Coghill D, Sonuga-Barke EJ. Annual research review: categories versus dimensions in the classification and conceptualisation of child and adolescent mental disorders--implications of recent empirical study. *J Child Psychol Psychiatry.* May 2012;53(5):469-89.
14. Gathje RA, Lewandowski LJ, Gordon M. The role of impairment in the diagnosis of ADHD. *J Atten Disord.* Mar 2008;11(5):529-37.
15. Gordon M, Antshel K, Faraone S, et al. Symptoms versus impairment: the case for respecting DSM-IV's Criterion D. *J Atten Disord.* Feb 2006;9(3):465-75.
16. Hoekstra PJ, Dietrich A. Attention-deficit/hyperactivity disorder: seeking the right balance between over- and undertreatment. *Eur Child Adolesc Psychiatry.* Aug 2014;23(8):623-5. doi:10.1007/s00787-014-0594-z
17. Balázs J, Keresztény A. Subthreshold attention deficit hyperactivity in children and adolescents: a systematic review. *Eur Child Adolesc Psychiatry.* Jun 2014;23(6):393-408.
18. Coon ER, Quinonez RA, Moyer VA, Schroeder AR. Overdiagnosis: how our compulsion for diagnosis may be harming children. *Pediatrics.* Nov 2014;134(5):1013-23.
19. Batstra L. *Hoe voorkom je ADHD? Door de diagnose niet te stellen* [How to prevent ADHD? By not making the diagnosis]. Nieuwezijds B.V.; 2012:176 pages.
20. Elder TE. The importance of relative standards in ADHD diagnoses: evidence based on exact birth dates. *J Health Econ.* Sep 2010;29(5):641-56.
21. Morrow RL, Garland EJ, Wright JM, Maclure M, Taylor S, Dormuth CR. Influence of relative age on diagnosis and treatment of attention-deficit/hyperactivity disorder in children. *CMAJ.* Apr 2012;184(7):755-62.
22. Frances A, Batstra L. Why so many epidemics of childhood mental disorder? *J Dev Behav Pediatr.* May 2013;34(4):291-2.
23. Hunt TKA, Slack KS, Berger LM. Adverse childhood experiences and behavioral problems in middle childhood. *Child Abuse Negl.* 05 2017;67:391-402.
24. Sayal K, Prasad V, Daley D, Ford T, Coghill D. ADHD in children and young people: prevalence, care pathways, and service provision. *Lancet Psychiatry.* Feb 2018;5(2):175-186.
25. Taylor E. Developmental neuropsychopathology of attention deficit and impulsiveness. *Dev Psychopathol.* 1999;11(3):607-28.
26. Taylor E, Chadwick O, Heptinstall E, Danckaerts M. Hyperactivity and conduct problems as risk factors for adolescent development. *J Am Acad Child Adolesc Psychiatry.* Sep 1996;35(9):1213-26.
27. Shaw M, Hodgkins P, Caci H, et al. A systematic review and analysis of long-term outcomes in attention deficit hyperactivity disorder: effects of treatment and non-treatment. *BMC Med.* Sep 2012;10:99.
28. Buitelaar JK. Discussies over aandacht tekort-hyperactiviteitstoornis (ADHD): feiten, meningen en emoties [Discussion about attention deficit hyperactive disorder (ADHD): facts, opinions and emotions]. *Nederlands tijdschrift voor geneeskunde* 2001. p. 1485-1489.
29. Graaf de R, Ten Have M, Dorsselaer S. *De psychische gezondheid van de Nederlandse bevolking. NEMESIS-2: Opzet en eerste resultaten* [The mental health of the Dutch population. NEMESIS-2: Design and first results]. Utrecht, The Netherlands: Trimbos Instutute; 2010.
30. Levelink B, Feron FJM, Dompeling E, van Zeben-van de Aa DMCB. Children With ADHD Symptoms: Who Can Do Without Specialized Mental Health Care? *J Atten Disord.* 01 2020;24(1):104-112.
31. Achenbach, M. T, Rescorla L. Manual for the ASEBA school-age forms & profiles. An integrated system of multi-informant assessment. 2001.
32. Efstratopoulou M, Simons J, Janssen R. Concordance among physical educators', teachers', and parents' perceptions of attention problems in children. *J Atten Disord.* Jul 2013;17(5):437-43.
33. Rescorla LA, Bochicchio L, Achenbach TM, et al. Parent-teacher agreement on children's problems in 21 societies. *J Clin Child Adolesc Psychol.* 2014;43(4):627-42.
34. Korsch F, Petermann F. Agreement between parents and teachers on preschool children's behavior in a clinical sample with externalizing behavioral problems. *Child Psychiatry Hum Dev.* Oct 2014;45(5):617-27.
35. Sayal K, Goodman R, Ford T. Barriers to the identification of children with attention deficit/hyperactivity disorder. *J Child Psychol Psychiatry.* Jul 2006;47(7):744-50.
36. Tatlow-Golden M, Prihodova L, Gavin B, Cullen W, McNicholas F. What do general practitioners know about ADHD? Attitudes and knowledge among first-contact gatekeepers: systematic narrative review. *BMC Fam Pract.* 09 2016;17(1):129.
37. Shaw K, Wagner I, Eastwood H, Mitchell G. A qualitative study of Australian GPs' attitudes and practices in the diagnosis and management of attention-deficit/hyperactivity disorder (ADHD). *Fam Pract.* Apr 2003;20(2):129-34.
38. Ghanizadeh A, Zarei N. Are GPs adequately equipped with the knowledge for educating and counseling of families with ADHD children? *BMC Fam Pract.* Jan 2010;11:5.
39. Sayal K, Mills J, White K, Merrell C, Tymms P. Predictors of and barriers to service use for children at risk of ADHD: longitudinal study. *Eur Child Adolesc Psychiatry.* May 2015;24(5):545-52.

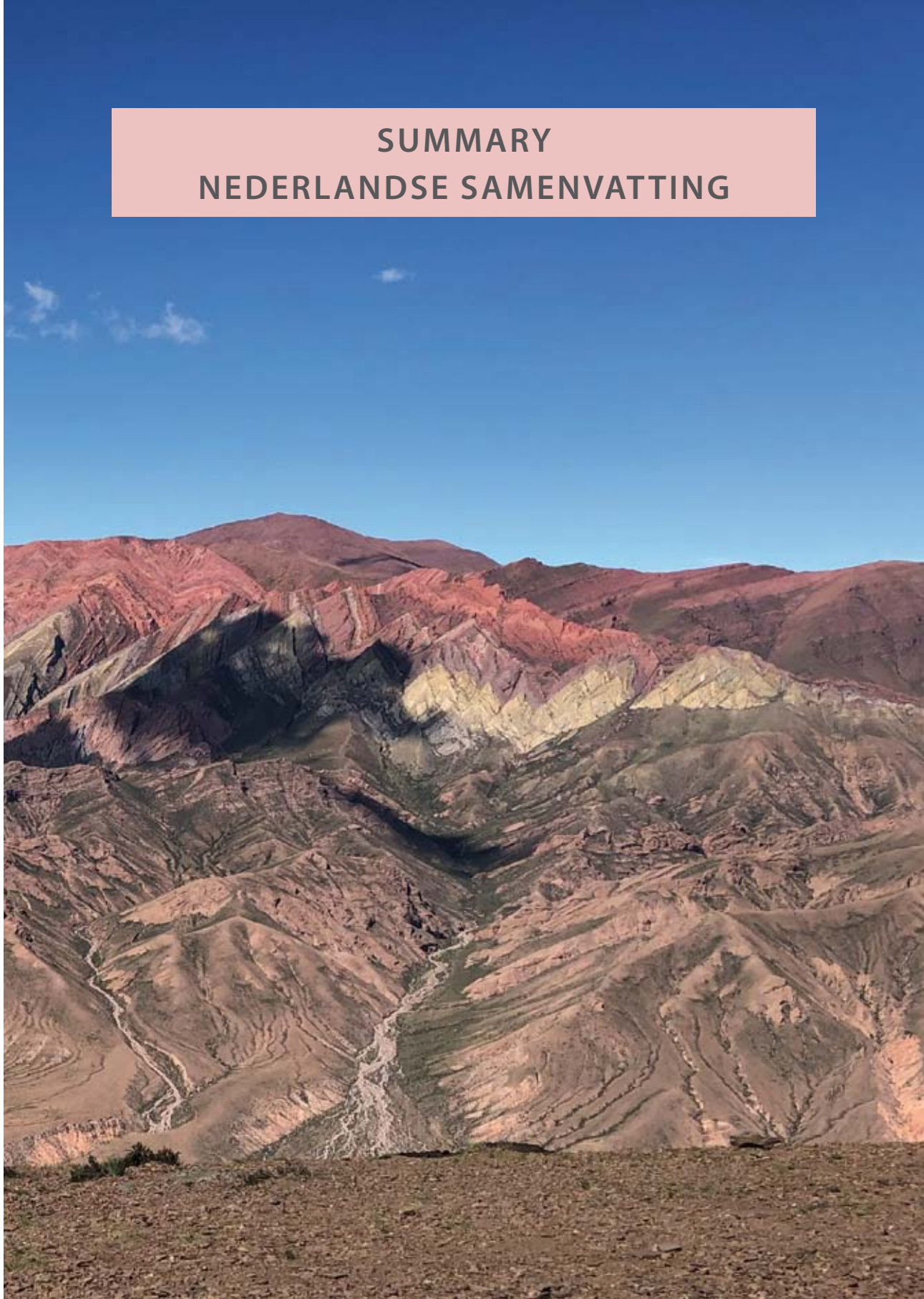
40. Biederman J, Mick E, Faraone SV, et al. Influence of gender on attention deficit hyperactivity disorder in children referred to a psychiatric clinic. *Am J Psychiatry.* Jan 2002;159(1):36-42.
41. Wessels L, Groenman A, Serra M, van den Hoofdakker B, Hoekstra P. Jeugdhulp voor kinderen met gedragsproblemen: Hoe staat de hulp ervoor sinds de transitie? [Youthcare for children with behavioural problemms: how is youthcare doing since the transition?] *Kind en Adolescent Praktijk* 2019. p. 22-29.
42. von Gontard A, Equit M. Comorbidity of ADHD and incontinence in children. *Eur Child Adolesc Psychiatry.* Feb 2015;24(2):127-40.
43. Jameson ND, Sheppard BK, Lateef TM, Vande Voort JL, He JP, Merikangas KR. Medical Comorbidity of Attention-Deficit/Hyperactivity Disorder in US Adolescents. *J Child Neurol.* 10 2016;31(11):1282-9.
44. Mogensen N, Larsson H, Lundholm C, Almqvist C. Association between childhood asthma and ADHD symptoms in adolescence--a prospective population-based twin study. *Allergy.* Sep 2011;66(9):1224-30.
45. Okur M, Ruzgar H, Erbey F, Kaya A. The evaluation of children with monosymptomatic nocturnal enuresis for attention deficit and hyperactivity disorder. *Int J Psychiatry Clin Pract.* Sep 2012;16(3):229-32.
46. Muskens JB, Velders FP, Staal WG. Medical comorbidities in children and adolescents with autism spectrum disorders and attention deficit hyperactivity disorders: a systematic review. *Eur Child Adolesc Psychiatry.* Sep 2017;26(9):1093-1103.
47. Adesman AR, Altshuler LA, Lipkin PH, Walco GA. Otitis media in children with learning disabilities and in children with attention deficit disorder with hyperactivity. *Pediatrics.* Mar 1990;85(3 Pt 2):442-6.
48. Bailly D, Dechoulydelenclave MB, Lauwerier L. Hearing impairment and psychopathological disorders in children and adolescents. Review of the recent literature. *Encephale.* 2003 Jul-Aug 2003;29(4 Pt 1):329-37.
49. van Avendonk MJ, Hassink-Franke LJ, Stijntjes F, Wiersma T, Burgers JS. [Summary of the Dutch College of General Practitioners' (NHG) practice guideline 'ADHD in children']. *Ned Tijdschr Geneeskd.* 2015;159:A8395.
50. Richtlijnontwikkeling LSM. *Multidisciplinaire Richtlijn voor diagnostiek en behandeling van ADHD bij kinderen en jeugdigen* [Multidisciplinar Guideline for diagnosis and management of ADHD in children and adolescents]. Trimbos instituut, Utrecht2005.
51. Chan E, Hopkins MR, Perrin JM, Herrerias C, Homer CJ. Diagnostic practices for attention deficit hyperactivity disorder: a national survey of primary care physicians. *Ambul Pediatr.* 2005 Jul-Aug 2005;5(4):201-8.
52. Rushton JL, Fant KE, Clark SJ. Use of practice guidelines in the primary care of children with attention-deficit/hyperactivity disorder. *Pediatrics.* Jul 2004;114(1):e23-8.
53. Wolraich ML, Bard DE, Stein MT, Rushton JL, O'Connor KG. Pediatricians' attitudes and practices on ADHD before and after the development of ADHD pediatric practice guidelines. *J Atten Disord.* May 2010;13(6):563-72.
54. Levelink B, Walraven L, Dompeling E, Feron FJM, van Zeben-van der Aa DMCB. Guideline use among different healthcare professionals in diagnosing attention deficit hyperactivity disorder in Dutch children; who cares? *BMC Psychol.* Jul 2019;7(1):43.
55. Faraone SV, Perlis RH, Doyle AE, et al. Molecular genetics of attention-deficit/hyperactivity disorder. *Biol Psychiatry.* Jun 2005;57(11):1313-23.

56. Faraone SV, Larsson H. Genetics of attention deficit hyperactivity disorder. *Mol Psychiatry.* 04 2019;24(4):562-575.
57. Demontis D, Walters RK, Martin J, et al. Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. *Nat Genet.* 01 2019;51(1):63-75.
58. Tistarelli N, Fagnani C, Troianiello M, Stazi MA, Adriani W. The nature and nurture of ADHD and its comorbidities: A narrative review on twin studies. *Neurosci Biobehav Rev.* 02 2020;109:63-77.
59. Martins-Silva T, Vaz JDS, Hutz MH, et al. Assessing causality in the association between attention-deficit/hyperactivity disorder and obesity: a Mendelian randomization study. *Int J Obes (Lond).* Apr 2019;doi:10.1038/s41366-019-0346-8
60. Sprich S, Biederman J, Crawford MH, Mundy E, Faraone SV. Adoptive and biological families of children and adolescents with ADHD. *J Am Acad Child Adolesc Psychiatry.* Nov 2000;39(11):1432-7.
61. Sonuga-Barke EJS, Kennedy M, Kumsta R, et al. Child-to-adult neurodevelopmental and mental health trajectories after early life deprivation: the young adult follow-up of the longitudinal English and Romanian Adoptees study. *Lancet.* 04 2017;389(10078):1539-1548.
62. Kessler RC, Amminger GP, Aguilar-Gaxiola S, Alonso J, Lee S, Ustün TB. Age of onset of mental disorders: a review of recent literature. *Curr Opin Psychiatry.* Jul 2007;20(4):359-64.
63. Sonuga-Barke EJ. Causal models of attention-deficit/hyperactivity disorder: from common simple deficits to multiple developmental pathways. *Biol Psychiatry.* Jun 2005;57(11):1231-8.
64. Mill J, Petronis A. Pre- and peri-natal environmental risks for attention-deficit hyperactivity disorder (ADHD): the potential role of epigenetic processes in mediating susceptibility. *J Child Psychol Psychiatry.* Oct 2008;49(10):1020-30.
65. Gard AM, Owens EB, Hinshaw SP. Prenatal Smoke Exposure Predicts Hyperactive/Impulsive but Not Inattentive ADHD Symptoms in Adolescent and Young Adult Girls. *Infant Child Dev.* 2016 Jul-Aug 2016;25(4):339-351.
66. Gustafsson P, Källén K. Perinatal, maternal, and fetal characteristics of children diagnosed with attention-deficit-hyperactivity disorder: results from a population-based study utilizing the Swedish Medical Birth Register. *Dev Med Child Neurol.* Mar 2011;53(3):263-8.
67. Okano L, Ji Y, Riley AW, Wang X. Maternal psychosocial stress and children's ADHD diagnosis: a prospective birth cohort study. *J Psychosom Obstet Gynaecol.* 09 2019;40(3):217-225.
68. Roigé-Castellví J, Murphy M, Hernández-Martínez C, et al. The effect of prenatal smoke exposure on child neuropsychological function: a prospective mother-child cohort study. *J Reprod Infant Psychol.* Feb 2020;38(1):25-37.
69. Roigé-Castellví J, Morales-Hidalgo P, Voltas N, Hernández-Martínez C, van Ginkel G, Canals J. Prenatal and perinatal factors associated with ADHD risk in schoolchildren: EPINED epidemiological study. *Eur Child Adolesc Psychiatry.* Apr 2020;doi:10.1007/s00787-020-01519-2
70. Russell G, Ford T, Rosenberg R, Kelly S. The association of attention deficit hyperactivity disorder with socioeconomic disadvantage: alternative explanations and evidence. *J Child Psychol Psychiatry.* May 2014;55(5):436-45.
71. Stadler DD, Musser ED, Holton KF, Shannon J, Nigg JT. Recalled Initiation and Duration of Maternal Breastfeeding Among Children with and Without ADHD in a Well Characterized Case-Control Sample. *J Abnorm Child Psychol.* Feb 2016;44(2):347-55.
72. Weile LKK, Wu C, Hegaard HK, Kesmodel US, Henriksen TB, Nohr EA. Alcohol Intake in Early Pregnancy and Risk of Attention-Deficit/Hyperactivity Disorder in Children Up to 19 Years of Age: A Cohort Study. *Alcohol Clin Exp Res.* Jan 2020;44(1):168-177.

73. Pressman LJ, Loo SK, Carpenter EM, et al. Relationship of family environment and parental psychiatric diagnosis to impairment in ADHD. *J Am Acad Child Adolesc Psychiatry.* Mar 2006;45(3):346-354.
74. Thapar A, Cooper M, Eyre O, Langley K. What have we learnt about the causes of ADHD? *J Child Psychol Psychiatry.* Jan 2013;54(1):3-16.
75. Silva D, Colvin L, Hagemann E, Bower C. Environmental risk factors by gender associated with attention-deficit/hyperactivity disorder. *Pediatrics.* Jan 2014;133(1):e14-22.
76. Sciberras E, Mulraney M, Silva D, Coghill D. Prenatal Risk Factors and the Etiology of ADHD-Review of Existing Evidence. *Curr Psychiatry Rep.* Jan 2017;19(1):1.
77. Clifton EAD, Perry JRB, Imamura F, et al. Genome-wide association study for risk taking propensity indicates shared pathways with body mass index. *Commun Biol.* 2018;1:36.
78. Strawbridge RJ, Ward J, Cullen B, et al. Genome-wide analysis of self-reported risk-taking behaviour and cross-disorder genetic correlations in the UK Biobank cohort. *Transl Psychiatry.* 02 2018;8(1):39.
79. Bateson P, Barker D, Clutton-Brock T, et al. Developmental plasticity and human health. *Nature.* Jul 2004;430(6998):419-21.
80. Heslehurst N, Simpson H, Ells LJ, et al. The impact of maternal BMI status on pregnancy outcomes with immediate short-term obstetric resource implications: a meta-analysis. *Obes Rev.* Nov 2008;9(6):635-83.
81. Marufu TC, Ahankari A, Coleman T, Lewis S. Maternal smoking and the risk of still birth: systematic review and meta-analysis. *BMC Public Health.* Mar 2015;15:239.
82. Roseboom T. De eerste 1000 dagen. *Het fundamentele belang van een goed begin vanuit biologisch, medisch en maatschappelijk perspectief.* first ed. Uitgeverij de Tijdstroom; 2018.
83. Timmermans YEG, van de Kant KDG, Reijnders D, et al. Towards Prepared mums (TOP-mums) for a healthy start, a lifestyle intervention for women with overweight and a child wish: study protocol for a randomised controlled trial in the Netherlands. *BMJ Open.* 11 2019;9(11):e030236.
84. Taskforce Rookvrije Start [Taskforce cigarette smoke free start].Retrieved from rookvrijestart.rokeninfo.nl.
85. Levelink B, van der Vlegel M, Mommers M, et al. The Longitudinal Relationship Between Screen Time, Sleep and a Diagnosis of Attention-Deficit/Hyperactivity Disorder in Childhood. *J Atten Disord.* Sep 2020:1087054720953897. doi:10.1177/1087054720953897
86. Lingineni RK, Biswas S, Ahmad N, Jackson BE, Bae S, Singh KP. Factors associated with attention deficit/hyperactivity disorder among US children: results from a national survey. *BMC Pediatr.* May 2012;12:50.
87. Miller CJ, Marks DJ, Miller SR, et al. Brief report: Television viewing and risk for attention problems in preschool children. *J Pediatr Psychol.* May 2007;32(4):448-52.
88. van Egmond-Fröhlich AW, Weghuber D, de Zwaan M. Association of symptoms of attention-deficit/hyperactivity disorder with physical activity, media time, and food intake in children and adolescents. *PLoS One.* 2012;7(11):e49781. doi:10.1371/journal.pone.0049781
89. Christakis DA, Zimmerman FJ, DiGiuseppe DL, McCarty CA. Early television exposure and subsequent attentional problems in children. *Pediatrics.* Apr 2004;113(4):708-13.
90. Demmer DH, Puccio F, Stokes MA, McGillivray JA, Hooley M. The Influence of Child Gender on the Prospective Relationships between Parenting and Child ADHD. *J Abnorm Child Psychol.* 01 2018;46(1):113-125.
91. Ellis B, Nigg J. Parenting practices and attention-deficit/hyperactivity disorder: new findings suggest partial specificity of effects. *J Am Acad Child Adolesc Psychiatry.* Feb 2009;48(2):146-54.

92. Tripp G, Schaughency EA, Langlands R, Mouat K. Family interactions in children with and without ADHD. *Journal of Child and Family Studies* 2007. p. 385-400.
93. Tarver J, Daley D, Sayal K. Beyond symptom control for attention-deficit hyperactivity disorder (ADHD): what can parents do to improve outcomes? *Child Care Health Dev.* Jan 2015;41(1):1-14.
94. Ra CK, Cho J, Stone MD, et al. Association of Digital Media Use With Subsequent Symptoms of Attention-Deficit/Hyperactivity Disorder Among Adolescents. *JAMA.* 07 2018;320(3):255-263.
95. Tamana SK, Ezeugwu V, Chikuma J, et al. Screen-time is associated with inattention problems in preschoolers: Results from the CHILD birth cohort study. *PLoS One.* 2019;14(4):e0213995. doi:10.1371/journal.pone.0213995
96. Gershon J. A meta-analytic review of gender differences in ADHD. *J Atten Disord.* Jan 2002;5(3):143-54.
97. Mowlem F, Agnew-Blais J, Taylor E, Asherson P. Do different factors influence whether girls versus boys meet ADHD diagnostic criteria? Sex differences among children with high ADHD symptoms. *Psychiatry Res.* 02 2019;272:765-773.
98. Costello EJ, Angold A. Developmental psychopathology and public health: past, present, and future. *Dev Psychopathol.* 2000;12(4):599-618.
99. Ministerie Volksgezondheid [Ministry of health and Sports]. Factsheet Stelselwijziging Jeugd, Jeugdwet [Change in Youth Care Law].2014. https://eacea.ec.europa.eu/national-policies/en/content/youthwiki/12-national-youth-law-netherlands
100. Wet Passend Onderwijs Rijksoverheid. [Inclusive Education Act] Retrieved from https://www.nji.nl/nl/Download-NJi/Publicatie-NJi/Children-and-youth-support-and-care-in-The-Netherlands.pdf
101. Brown NM, Brown SN, Briggs RD, Germán M, Belamarich PF, Oyeku SO. Associations Between Adverse Childhood Experiences and ADHD Diagnosis and Severity. *Acad Pediatr.* 2017 May - Jun 2017;17(4):349-355.

SUMMARY
NEDERLANDSE SAMENVATTING



SUMMARY

Both genetic and environmental factors influence the development and expression of attention-deficit/hyperactivity disorder (ADHD). A child is diagnosed with ADHD when his/her problems meet the ADHD classification, based on five criteria described in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Criterion A of the DSM-5 describes these symptoms of inattention, hyperactivity and impulsivity. Symptoms can be due to ADHD, however these behavioural symptoms can also be due to other causes, for example problems at home, many hours of screen time or short sleep duration, or specific learning problems. Criterion B emphasises that behavioural symptoms must be present before the age of twelve. Correct interpretation of this criterion requires knowledge of the normal development of a child, to differentiate between symptoms of inattention and hyperactivity which are a normal variation of a (young) child's behaviour, and symptoms that are no longer appropriate for the level of development. Criteria C and D relate to the fact that symptoms must present themselves in more than one setting, for example at home and at school, and cause significant impairment. This requires knowledge of the use and interpretation of information from multiple informants. Finally, criterion E evaluates if symptoms are not caused by psychological and psychiatric problems other than ADHD. So, professionals also need to have knowledge of other psychological and psychiatric problems. Considering all the above mentioned critaria, it is evident that correct assessment of a child with behavioural symptoms of ADHD requires knowledge of possible causes of inattention and hyperactivity, the development of children, the influence of the (social) environment, and psychopathology. Specialists, such as child and adolescent psychiatrists and psychologists, are trained to evaluate all these criteria. However, in the Netherlands many other disciplines are involved besides cild and youth psychiatrists and psychologists in the identification, diagnosis and treatment of children with ADHD, such as pediatricians, paediatricians, general practitioners and social workers from community teams. These professionals often have their own specific qualities with regard to the evaluation of symptoms of attention deficit and hyperactivity.

In 2015 youth care in the Netherlands was transformed, and youth care and specialised mental health care for children became a responsibility of the municipalities. Since then, youth care focusses on the strengths, capacities and resilience of both the parents and child. Conform the new Youth Act (2015), care should be 'demand driven', and not be based on the diagnosis of the child (for example ADHD), but on what the child and the family say they need (for example, support with personal management). Primary care should be easily accessible, and expensive second- and third-line care should only be used if necessary.

This thesis focused on the behavioural symptoms and characteristics of ADHD in relation to the transition and transformation thoughts of youth care in the Netherlands. In addition, associations between various environmental factors and ADHD were studied. Overall, results were evaluated from the perspective of social pediatricians, based on the biomedical and psychosocial model.

As the new Dutch Youth Act has the intention to reduce specialized mental health care for children with symptoms of ADHD, for **chapters 2**, characteristics of 261 children referred to a specialized ADHD clinic between September 2011 and November 2015, just before introduction of this new Youth Act, were studied. The research focused on specific factors which were decisive to refer children to specialized mental healthcare. Prior to their visit, families provided details about symptom severity, development of the child, and demographic characteristics from the family trough screening questionnaires for ADHD, and co-morbidities, and open questionnaires filled in by parents and the teacher. Many of the children

who were registered at the ADHD clinic were found not to be in need of specialized mental health care, according to the transformation ideas of the newe Dutch Youth Act. care. Over 50% of the 261 studied children could be supported or treated by primary or community care according to the criteria of the new Youth Act, and this study showed the importance to develop proper triage strategies to make the new Dutch Youth act a success. Multivariate logistic regression analysis showed that children with divorced parents or (sub)clinical scores on the Child Behavior Check List (CBCL) or the Teacher Report Form (TRF) were associated with referral to specialized care. This association was most likely explained by the high psychiatric comorbidity rates associated with ADHD, reflected in these questionnaires. Although the CBCL and TRF were statistically significant associated with referral to specialized care, these questionnaires cannot be used alone for clinical practice to differentiate between levels of care. Overall characteristics of children refereed to the ADHD-clinic were heterogeneous, and clinal decision making was necessary to differentiate between levels of care.

For **chapter 3**, data from the same group as used in chapter 2 were studied, to gain insight into associations between *symptoms* of inattention, hyperactivity and impulsivity, and somatic comorbidities. Characteristics of the 261 children aged 6-18 years, who were referred to the ADHD-clinic, showed delayed development based on parent questionnaire and history taking in 31%, abnormalities at history taking in 34%, and abnormal physical examination in 26% of the total group. Physical symptoms were diverse, and no significant differences in somatic comorbidities were found between children with ADHD (with or without comorbidity), and children who did *not* meet the criteria for an ADHD classification. This chapter showed that in order to provide well-being for children, it is important to also consider physical problems when evaluating children with (only) symptoms of inattention and/or hyperactivity. Translated to the premise of the Youth Act, this means that a physician must be involved in any assessment of a child with *symptoms* of attention deficit or hyperactivity, also in primary care. In particular, physical problems that have a multifactorial aetiology like ADHD, for example enuresis, should be evaluated.

As adherence to ADHD guidelines is important for proper evaluation of ADHD symptoms, for **chapter 4** the involvement of various healthcare professionals in diagnosing ADHD, and their use of ADHD guideline, was analysed. In the Netherlands a wide range of healthcare professionals are involved in the care for children with symptoms of ADHD. For this study, surveys were sent among others to, child & youth psychiatrists, psychologists, youth doctors, paediatricians, and GPs to evaluate their involvement in diagnosing ADHD and the use of ADHD guidelines. Only half of the respondents indicated to be involved in diagnosing ADHD (186 of the 362 respondents), including some paediatricians (18 of the 40). Despite the fact that reported ADHD guideline use was relatively low (64%), child & youth psychiatrists, psychologists and paediatricians reported high adherence with key elements of the ADHD guidelines, like gathering information from a third party (>90%) and performing a developmental history (>88%). The use of standardized interviews was low (<52%), and information from third parties was obtained in different ways, increasing the risk of variation in clinical decision-making between professionals. Very few GPs returned the survey (111/1450), and of those who did, only a few indicated to be involved in diagnosing ADHD (n=13). Because this was a quantitative study, no statements could be made about the quality of ADHD care by primary care. However, as GPs should participate in ADHD care according to the premise of the Youth Act, results showed the importance to evaluate their knowledge and involvement. Qualitative research is necessary to evaluate this in detail. Intercollegial consultative networks could be an opportunity to support GPs to give appropriate care to children with (symptoms related to) ADHD.

The second part of this thesis focused on various environmental factors which may be associated with ADHD, using data from the KOALA Birth Cohort Study. The KOALA Birth Cohort Study is an ongoing study, following more than 2500 Dutch families with a child born between 2001 and 2003, starting during pregnancy. Questionnaires were sent to parents containing a wide variety of questions concerning health, diseases, and all kind of (environmental) factors that may influence health, growth and development of a child. The environment interacts with a child's genetic disposition and the childs development. This already starts in the womb, when the unborn child is relatively protected. From birth, the role of the environment increases. **Chapter 5** focused on associations between various pre-, peri-, and post-natal factors, and an ADHD diagnosis at the age of 8-10 years. Prenatal data of 1807 parent-child pairs, included pre-pregnancy Body Mass Index (BMI) of the mother, education level of the mother, smoking, and alcohol use. Peri- and postnatal data included among others mode of birth, gestational age and birth weight, gender, initiation and duration of breast feeding, marital discord, daily routine and perceived psychosocial stress. Multivariate logistic regression analysis showed that low maternal education level, prenatal maternal overweight and obesity (BMI >25 kg/m^2), prenatal maternal smoking, male gender, marital discord, and no daily family routine were all associated with childhood ADHD. Unfortunately, data on psychiatric diagnosis off the parents were lacking due to the study design. Therefore, it could not be completely ruled out that results were partly due to genetic pathways that mediate the association between several environmental factors and ADHD. In addition, factors like low maternal education level and marital discord may enhance gene-environment interaction. Thence, results support the idea that early, low-threshold support of families with psychosocial risk factors could reduce dysfunction in children. Results also encourage initiatives aimed at early prevention of smoking, and reduction of overweight in mothers. In addition to the prevention of maternal morbidity, such preventive programs may also yield secondary health benefits for the children of these women.

Chapter 6, presents results from the longitudinal association between ADHD and the environmental factors recreational screen time (television- and computer time) and total sleep duration, using the same child-parent pairs as used for chapter 5. General estimating equation logistic regression analysis showed no longitudinal associations between hours of screen time and/or sleep duration at the age 2, 4 and 6 years and an ADHD diagnosis at the age of 8 years. However, in the cross-sectional liniair regression analysis at age 2, a small statistically significant association was found between more tv time, less sleep duration, and higher scores on externalizing behaviour measured with the Child Behavior Check List (CBCL/2-3). Thereby, these results demonstrated the importance of longitudinal research. Just like this study, other literature showed associations between screen time and sleep and behavioural characteristics of ADHD. The current results showed the importance to incorporate questions concerning screen time and sleep in history taking when evaluating a child because of symptoms of inattention and hyperactivity, in order not to confuse these behavioural characteristics with an ADHD diagnosis.

Finally, for **chapter 7**, the 1807 parent-child couples from the KOALA Birth Cohort were included to study associations between general parenting measured with the Comprehensive General Parenting Questionnaire (CGPQ), and ADHD at the age of 8 years. In addition, possible interactions with gender were evaluated. Using multivariate linear regression analysis, this descriptive study showed that ADHD was associated with significantly lower scores on the general parenting construct Nurturance/Structure. Parents scored specifically lower on two sub-constructs of the general construct Nurturance/Structure, namely Autonomy Support and Scaffolding/Consistency. Due to the mutual influence of child- and parents' behaviour, no statements about the direction of the associations found could be made. No

significant interaction between ADHD and gender was found. This may be due to the use of children with an ADHD diagnosis as a dependent variable. In contrast with other studies, the parental scores on the sub-constructs Inconsistent Discipline and Punishment did not differ between parents with or without a child with ADHD. This study provided insight in the daily practice of parenting, and gave a possible direction to support parents with children with ADHD. Parental guidance in particular did not seem to be primarily aimed at reducing ADHD symptoms in the child, but at reducing the child's dysfunction by offering him/her more support.

In the general discussion, results from the studies were combined with intentions of the transition and transformation of youth care, and Duthc preventive programs. In addition, the current role of paediatricians with regard to ADHD was discussed, as less and less paediatricians seem involved.
Given the complexity of an ADHD diagnosis, and the heterogeneity of child characteristics found in the studied group of children, it is important to carefully consider how to discriminate between the necessary level of care for each individual child. Possible solutions were discussed, such as a multidisciplinary consultative flexible network. These networks should consist of permanent partners working in primary care, who can consult specialists depending on a child's problems. Within these networks, consideration should also be given to various somatic problems associated with (symptoms related to) ADHD. However, before solutions can be implementated, further research will be necessary, for example qualitative research considering referral pathways and knowledge of primary care teams, related to ADHD. In addition, it is important to consider how to retain knowledge of pediatricians with regard to ADHD, as ADHD becomes less and less part of their job. One possibility would be exchange internships with child & youth psychiatry, to train pediatricians in the interpretation of behavior, and child and youth psychiatrists in physical examination.
The results from the studies, analysing associations between various environmental risk factors and ADHD illustrated the complex associations between environment and ADHD. Finding no longitudinal association between screen time, nor sleep and ADHD, emphasized the importance of careful history taking. The associations of pre- and perinatal risk factors such as maternal smoking, high BMI and low maternal education underlined the importance of several existing Dutch preventive programs aimed at reducing smoking, and the support of vulnerable families (Smoke Free Generation and Solid Start). Maybe these preventive programs, in addition to health gains for the mother, also provide additional health gains for the child as prevention may result in a decrease in ADHD-associated behavior and therefor prevent growing into deficit.
Overall, studies emphasized never to evaluate symptoms of inattention, hyperactivity and impulsivity from a one-dimensional level, but always incorporate bio-, psycho-, socio-, and transactional perspectives. Therefor, intensive collaboration between different healthcare domains can yield tremendous healthcare benefists. It is in the interest of all children with behavioral characteristics of ADHD to optimize collaboration between healthcare domains, and thus optimize the care for these children, and to compare the additional costs with the health benefits to be achieved.

SAMENVATTING

Zowel genetische als omgevingsfactoren beïnvloeden de ontwikkeling en expressie van attention-deficit/hyperactivity disorder (ADHD). Bij een kind wordt de diagnose ADHD gesteld wanneer zijn/haar problemen voldoen aan de ADHD-classificatie. Deze classificatie staat beschreven in de Diagnostic and Statistical Manual of Mental Disorders (DSM-5) en is gebaseerd op vijf criteria. Criterium A van de DSM-5 beschrijft de gedragsymptomen van onoplettendheid, hyperactiviteit en impulsiviteit. Deze gedragssymptomen kunnen het gevolg zijn van ADHD, maar kunnen ook andere oorzaken hebben, zoals bijvoorbeeld problemen thuis, vele uren schermtijd, slaaptekort of specifieke leerproblemen. Criterium B benadrukt dat de gedragssymptomen aanwezig moeten zijn vóór de leeftijd van twaalf jaar. Een juiste interpretatie van dit criterium vereist kennis van de normale ontwikkeling van een kind, zodat onderscheid gemaakt kan worden tussen symptomen van onoplettendheid en hyperactiviteit die een normale variatie zijn van het gedrag van een (jong) kind, en symptomen die niet langer passen bij de leeftijd en het ontwikkelingsniveau. Criteria C en D hebben betrekking op het feit dat symptomen zich in meer dan één setting moeten voordoen, bijvoorbeeld zowel thuis als op school, en daar moeten leiden tot disfunctioneren. Dit vereist kennis van het gebruik en interpretatie van informatie van meerdere informanten. Ten slotte beoordeelt criterium E of de symptomen niet kunnen worden verklaard door de aanwezigheid van andere psychologische en psychiatrische problemen dan ADHD. Professionals moeten dus ook kennis moet hebben van andere psychologisch of psychiatrische diagnoses. Bovengenoemde vijf criteria benadrukken dat een juiste beoordeling van een kind met gedragssymptomen van ADHD kennis vereist van de normale ontwikkeling van kinderen, de mogelijke oorzaken van aandachtstekort en hyperactiviteit, de invloed van de (sociale) omgeving op een kind, en de psychopathologie. Specialisten, zoals kinder- en jeugdpsychiaters en (kinder)psychologen, worden opgeleid om deze criteria te beoordelen. Echter, in Nederland zijn ook vele andere disciplines betrokken bij de signalering, diagnosestelling en behandeling van kinderen met ADHD, zoals jeugdartsen, kinderartsen, huisartsen en hulpverleners uit sociale wijkteams. Deze professionals hebben vaak hun eigen specifieke kwaliteiten ten aanzien van de evaluatie van symptomen van aandachtstekort en hyperactiviteit.
Sinds 2015 is in Nederland een nieuwe Jeugdwet van kracht, en zijn gemeenten verantwoordelijk voor de jeugdzorg en gespecialiseerde geestelijke gezondheidszorg (GGZ) voor kinderen (transitie jeugdzorg). De jeugdzorg werd getransformeerd, en sindsdien richt deze zorg zich op de sterke punten, capaciteiten en veerkracht van zowel de ouders als het kind. Conform de Jeugdwet moet de zorg vraag gestuurd zijn en niet gebaseerd op de diagnose van het kind (bijvoorbeeld ADHD), maar op wat het kind en het gezin zeggen nodig te hebben (bijvoorbeeld ondersteuning bij persoonlijke organisatie). Eerstelijns zorg moet makkelijk toegankelijk zijn en dure tweede- en derdelijns zorg moet alleen worden gebruikt wanneer dit noodzakelijk is.

Dit proefschrift richtte zich op de gedragssymptomen en kenmerken van ADHD in relatie tot de transitie en transformatiegedachten van de jeugdzorg in Nederland. Daarnaast werden associaties tussen diverse omgevingsfactoren en ADHD bestudeerd. Resultaten werden beoordeeld vanuit het perspectief van kinderartsen-sociale pediatrie, gebaseerd op het biopsychosociale model.

Omdat de nieuwe Nederlandse Jeugdwet de intentie heeft om de gespecialiseerde geestelijke gezondheidszorg voor kinderen met ADHD-symptomen af te bouwen, is voor **hoofdstuk 2** gekeken naar kenmerken van 261 kinderen die tussen september 2011 en november 2015, net voor invoering van de nieuwe Jeugdwet, verwezen werden naar een ADHD-kliniek. In de onderzoeksgroep werd bestudeerd

of specifieke factoren bepalend waren voor hulp of onderzoek door de gespecialiseerde GGZ. Voorafgaand aan hun bezoek aan de ADHD-kliniek gaven ouders/verzorgers inzicht in de ernst van de ADHD-symptomen, de ontwikkeling van het kind en demografische kenmerken van het gezin/verzorgers. Dit werd gedaan aan de hand van screeningslijsten voor ADHD en comorbiditeiten en open vragenlijsten die werden ingevuld door de ouders en de leerkracht. Veel kinderen die bij de ADHD-kliniek werden aangemeld, bleken (conform de transformatiegedachte van de nieuwe Jeugdwet) geen specialistische GGZ-hulp nodig te hebben. Ruim 50% van de 261 onderzochte kinderen zou ook ondersteund of behandeld kunnen worden door eerstelijnszorg, waarmee deze studie het belang aantoonde om goede triagestrategieën te ontwikkelen om het nieuwe Nederlandse beleid tot een succes te maken. Uit multivariate logistische regressieanalyse kwam een significante associatie naar voren tussen kinderen met gescheiden ouders of (sub) klinische scores op de Child Behaviour Check List (CBCL) of de Teacher's Report Form (TRF), en een verwijzing naar de gespecialiseerde GGZ. Deze bevinding wordt hoogstwaarschijnlijk verklaard door de sterke associatie tussen ADHD en psychiatrische comorbiditeit, wat deels weerspiegeld werd in deze vragenlijsten. Hoewel hogere scores op de CBCL en TRF statistisch significant waren geassocieerd met een verwijzing naar de GGZ, kunnen deze in de praktijk niet gebruikt worden om een volledig onderscheid te maken tussen eerstelijns zorg of gespecialiseerde zorg. De kenmerken van de kinderen uit de onderzoeksgroep waren heterogeen, en besluitvorming tussen zorgniveaus was alleen mogelijk op basis van uitvoerige anamnese.

Voor **hoofdstuk 3** werd dezelfde groep als in hoofdstuk 2 bestudeerd, om inzicht te krijgen in associaties tussen symptomen van aandachtstekort, hyperactiviteit en impulsiviteit, en somatische comorbiditeiten. In de groep van 261 kinderen, in de leeftijd van 6-18 jaar, werd op basis van de oudervragenlijst en anamnese bij 31% een vertraagde ontwikkeling gevonden, bij 34% een afwijkende somatische anamnese en bij 26% een abnormaal lichamelijk onderzoek. De lichamelijke symptomen waren divers en er werden geen significante verschillen in somatische comorbiditeit gevonden tussen kinderen met ADHD (met of zonder comorbiditeit) en kinderen die niet voldeden aan de criteria voor een ADHD-classificatie. Deze resultaten lieten zien dat het belangrijk is om zowel bij de evaluatie van kinderen met (enige) symptomen van aandachtstekort en/ of hyperactiviteit, als bij de evaluatie van kinderen met een volledige ADHD-diagnose, oog te hebben voor lichamelijke problemen. Vertaald naar het uitgangspunt van de Jeugdwet, betekent dit dat een arts bij elke beoordeling van een kind met symptomen van aandachtstekort of hyperactiviteit moet worden betrokken, ook in de eerste lijn. Hierbij moet met name aandacht zijn voor lichamelijke problemen welke net als ADHD een multifactoriële etiologie hebben, zoals bijvoorbeeld enuresis.

Omdat naleving van ADHD-richtlijnen belangrijk is voor een goede evaluatie van ADHD-symptomen, werd voor **hoofdstuk 4** de betrokkenheid van verschillende zorgprofessionals bij het diagnosticeren van ADHD en het gebruik van ADHD-richtlijnen geanalyseerd. In Nederland is een breed scala van zorgprofessionals betrokken bij de zorg voor kinderen met (symptomen van) ADHD. Voor deze studie werden enquêtes gestuurd naar kinder- en jeugdpsychiaters, psychologen, jeugdartsen, kinderartsen en huisartsen om hun betrokkenheid bij het diagnosticeren van ADHD en het gebruik van ADHD-richtlijnen te evalueren. Slechts de helft van de respondenten gaf aan betrokken te zijn bij het diagnosticeren van ADHD (186 van de 362 respondenten), waaronder enkele kinderartsen (18/40). Ondanks het feit dat het gerapporteerde gebruik van ADHD-richtlijnen relatief laag was (64%), rapporteerden kinder- en jeugdpsychiaters, psychologen en kinderartsen een hoge mate van naleving van belangrijke elementen van de ADHD-richtlijnen, zoals het verzamelen van informatie van een derde partij (>90%) en het afnemen van een ontwikkelingsanamnese (>88%). Het gebruik van gestandaardiseerde interviews was laag (< 52%) en informatie van derden werd op verschillende manieren verkregen, waardoor het risico op variatie in klinische besluitvorming tussen professionals toenam. Zeer weinig huisartsen retourneerden de enquête (111/1450), en van degenen die dat wel deden, gaven er slechts enkelen aan betrokken te zijn bij het diagnosticeren van ADHD (13/111). Omdat dit een kwantitatief onderzoek was, konden geen uitspraken worden gedaan over de kwaliteit van de ADHD-zorg door de eerste lijn. Echter, aangezien huisartsen volgens het uitgangspunt van de Jeugdwet een belangrijk aandeel in de ADHD-zorg zouden moeten krijgen, is het belangrijk om hun kennis en betrokkenheid in vervolgonderzoeken te evalueren. Intercollegiale consultatie met specialisten in de regio (bijvoorbeeld kinderpsychologen of kinder- en jeugdpsychiaters) zou huisartsen kunnen ondersteunen bij hun zorg voor kinderen met (symptomen gerelateerd aan) ADHD.

Het tweede deel van dit proefschrift, richtte zich op diverse omgevingsfactoren die mogelijk geassocieerd zijn met ADHD. Hierbij werd gebruik gemaakt van gegevens verzameld in de KOALA Birth Cohort Study. De KOALA Birth Cohort Study is een studie die meer dan 2500 Nederlandse gezinnen volgt met een kind geboren tussen 2001 en 2003, beginnend tijdens de zwangerschap. Aan ouders zijn vragenlijsten gestuurd met een grote verscheidenheid aan vragen over gezondheid, ziekten en allerlei (omgevings) factoren die de gezondheid, groei en ontwikkeling van een kind kunnen beïnvloeden. De omgeving van een kind interacteert met de genetische predispositie van het kind en zijn ontwikkeling. Dit begint al in de baarmoeder, wanneer het ongeboren kind relatief beschermd is. Vanaf de geboorte neemt de rol van de omgeving toe. **Hoofdstuk 5** richtte zich op associaties tussen verschillende pre-, peri- en postnatale factoren en een ADHD-diagnose op de leeftijd van 8-10 jaar. Prenatale gegevens van 1807 ouder-kind paren bevatte informatie over de Body Mass Index (BMI) van de moeder vóór de zwangerschap, het opleidingsniveau van de moeder, roken en alcoholgebruik. Peri- en postnatale gegevens die werden geanalyseerd waren wijze van bevallen, zwangerschapsduur en geboortegewicht, geslacht, aanvang en duur van borstvoeding, huwelijksproblemen, dagelijkse routine in het gezin en ervaren psychosociale stress. Multivariate logistische regressieanalyse toonde aan dat een laag opleidingsniveau van de moeder, prenataal overgewicht en obesitas bij de moeder (BMI> 25 kg/m^2), prenataal roken door de moeder, mannelijk geslacht, huwelijksproblemen en ontbrekende dagelijkse gezinsroutine significant geassocieerd waren met ADHD op de kinderleeftijd. Helaas werden in de KOALA studie geen gegevens over de psychiatrische diagnose van de ouders verzameld waardoor niet volledig kan worden uitgesloten dat de resultaten gedeeltelijk werden beïnvloed door genetische factoren. Daarnaast zouden factoren zoals een laag opleidingsniveau van de moeder en huwelijksproblemen de interactie tussen genen en omgeving kunnen versterken. De resultaten ondersteunden wel de hypothese dat vroege, laagdrempelige ondersteuning van gezinnen met psychosociale risicofactoren disfunctioneren bij kinderen zou kunnen verminderen. De resultaten moedigen ook initiatieven aan die gericht zijn op vroegtijdige preventie van roken en vermindering van overgewicht bij (aanstaande) moeders. Naast het voorkomen van maternale morbiditeit kunnen dergelijke preventieve programma's mogelijk ook secundaire gezondheidsvoordelen opleveren voor de kinderen van deze vrouwen.

In **hoofdstuk 6** zijn de resultaten beschreven van de longitudinale associatie tussen ADHD en de omgevingsfactoren 'recreatieve schermtijd (televisie- en computertijd) en totale slaapduur' bestudeerd in dezelfde kind-ouder paren van de KOALA studie als in hoofdstuk 5. General estimating equation logistische regressieanalyse toonde geen longitudinale associaties tussen uren schermtijd en/of slaapduur op de leeftijd van 2, 4 en 6 jaar en een ADHD-diagnose op de leeftijd van 8 jaar. Echter, de cross-sectionele

lineaire regressieanalyse op de leeftijd van 2 jaar liet wel een (kleine) statistisch significante associatie zien tussen meer tv-tijd, minder slaapduur en hogere scores voor externaliserend gedrag gemeten met de Child Behavior Check List (CBCL/ 2-3). Deze resultaten maken het belang van longitudinaal onderzoek duidelijk. Net als in dit onderzoek, laten diverse andere studies associaties zien tussen schermtijd, slaap en gedragskenmerken passend bij ADHD. De huidige resultaten toonden aan dat het belangrijk is om vragen over schermtijd en slaap in de anamnese op te nemen tijdens evaluatie van een kind met symptomen van aandachtstekort en hyperactiviteit, om deze *gedragskenmerken* niet te verwarren met een ADHD-diagnose.

Ten slotte werden in **hoofdstuk 7** mogelijke associaties tussen ADHD en opvoeding, gemeten met de Comprehensive General Parenting Questionnaire (CGPQ), bestudeerd bij de 1807 ouder-kind paren uit het KOALA Birth Cohort. Daarbij werden mogelijke interacties met het geslacht geëvalueerd. Middels multivariate lineaire regressieanalyse, toonde deze beschrijvende studie aan dat ADHD geassocieerd was met significant lagere scores op het algemene opvoedingsconstruct 'Koesteren/ Structuur', en met name lagere scores op twee subconstructen van dit algemene construct 'Koesteren/ Structuur', te weten 'Autonomie Support' en 'Ondersteuning/ Consistentie'. Doordat het gedrag van het kind en de ouders elkaar wederzijds beïnvloeden, konden geen uitspraken worden gedaan over de richting van de gevonden associaties. Er werd geen significante interactie tussen ADHD en geslacht gevonden. Dit kan zijn veroorzaakt doordat kinderen met een ADHD-diagnose als dependent variabele zijn gebruikt. In tegenstelling tot andere onderzoeken waren de scores van de ouders op de subconstructen 'Inconsistente Discipline' en 'Straf' niet verschillend tussen ouders met of zonder een kind met ADHD. De resultaten van deze studie boden inzicht in de dagelijkse praktijk van opvoeden en gaven een mogelijke richting om ouders met kinderen met ADHD te ondersteunen. Hierbij leek met name ouderbegeleiding niet primair gericht te moeten zijn op het verminderen van ADHD-symptomen bij het kind, maar op verminderen van disfunctioneren van het kind door hem/haar meer ondersteuning te bieden.

In de algemene discussie werden de resultaten van de diverse onderzoeken in dit proefschrift besproken tegen de achtergrond van de nieuwe Jeugdwet in Nederland en Nederlandse preventieprogramma's. Daarnaast werd de huidige rol van kinderartsen in relatie tot de diagnostiek en zorg voor kinderen met (een vermoeden van) ADHD geëvalueerd, aangezien steeds minder kinderartsen bij deze zorg betrokken lijken te zijn. De combinatie van de complexiteit van een ADHD-diagnose en de heterogeniteit van kind-kenmerken die in de bestudeerde groep kinderen werd gevonden, maakte duidelijk dat een zorgvuldige afweging nodig is voordat een keuze gemaakt kan worden welk zorgniveau past bij het individuele kind. Mogelijke oplossingen werden besproken, zoals de inzet van flexibele multidisciplinaire consultatieve netwerken. Deze netwerken zouden moeten bestaan uit vaste partners werkzaam in de eerste lijn, welke afhankelijk van de problemen van een kind specialisten kunnen consulteren. Binnen deze netwerken dient ook aandacht te worden besteed aan verschillende somatische problemen die samenhangen met (symptomen gerelateerd aan) ADHD. Echter, voordat oplossingen kunnen worden geïmplementeerd, is verder onderzoek nodig, zoals bijvoorbeeld kwalitatief onderzoek naar verwijsgedrag in de eerste lijn, en kennis over ADHD en mogelijke oorzaken van gedragskenmerken van ADHD. Daarnaast is het belangrijk om aandacht te besteden aan het behoud van kennis over ADHD bij kinderartsen, omdat kinderartsen steeds minder bij deze zorg betrokken zijn. Een mogelijkheid zou zijn om tijdens de opleiding arts-assistenten kindergeneeskunde en psychiatrie uit te wisselen, zodat kinderartsen de kans krijgen gedragskenmerken te leren interpreteren, en kinder- en jeugdpsychiaters meer kennis opdoen van somatisch onderzoek bij kinderen.

De studies die associaties tussen diverse omgevingsfactoren en ADHD analyseerden, illustreerden de complexiteit van deze associaties, en het bleek een uitdaging om de richting van verschillende associaties vast te stellen. Het ontbreken van een longitudinaal verband tussen schermtijd en/of slaap en ADHD op de kinderleeftijd, benadrukte het belang van longitudinaal onderzoek. Daarnaast toonde deze studie ook het belang van een zorgvuldige anamnese met vragen gericht op schermtijd en slaap, omdat externaliserend gedrag wel geassocieerd bleek met meer schermtijd en minder slaap op jonge leeftijd. De associaties tussen maternale risicofactoren zoals roken, hoog BMI en laag opleidingsniveau van de moeder en ADHD bij het kind op jonge leeftijd, onderstreepten het belang van reeds bestaande preventieve programma's in Nederland gericht op het verminderen van roken en de ondersteuning van kwetsbare gezinnen (Rookvrije Generatie en Kansrijke Start). Mogelijk dat deze preventieve programma's naast gezondheidswinst voor de moeder, ook extra gezondheidswinst voor het kind opleveren doordat preventie mogelijk afname van gedragskenmerken van ADHD kan geven en daarmee 'growing into deficit' voorkomt.

Alle studies benadrukten dat symptomen van aandachtstekort, hyperactiviteit en impulsiviteit nooit ééndimensionaal moeten worden geëvalueerd, maar dat de gedragskenmerken van ADHD altijd vanuit biomedische, psychosociale en transactionele perspectieven moeten worden beoordeeld. Intensieve samenwerking tussen verschillende domeinen binnen de gezondheidszorg kan daardoor grote gezondheidswinst opleveren. Het is in het belang van alle kinderen met gedragskenmerken van ADHD om deze samenwerking te intensiveren en daarmee de zorg voor deze kinderen te optimaliseren, en de meerkosten hiervan af te zetten tegen de te behalen gezondheidswinst.

IMPACT PARAGRAPH

IMPACT PARAGRAPH

Relevance

In 2015 youth care in the Netherlands underwent a major transition and transformation. One purpose of this transformation was to focus on what the child and family say they need, and not on a diagnosis of the child. Youth care had to become easily accessible, and care had to take place as much as possible in the community or by primary care. The first part of this thesis focused on (health)care for children with symptoms of attention-deficit/hyperactivity disorder (ADHD), just before the transition and transformation of youth care. Biomedical, and psychosocial determinants of children referred to an ADHD clinic were studied in order to find characteristics applicable for triage between primary or specialized care. Adequate triage of children with symptoms of inattention and hyperactivity is necessary to prevent serious problems, and to avoid over- and misdiagnosis. In addition, the involvement of (healthcare) professionals, and their use of ADHD guidelines after the transformation of youth care were studied, in order to gain insights into diagnostic process. Overall, results of the first part of this research intended to discuss the referral of children with (symptoms related to) ADHD in the light of the transformation idea of youth care, and the role of paediatricians. Part two stemmed from a social paediatric framework, and studied the association between a wide variety of environmental risk factors associated with ADHD. Associations between childhood ADHD and pre-, peri- and postnatal risk factors, recreational screen time, sleep and general parenting were studied. Data from the KOALA Birth Cohort Study were used for these studies, to find risk factors suitable for intervention, and opportunities for early support or prevention.

Bio-psycho-social characteristics and the healthcare system

Almost 50% of the children who were referred to an ADHD clinic, and analysed for this thesis, could have been treated or supported by primary care, according to the rationale of the new Youth Act. Biopsychosocial characteristics of these children were heterogeneous. No simple child- or social characteristic nor screening list was able to differentiate between the need for primary or specialized care. In addition, also children with *only symptoms* of inattention and / or hyperactivity showed physical problems. The survey, evaluating involvement of professionals after the transition of youth care, revealed that only a few paediatricians or GPs were involved in diagnosing ADHD. Only paediatricians reported to perform regular physical examination.

Adequate differentiation of children with symptoms of inattention and hyperactivity who need primary or specialized care requires:
• knowledge of developmental and psychosocial factors, and ability to integrate this data
• attention to biomedical / physical factors

As youth care is currently organized by the municipalities, it is important to examine within their regions what the options are for adequate evaluation of children with symptoms of inattention and hyperactivity. A possible solution could be individual training of GPs, community workers, and other professionals involved in primary care or at the community level, with focus on the bio-, psychosocial- and transactional model. However, healthcare professionals who assessed children with symptoms related to ADHD before the transition, and those who are still involved in diagnosing ADHD, already have (part of) this knowledge. Therefore, another solution could be to use their specific knowledge, by creating multidisciplinary consultation networks. Ideally, a team in primary care, consisting of physician

assistant mental health care, and a community worker, in combination with a doctor (GP, youth doctor, paediatrician working in primary care) should evaluate problems of the child and family. The physician assistant can score screening lists, and collect data from the school and sport club, and have a consultation targeting ADHD symptoms and possible impairment. The doctor does the medical history taking and the physical examination. Depending on the observed problem(s), other professionals like child & youth psychiatrists or psychologists, should be consulted as part of the triage. Paediatricians, or social paediatricians, could be specifically involved whenever there is a combination of complex medical history/problems and symptoms of inattention and/or hyperactivity and impulsivity. Although deploying more professionals during triage will increase healthcare costs, these extra costs will far be outbalanced by the prevention of over- and misdiagnosis of children. By investing in these multidisciplinary networks (both time and finances), (health)care professionals will learn from each other, and child evaluation will become increasingly interdisciplinary. Ideally, this will be a self-learning system, and consultation will eventually go faster, with fewer professionals needed. An added advantage is, that this flexible multidisciplinary consultative network can also be used for healthcare professionals only involved in the medical treatment ADHD or teachers.

Although not the scope of the studies in this thesis, it is important to realise that less involvement of paediatricians in ADHD care will eventually lead to loss of knowledge among paediatricians about ADHD. It is important to incorporate knowledge about ADHD in the paediatric traineeship. Recognizing a neurodevelopmental disorder as ADHD is possible through education, but also through (mandatory) internships in youth care, or child & youth psychiatry, as part of their traineeship. By exchanging with trainees in child & youth psychiatry, interdisciplinary thinking by paediatricians and child & youth psychiatrists is stimulated, and probably child & youth psychiatrists will also become more comfortable with physical examination.

Environmental factors

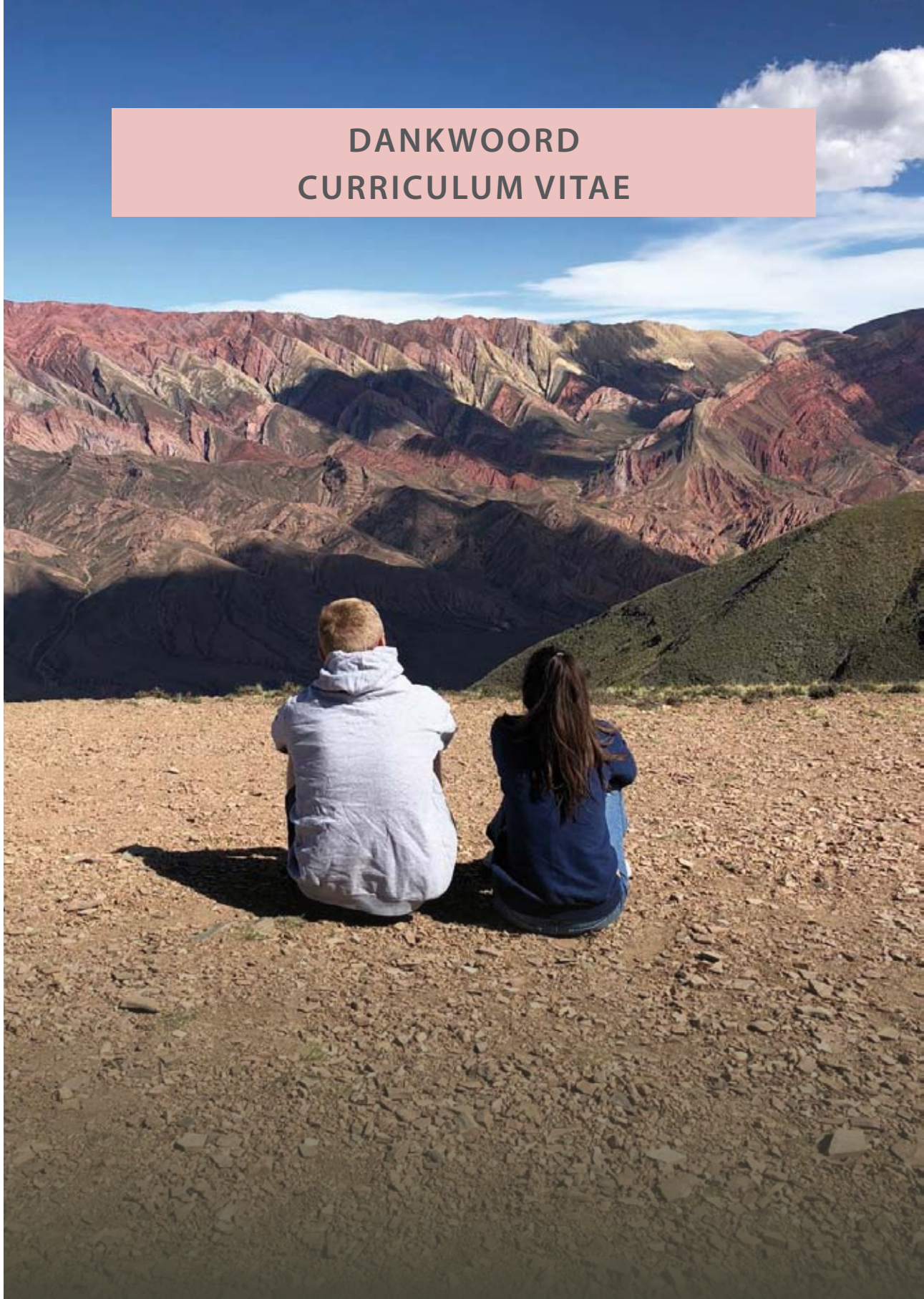
No longitudinal association between recreational screen time, total sleep duration and ADHD was found. However, externalizing behaviour was associated with more screen time and/or less sleep at the age of two, without longitudinal association with ADHD at the age of 8 years. It is importance to carefully evaluate possible causes of behavioral symptoms at a young age, and not to confuse behavior with a full diagnosis. These findings also emphasize the importance of longitudinal research. Questions about screen time and sleep duration should always be included when assessing a child with symptoms of inattention, hyperactivity and impulsivity.

The pre- and early postnatal risk factors found to be associated with ADHD were maternal smoking, prenatal Body Mass index > 25 kg/m^2, low maternal education level, marital discord, and no daily family routine. Maternal smoking and obesity are also associated with other health related problems, like premature birth, or wheezing in childhood. Low maternal education and marital discord may lead to (psycho) social stress. These findings underline the importance of (Dutch) preventive programs aimed at reducing these risk factors, whereby these programs may also provide secondary health benefits, like a decrease in ADHD. Given the nature of the risk factors, a combination of both personalized prevention and prevention on a group level is important. In the Netherlands a well-known program is 'De Rookvrije Generatie' (moke-free generation), which focuses not only on the individual, but also focuses for example on smoke free public spaces. It is important that the government continues to pursue a discouraging policy towards smoking, to allow the next generation to grow up smoke free. A preventive program called 'Kansrijke Start' (Solid Start), a government program aimed at vulnerable families, also has the potential to influence early risk factors. However, this program will only succeed, if it is supported by major governmental projects, such as poverty reduction, and equal opportunities for education for everyone. Research has started to study the ability of healthcare workers who encounter pregnant women, to recognize vulnerabilities, and to evaluate if they have barriers to talk about specific issues. These data will be useful to increase collaboration between the medical and psychosocial domain.

An association was found between ADHD and reduced scores on the construct Nurturance/Structure of general parenting. Especially the lower scores on the sub-constructs Scaffolding/Consistency and Autonomy Support provide a more specific direction for parent support. However, due to the study design it is not possible to determine the direction of the association, and the association between parenting and behavior should be studied in detail in new birth cohorts.

Children with ADHD are unique, versatile and have special characteristics. They deserve an assessment by experienced professional(s), as close to home as possible. This research has not produced a new screening tool, diagnostic method or treatment for ADHD. This study showed that one dimensional assessment of symptoms related to ADHD is not enough. Careful assessment of risk factors associated with ADHD is necessary, not only during a diagnostic process, but also through preventive programs. Transformation of youth care will only have the intended effect when professionals, municipalities and the government work together. This collaboration should be aimed at creating solutions in order to personalize ADHD care, in combination with joining forces to strengthen existing preventive programs.

DANKWOORD
CURRICULUM VITAE



DANKWOORD

Eerlijk? Ik had nooit gedacht ooit een dankwoord voor een proefschrift te schrijven. Maar dankzij het vertrouwen en de hulp van velen zet ik nu bijna de laatste punt. Talloze mensen trof ik de afgelopen jaren en ik weet zeker dat ik mensen in dit dankwoord zal vergeten. Mijn excuus daarvoor, weet dat ik jullie niet minder dankbaar ben.

Lieve Thea, zonder jou was dit proefschrift er nooit geweest. Ik ben jou heel dankbaar voor alle kansen die je mij hebt gegeven. De eerste keer dat ik je sprak eindigde meteen in een sollicitatie voor een fellow plek en jij concludeerde dat promoveren, ondanks mijn scepsis, toch een goed idee was. Je hebt me vervolgens een prachtige opleiding geboden, en heel veel geleerd over netwerkgeneeskunde en de sociale pediatrie. Helaas liep het zo anders dan we het ons hadden voorgesteld, maar ondanks dat bleef je me steunen, en reageerde je razendsnel op mijn mails. Thea, je bent een fantastische vrouw, dankbaar dat ik jou heb ontmoet, het heeft mijn werkende leven zo positief beïnvloed.

Prof. dr. E. Dompeling, beste Edward, wat ontzettend fijn dat jij bereid was om als professor kinderlonggeneeskunde mee te denken over een onderwerp als ADHD. De wijze waarop jij structuur bracht is ongelovelijk en heeft me enorm geholpen. Maar het was vooral jou altijd opbouwende en positieve manier van reageren die me energie gaf en me de ruimte bood om kritisch naar mijn eigen werk te kijken. Ik heb heel veel van je geleerd, en ben je heel dankbaar dat je deze promotie mogelijk hebt gemaakt.

Prof. dr. F.J.M. Feron, beste Frans, wat was het fijn om samen met Thea op jouw kamer vanuit verschillende perspectieven te denken over ADHD. Je enorme ervaring en duidelijke argumentatie hebben mij veel nieuwe inzichten gegeven. Jouw humor en lach maakten elke bijeenkomst een feestje. Dank je wel dat je ook na je pensioen op zo'n prettige manier betrokken bent gebleven.

Lieve oud-collega's van het SJG Weert, lieve Mieke, Simone, Elly en Carlo, wat was het bijzonder om samen een nieuwe vakgroep te vormen. We creëerden mogelijkheden voor een echte ADHD-poli, één van de eersten in Nederland destijds. Jullie gaven mij de ruimte mijn blik te verbreden, door mij de kans te geven om buiten het ziekenhuis te gaan werken. Mirande, hartelijk bedankt voor je enorme enthousiasme en inzet. Jouw nauwkeurigheid maakte het mogelijk veel informatie te verzamelen en vast te leggen over alle kinderen die we samen zagen op de ADHD-poli. Mieke en Leonie, dank jullie wel voor het voortzetten van deze zorg voor alle kinderen en hun gezinnen. Sabine van Elst, dankzij jouw visie is de samenwerking tussen het SJG en MediPsy tot stand gekomen en werd de ADHD-poli geprofessionaliseerd. Jij maakte het ook mogelijk data over de kinderen te blijven verzamelen, veel dank daarvoor.

Beste vakgroep kindergeneeskunde van het Maastricht UMC+, dank jullie wel voor jullie belangstelling en motiverende woorden. Speciale dank voor Merel, wat fijn om iemand te hebben die zo precies aanvoelde hoe zwaar zo'n laatste jaar is, met chocolade, lieve kadootjes, tegeltjeswijsheid, een luisterend oor en veel goede tips maakte je het allemaal een stuk luchtiger. Je hebt me het vertrouwen in mezelf gegeven wat ik nodig had. Monique, je bent een fijne kamergenoot, zo fijn om met iemand te kunnen praten die in hetzelfde schuitje zit. Ik heb bewondering voor alles wat je doet. Flore, het was heerlijk om samen een huisje te delen, dank voor de gevulde koelkast en lieve woorden die ik altijd weer trof. Ook als sectiehoofd wil ik je bedanken voor de ruimte die je steeds probeerde te creëren om dit proefschrift tot een goed einde te brengen.

Alle AIOS die ik heb ontmoet de afgelopen jaren hebben op hun eigen manier bijgedragen. Jullie enthousiasme om te leren werkt zo aanstekend, en het motiveerde mij onbekende paden te bewandelen. Een aantal van jullie heeft me, waarschijnlijk onbewust, veel tijd bespaard. Zoals Linda, die me net op tijd het werken met EndNote uitlegde. Ik wil jullie bedanken voor het vertrouwen wat jullie me steeds geven, ik verheug me erop om de komende jaren zo prettig te blijven samenwerken.

Docenten op YouTube, bedankt voor jullie duidelijke colleges statistiek en SPSS (en bedankt Bas en Tom, fijn dat dat jullie me wezen op het bestaan van deze colleges).

Beste Sander, Lonneke en Simone jullie hebben me enorm geholpen met het verzamelen van data, literatuur en hebben kritisch meegedacht over de interpretatie van deze gegevens. Lonneke, jouw enthousiasme was verfrissend, samen hebben we veel tijd doorgebracht en ik vind het super dat je uiteindelijk besloten hebt je weg in de psychiatrie te vervolgen. Simone, dankzij jouw hulp kreeg ik snel veel meer inzicht in ADHD en media gebruik. Zo fijn dat je daarna samen met Anne en mij onderzoek bent gaan doen naar risico factoren bij zwangeren, ik hoop in de toekomst nog veel met je te mogen samen werken.

Beste Carel, dankzij een kort stukje in een huisartsenblad kwamen we met elkaar in contact, en wat heb jij mij vervolgens veel geleerd. Vele uren heb ik samen met jou staand achter je bureau doorgebracht, waarbij jij steeds met enorm veel geduld al mijn berekeningen nog eens kritisch na liep. Het was fantastisch om de rijkdom van alle verzamelde data van de Koala Birth Cohort Study te ontdekken, en leerzaam om het onderwerp ADHD vanuit de epidemiologie te bekijken, dank je wel voor je enorme hulp en steun! Petra Hurks, wat een geluk dat ik jou heb leren kennen, zo prettig hoe je verschillende argumenten inbracht die mij weer aan het denken zetten. Ik vind het ontzettend leuk om samen met jou en Carel nieuwe studenten te begeleiden. Esther Sleddens, bedankt voor de fijne gesprekken over opvoedstijlen, en Marjolein van de Vlegel ontzettend bedankt voor je enorme bijdrage aan het onderzoek naar vroege risicofactoren en ADHD, ik wens je veel succes met je eigen promotie. Jessica Gubbels, Monique Mommers, jullie hebben mij geleerd elk woord dat ik opschrijf kritisch te bekijken, veel dank voor jullie waardevolle input.

De leden van de leescommissie, prof. dr. J.J.M.H. Strik, prof. dr. E.M. van de Putte, prof. dr. M.E.A. Spaanderman, prof. dr. B.J. van den Hoofdakker en dr. R. Wassenberg wil ik hartelijk bedanken voor hun tijd en aandacht tijdens hun kundige beoordeling van dit proefschrift.

Collega opleiders sociale pediatrie in Nederland, dank jullie wel voor het vertrouwen dat jullie me hebben gegeven toen ik onverwacht de taken van Thea over nam. Ook veel dank voor de steun tijdens de recente visitatie, mede daardoor kunnen we door met de opleiding van Esther in Maastricht tot kinderarts-sociale pediatrie.

Lieve Bas, zo bijzonder hoe we elkaar de afgelopen 30 jaar steeds opnieuw tegenkwamen. Ik vind jouw benadering van sociale kindergeneeskunde verfrissend en kan veel leren van jouw directheid in een overleg. Ik ben blij dat onze samenwerking nu jij aan een nieuwe uitdaging bij de Mutsaersstichting begint intensief zal blijven. Lieve Hans, niemand heeft zo'n groot hart voor zijn patiënten en kan met zulke mooie beeldspraken iemand in beweging zetten, al wil ik het nog zo graag, dat ga ik nooit leren. Lieve Nicole, Inge, Roel, wat was het raar voor jullie dat ik tijdens jullie fellowship de rol van opleider noodgedwongen van Thea moest overnemen. Dank voor jullie vertrouwen en geduld.

Lieve Anne, mijn maatje vanaf de dag dat we samen startten als fellow kinderarts-sociale pediatrie. Ik kan op niemand zo bouwen als op jou, altijd bereid om mee te denken of iets over te nemen. Je frisse en kundige blik helpen me steeds weer. Maar als we het allebei even niet meer weten, dan zet jij je secondant in, lieve Bob, die meteen uitlegde wat de do's en don'ts zijn bij een onderzoek. Niet voor niets koos ik jou als paranimf, ik vind het geweldig dat je nu onderdeel bent van het opleidingsteam, en weet zeker dat we samen met Bas de opleiding sociale pediatrie goed zullen blijven vormgeven. Ik verheug me op ons onderzoek naar psychosociale risicofactoren en zwangerschap, je bent een top collega!

Heidi, mijn steun en toeverlaat, achter de schermen ben jij degene die zorgt voor de logistiek van de sociale pediatrie. Dank je wel Heidi, je regelt alles zo goed voor ons. Ook heb je mij en de sociale kindergeneeskunde enorm ondersteund en geholpen op de moeilijke momenten. Ik hoop dat je nog heel lang onderdeel blijft van ons team. Ook alle anderen, Peggy, Anne, Natasha, Dyone, Vera, Zenabou en Sabine, ik wil jullie heel hartelijk bedanken voor jullie ondersteuning en snelle hulp.

Lieve vrienden en vriendinnen, wat fijn dat jullie er zijn! Lieve Kiki, Bas, Nicky, Jack, Wendy, Maurice, Séverine en Dennis, zo lief hoe jullie jaar in, jaar uit, vroegen hoe het ging en wanneer er nu eindelijk eens een feestje zou komen. Jullie hadden steeds vertrouwen (of deden alsof) daar heb ik veel energie uit geput. Dank jullie wel voor alle gezellige afleiding, onze Wijn & Spijs avonden, Weerter Kwis avonturen, weekendjes weg naar Efteling en Winterberg, en gewoon heel veel gezellige momenten samen. Misschien moet dit feestje nu toch even wachten, maar ik beloof jullie dat het er komt! Séverine, zo fijn dat jij mij bij het maken van dit boekje helpt. Lieve Kiki, ik bewonder hoe jij ergens voor gaat wanneer je erin gelooft, en daarom koos ik jou om op de laatste dag als paranimf naast mij te staan. Lieve Jacqueline, Sabine en Marie-José, jullie zijn fantastische vriendinnen. Ook al zie ik jullie niet meer zoveel, onze avondjes met de meiden koester ik, en ik hoop dat er nog heel veel zullen volgen (en ook dat jubileum weekend weg, als deze pandemie eindelijk is opgelost!)

Lieve familie, op afstand probeerden jullie zo goed mogelijk te volgen wat ik de afgelopen jaren heb gedaan en daar ben ik jullie allemaal dankbaar voor. Mama en papa, van jullie leerde ik dat afkomst, geslacht of opleidingsniveau nooit mag leiden tot ongelijke kansen in een samenleving. Dit heeft mijn kijk op de wereld beïnvloed, en gemaakt dat ik koos voor de sociale kindergeneeskunde. Dank jullie wel voor alle kansen die jullie mij hebben gegeven. Daarnaast hebben jullie met heel veel liefde, toewijding en veel lekkere hapjes altijd gezorgd voor mijn mannen wanneer ik druk was, veel dank daarvoor. Roel en Marry, het is duidelijk dat jullie als geen ander weten wat het is om dit traject te doorlopen, dank jullie wel voor al jullie interesse de afgelopen jaren, het was fijn om te voelen dat jullie zo meeleefden. Anne, Eric, Elsbeth, Eduard, Isa, Suus, Mirte en Daaf, wat gaat de tijd toch snel. Zo fijn hoe onze kinderen elkaar ondanks de afstand steeds weer opzoeken en snel vinden. Dank jullie wel voor alle gezelligheid en oprechte interesse in mijn (steeds weer wisselende) bezigheden.

Lieve Bas, Tom en Rens, jullie zullen wel helemaal klaar zijn met het geklets over onderzoek, het zit erop! Zo trots ben ik op jullie alle drie. Bas, zo evenwichtig en zachtaardig, ik vind het zo knap dat je een spannende uitdaging bent aangegaan door een tussenjaar naar Argentinië te kiezen na het behalen van je diploma, wat heb je daar veel gedaan, en wat heb ik genoten van die week samen. Speciale dank Bas voor het helpen met invoeren van alle referenties en je hulp wanneer mijn wiskundige kennis ernstig tekortschoot. Tom, zo attent en betrokken, ik vind het superknap dat je ondanks alle moeilijkheden door Corona toch je diploma hebt gehaald, en zo fantastisch om te zien hoe je nu geniet van je vervolg-

opleiding. Iedere werkgever wil jou hebben met je tomeloze inzet en charme. Dank voor al die koppen koffie en lekker hapjes die je steeds weer spontaan kwam brengen. Rens, zo onderzoekend en geïnteresseerd, ik vind het zo knap wat je allemaal al zelf hebt gecreëerd, als iets jou aandacht heeft, verdiep je je daar helemaal in. Daarmee ben je een veel betere onderzoeker dan mama, houd dat vast! Lieve Ilse, wat fijn dat jij zo van spelletjes houdt, het is fijn om je er de afgelopen twee jaar bij te hebben, jij bedenkt altijd wel een leuk spelletje ter afleiding waardoor ik steeds weer energie kreeg.

Ernest, al 28 jaar ben jij er altijd voor mij. Jouw eeuwige optimisme en lach, daar kan niets tegenop. Vanaf het moment dat je ontdekte dat administratie en huishouden niet mijn sterkste kanten zijn, nam jij die taak op je. Daarnaast heb je de afgelopen vier jaar, ondanks je eigen drukke baan, alles gedaan om mij te ondersteunen en er te zijn voor ons gezin. Ik vind geen woorden waarmee ik kan uitdrukken hoe dankbaar ik je daarvoor ben! Nooit heb ik je horen klagen wanneer ik weer een weekend achter mijn bureau doorbracht. Met zoveel liefde ben je er altijd voor de kinderen, Benji en Bink, de schaapjes (die ik zo graag wilde, maar jij al wist voordat ze er waren dat jij er natuurlijk voor zorgt) en al die verschillende katten. Deze enorme hobbel is genomen, wie had dat gedacht, ik houd van je.

CURRICULUM VITAE

Birgit Levelink was born on August 17th, 1972 in Eindhoven, The Netherlands. After finishing high school education at the Gertrudis Lyceum Roosendaal in 1990, she started studying medicine at the Radboud University Nijmegen. As part of her curriculum, she attended several elective internships in primary health care in India, Ghana and El Salvador. After obtaining her medical degree in 1997, she worked at the paediatric surgical intensive care unit of The Erasmus MC Sophia Children's Hospital in Rotterdam. From 1998 till 2004 she was a paediatric resident at the Radboud University Medical Centre Nijmegen and the Jeroen Bosch Hospital in 's Hertogenbosch, under supervision of prof. dr. R.C.A. Sengers and dr. J.H. Hoekstra. Her first job as a general paediatrician was at the paediatric department of the Sint Jans Gasthuis Weert (SJG). Together with an enthusiastic team of young paediatricians, new ideas to improve the care for children were developed. She set up an outpatient clinic for children with problems related to symptoms of attention-deficit/hyperactivity disorder (ADHD clinic), and provided training on ADHD for parents and professionals in the region. For the benefit of children with behavioural and developmental problems, she developed an intensive collaboration with Riagg Zuid Weert, an institute for child and youth psychiatry, which ultimately led to a new position for herself at Riagg Zuid in 2011. Together with the SJG and MediPsy (psychology practice), the ADHD clinic was professionalised, and she began collecting data to study characteristics of children visiting the ADHD clinic.

In 2014 she started a fellowship in social paediatrics, under supervision of dr. D.M.C.B. van Zeben-van der Aa and drs. J.C.M. Jansen. She fulfilled internships at Adelante, a child rehabilitation institute, and the Mutsaersstichting, an institute for child and youth psychiatry and youth care. After finishing her fellowship and her registration as social paediatrician, she stayed at the Mutsaersstichting, to assist drs. J.C.M. Jansen to expand the knowledge of multidisciplinary care for children with eating disorders to the middle region of Limburg. Since 2017 she works as a social paediatrician at the Maastricht University Medical Centre, where she started her PhD research under supervision of prof. dr. E. Dompeling, prof. dr. F.J.M. Feron and dr. D.M.C.B. van Zeben-van der Aa. Besides clinical tasks, she coordinates the multidisciplinary child protection teams of the Maastricht University Medical Centre, and participates in various projects in the South Limburg region like 'Kansrijke Start', in order to integrate the psychosocial and the medical domain. She contributed to various nationwide projects, like the working group 'Right care on the right place' aimed at better care for children with ADHD, and the working group who created the new 'ADHD standard of care'. She still is a member of the 'Dutch advocacy committee for children' and the 'Integrated child care network', and recently she became an ambassador of the 'Movement against child abuse Limburg'.

In 1999, she married Ernest van Wijk, and they have three sons, Bas (2001), Tom (2003) and Rens (2008). Together with their dogs, cats and sheep's they live in Nederweert, and they love to make journeys to challenging places.