The pathway to an ADHD diagnosis
Exploring the influence of factors at the structural, community, family and child level

PhD dissertation

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Preface

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Kathrine Bang Madsen
Aarhus, June 2017
This thesis is based on the following papers:

**Paper I**

**Paper II**

**Paper III**

**Paper IV**
Madsen KB, Mikkelsen SH, Rask CU, Niclasssen J, Olsen J, Simonsen M, Obel C. Depression-related distortions in maternal reports of child hyperactivity/inattention problems. *Submitted*
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Abbreviations

ADHD  Attention deficit hyperactivity disorder
ASD   Autism spectrum disorder
CI     Confidence interval
CD     Conduct disorder
CRS   Civil Registration System
DMBR  Danish Medical Birth Register
DNBC  Danish National Birth Cohort
DPCR  Danish Psychiatric Central Register
DSM   Diagnostic and Statistical Manual of Mental Disorders
GIS   Geographic Information System
GP    General practitioner
HKD   Hyperkinetic disorder
ICD   International Classification of Diseases
OCD   Obsessive compulsive disorder
OR    Odds ratio
PR    Prevalence ratio
SD    Standard deviation
SES   Socioeconomic status
SDQ   Strengths and Difficulties Questionnaire
SNRI  Serotonin and Noradrenaline Reuptake Inhibitor
SSRI  Selective Serotonin Reuptake Inhibitor
WHO  World Health Organisation
Introduction

“A classification is a way of seeing the world at a point in time”, wrote the former director of the World Health Organization (WHO) Norman Sartorius in the introduction to the International Classification of Diseases (ICD-10) [1]. Diagnoses, including child psychiatric diagnoses, are a product of our time and the result of both scientific progress and societal changes. Child psychiatric diagnoses are not natural entities waiting to be discovered but a categorisation that is useful as the starting point for receiving help and treatment [2]. This categorisation will change as new discoveries are made alongside with social, political and cultural changes.

Attention Deficit Hyperactivity Disorder (ADHD) has been a central issue in both public and scientific debates, and the disorder has even been called the ‘diagnosis du jour’ [3-5]. Increasing rates of ADHD diagnoses and treatment have fuelled concerns about over-diagnosing and unnecessary medicalization of children. Additionally, the media have contributed with stories on the promotion of certain disorders, such as ADHD, led by the pharmaceutical companies. These sensational stories have focused more on isolated cases than on giving a full and nuanced picture of the disorder. The impact of negative media publicity on ADHD treatment may play a vital role in the shaping of the public opinion as well as the opinion of children with ADHD, their parents, teachers, professionals and politicians [6-8]. Everybody seems to have an opinion about ADHD, and a lot of people have a stereotypical picture of who gets the diagnosis [9]. Unfortunately, misconceptions and lack of knowledge about what constitutes the diagnosis appear to be common [10, 11].

In the scientific community, there is general agreement that ADHD is a valid diagnosis and that affected children would benefit from treatment (both medical and psycho-social) [12]. However, some issues remain about the reliability of the diagnosis. First, the ADHD behaviour, which includes hyperactivity, inattentiveness and impulsiveness, is not easily distinguished from normal behaviour. Although ADHD is defined categorically for clinical purposes, it has been argued that ADHD is better viewed as a trait that is continuously distributed in the general population [13]. Defining the cut-point between normal and abnormal has shown to be somewhat arbitrary. Second, the diagnosis is based on observations about how children behave, but observations from different informants (and with different characteristics) are often discrepant. The diagnostic criteria have been developed to serve as an objective standard for diagnostics, but the use of diagnostic classifications will, nevertheless, imply some degree of interpretation from the professionals based on their subjective conceptions of normality [14].

This highlights the importance of investigating the factors that might influence whether a child will receive or not receive an ADHD diagnosis in the process from initial recognition to referral and final diagnosis. In the pathway to an ADHD diagnosis, detection, referral and diagnosis are all vulnerable to the influences of factors at the structural, community, family and child level.
The ADHD diagnosis

Contrary to popular belief, ADHD is not a newly identified condition; it has been recognised for at least a hundred years. Back in 1902, the first professor in paediatrics in England, George Still, described symptoms similar to our perception of ADHD today. He presented a series of three lectures at the Royal College of Physicians in London, entitled “Goulstonian lectures”, which were later published in the Lancet [15]. Many of Still’s descriptions indicate that children in the early twentieth century showed clear symptoms of ADHD. Although, most of the symptoms listed by Still and described in his cases do not refer directly to ADHD, his lectures are considered by many to mark the scientific starting point of the history of ADHD [16].

About 50 years later, the idea emerged that some disturbances of behaviour were the result of brain damage or ‘minimal brain dysfunction’. However, this concept was questioned when epidemiological studies systematically examined the causes of behaviour problems in childhood. The classification of mental disorders that emerged in the 1980s in the Diagnostic and Statistical Manual of Mental Disorders (DSM-III) by the American Psychiatric Association and in the Classification of Diseases (ICD-9) by the World Health Organization (WHO), put to one side the aetiological theories and focused solely on the description of problems at a behavioural level [17].

Since then, both of these classification systems have been changed, and new descriptions of mental disorders have emerged. The latest version of the ICD-10 came in 1992, and the most recent version of the DSM-V was released in 2013 [1, 18].

Definitions of ADHD and diagnostic criteria

ADHD is a diagnostic category in the DSM-IV and the more recent DSM-V [18, 19]. In Europe, the broadly equivalent diagnosis being used is hyperkinetic disorder as defined in the ICD-10 [1]. This definition is known to capture a more severely affected group of individuals [20].

In the DSM-V, ADHD is defined by a list of nine inattentive symptoms and nine hyperactive impulsive symptoms. To render the diagnosis, children must manifest six symptoms, or more, in one or two of the symptom domains, to a degree that substantially interferes with the daily functioning in two or more settings (Table A, Appendix) [18]. The key diagnostic symptoms of ADHD are shown in Table 1. The DSM-V states that diagnostic assessments of ADHD cannot be done accurately without consulting informants who have seen the individual in multiple settings and that multiple informants are beneficial, although not required, in formulating the diagnosis [18].

The ICD-10 diagnosis of hyperkinetic disorder (HKD) requires the definite presence of abnormal levels of inattention and restlessness 1) that are pervasive across situations and persistent over time, 2) that can be demonstrated by direct observation, and 3) that are not caused by other disorders, such as autism or affective disorders (Table B, Appendix). The HKD diagnosis requires the presence of at least six inattention problems, three activity problems and one impulsivity problem. The
diagnosis cannot rely solely on the report of the parent or the teacher (Table B, Appendix) [21].

Table 1. Key diagnostic symptoms of ADHD [18].

<table>
<thead>
<tr>
<th>Inattentive symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Does not give close attention to details or makes careless mistakes</td>
</tr>
<tr>
<td>• Has difficulty sustaining attention in tasks or play activities</td>
</tr>
<tr>
<td>• Does not seem to listen when spoken to directly</td>
</tr>
<tr>
<td>• Does not follow through on instructions and fails to finish school work, chores, or</td>
</tr>
<tr>
<td>duties in the workplace</td>
</tr>
<tr>
<td>• Has difficulty organizing tasks and activities</td>
</tr>
<tr>
<td>• Avoids, dislikes, or is reluctant to engage in tasks that require sustained mental</td>
</tr>
<tr>
<td>effort</td>
</tr>
<tr>
<td>• Loses things necessary for tasks or activities</td>
</tr>
<tr>
<td>• Is often easily distracted</td>
</tr>
<tr>
<td>• Is often forgetful in daily activities</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hyperactivity or impulsivity symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Fidgets with hands or feet or squirms in seat</td>
</tr>
<tr>
<td>• Leaves seat in classroom or in other situations in which remaining seated is</td>
</tr>
<tr>
<td>expected</td>
</tr>
<tr>
<td>• Runs about or climbs excessively in situations in which it is inappropriate</td>
</tr>
<tr>
<td>• Has difficulty playing or engaging in leisure activities quietly</td>
</tr>
<tr>
<td>• Is often &quot;on the go&quot; or often acts as if &quot;driven by a motor&quot;</td>
</tr>
<tr>
<td>• Talks excessively</td>
</tr>
<tr>
<td>• Blurs out answers before questions have been completed</td>
</tr>
<tr>
<td>• Has difficulty awaiting turn</td>
</tr>
<tr>
<td>• Interrupts or intrudes on others</td>
</tr>
</tbody>
</table>

Both classification systems largely recognise the same behavioural problems, but they differ in the way that symptoms are weighted and combined into categories. An ICD-10 diagnosis of HKD requires symptoms in all three groups: inattention, hyperactivity, and impulsivity. In the DSM-V, the ADHD diagnosis only requires symptoms of either inattention or hyperactivity-impulsivity. The DSM distinguishes between three subtypes of ADHD: predominantly hyperactive/impulsive, predominantly inattentive, or combined. Even though the ICD-10 is the main classification system applied clinically in the Nordic countries, the ADHD concept is used by both clinicians and researchers. Therefore, the concept of ADHD will be used throughout this thesis.

Aetiology

The aetiology of ADHD involves the interplay of multiple genetic and environmental factors. On the one hand, it is a highly heritable disorder (estimated to be around 70–80% of the genetic variation). On the other hand it can develop due to lesions of the brain, other environmental factors, such as deprivation, or a combination of several of these factors [22, 23]. The diagnosis of ADHD does not imply a medical or neurological cause. Likewise, the presence of psychosocial adversity or risk factors should not exclude the diagnosis of ADHD [17].

Treatment of ADHD

A number of guidelines to the management of ADHD have been developed: in the US by the American Academy of Pediatrics and the American Academy of Child and Adolescent Psychiatry [24, 25], in Europe by the Eunethydis European ADHD Guidelines Group [26], in the UK by the National Institute for Health and Care
Excellence [27] and in Denmark by the National Health Authority [28]. All guidelines recommend the use of pharmacological treatment, however, it should be prescribed in conjunction with behavioural interventions, such as parental psychoeducation, parent management training and classroom management strategies [13]. In a meta-analysis of the efficacy of stimulant treatment, Faraone and Buitelaar found a significant effect of stimulant treatment on core ADHD symptoms, with amphetamine products modestly more efficacious than methylphenidate products [29]. Although the authors of a recent Cochrane systematic review on methylphenidate for children and adolescents with ADHD argues that there is low quality of evidence of methylphenidate trials, they do agree that methylphenidate has some effect but that the effect sizes, reported in reviews and meta-analyses, are questionable [30]. Although there is limited support for the efficacy of non-pharmacological treatments for the core symptoms of ADHD, a recent meta-analysis showed small but significant reductions in ADHD symptoms with free fatty acid supplementation and artificial food colour exclusion [31]. In addition, the authors request for better evidence for the efficacy of behavioural interventions and cognitive training before they can be supported as treatments for the core ADHD symptoms [31]. In Denmark the National Health Authority promote the use of evidence-based behavioural parenting interventions [28]. In a recent Danish study of a community-based behavioural parent training model to address ADHD-related concerns in the voluntary sector, the authors found no effect on core ADHD symptoms compared to the control group [32]. However, a significantly greater improvement in parenting behaviour, parenting sense of competence, child functional impairment, parental stress and parental depressive symptoms was found, with maintenance of gains at four months of follow-up [32].

Prevalence of ADHD and time trends
In several countries, ADHD is the most commonly diagnosed childhood behavioural disorder. A recent review by Polanczyk et al. presented a worldwide-pooled prevalence of ADHD of 3.4% (95% CI: 2.6-4.5%) based on 41 studies conducted in 27 countries [33]. The review detected significant heterogeneity among study prevalence estimates, but this could in part be explained by methodological differences between the studies due to sampling, representativeness and use of different diagnostic interviews [33]. The recorded prevalence of ADHD has been increasing for the last decades in a number of countries. The same tendency has been observed for many other child psychiatric conditions, such as Autism Spectrum Disorder (ASD), Obsessive-Compulsive Disorder (OCD) and Tourette’s syndrome [34-37]. This has fuelled concern about whether the true prevalence of the disorder has increased over time. However, in a recent meta-analysis, Polancszuk et al. demonstrated that no evidence suggests an increase in the past three decades in the number of children who meet the criteria for ADHD when standardized diagnostic procedures are followed [38]. It has been suggested that increases in incidence of clinical diagnoses of child psychiatric disorders are largely explained by a broadening of diagnostic definitions in combination with more attention and better recognition by professionals [35, 39, 40]. Most studies including a direct comparison of the rates of parents or teacher reports of hyperactivity/inattention using equivalent epidemiological samples and symptom screening instruments have found no evidence for a systematic increase in the prevalence of ADHD-related difficulties.
[39, 41, 42]. This highlights the importance of distinguishing between the disorder ADHD and the diagnosis ADHD.

**Geographic variation in the prevalence of ADHD diagnosis and treatment**

The true variation in the prevalence of the ADHD disorder is probably not between different countries as demonstrated in the review by Polanczyk et al. [38]. However, large geographical variations in the prevalence of the ADHD diagnosis and the use of prescribed medications have been reported both within and between the Nordic countries and the US [43-49]. A study based on data from 2007 from the national prescription databases in Denmark, Finland, Iceland, Norway and Sweden found a significant difference in ADHD medication use between the Nordic countries. The prevalence of use varied from a low use of 1.23 per 1000 inhabitants in Finland to a high use of 12.46 per 1000 in Iceland [49]. Geographical variations are also found within countries. In Norway, the diagnostic prevalence of ADHD by county among children aged 6-12 years ranged from 1.1 to 3.4 % [47]. In Denmark the regional incidence of dispensed ADHD medications among children aged 5-17 years ranged from 3.59 to 7.07 per 1000 children during 2010-2011 [48]. In Germany, lower ADHD medication rates were found in rural regions than in urban regions [50]. Similar differences have been reported in Sweden and even larger variations between regions and states have been identified in the US [43, 46, 47, 51-53].

**Organisation of healthcare in Denmark**

In Denmark, healthcare is tax-financed and, according to Danish legislation, all citizens are offered free and equal access to healthcare services [54]. The organisation of Danish healthcare is placed in three political and administrative levels: government level, regional level and municipal level. The public healthcare services are decentralised and the responsibility is divided between the five regions and 98 municipalities. The Danish regions; North Denmark Region, Central Denmark Region, Region of Southern Denmark, Region Zealand and Capital Region are responsible for the running of secondary care (hospitals), and the municipalities are accountable for primary care, public healthcare, school healthcare services, prevention and rehabilitation. The costs of ADHD medications and most other prescriptive medications can be reimbursed [55].

In 2016, national clinical guidelines for referral, evaluation and treatment of children and adolescents with ADHD in Denmark were published [56]. In Figure 1 the administrative pathway to diagnostic evaluation is shown. When employees in municipal authorities (schools, day-care centres, etc.) identify a child or a young person with ADHD-like symptoms, the municipality will often refer them directly to the child and adolescent psychiatric hospital wards. If the parents are concerned with their child’s health, the primary care (i.e. general practitioners (GPs)) is usually the first level of health service to be accessed by parents. After performing a specific examination and assessment, the GP will decide whether to contact child psychiatric specialists in private practices or in public psychiatric hospitals. The ADHD diagnosis is often made by a child and adolescent psychiatric specialist after carrying out thorough diagnostic evaluation [56].
Structural, community, family and child factors
Considering the large geographical variation in the ADHD diagnosis both within and between countries, it becomes evident that factors besides the child’s ADHD symptoms must have an influence on whether a child gets a diagnosis or not. Studies have reported that only about 20-25% of children with mental health problems are in contact with specialist mental health services [57, 58]. Barriers and facilitators in the pathway to an ADHD diagnosis may occur at multiple levels [59].

Inspired by Dahlgren and Whitehead’s model of the main determinants of health [60], I suggest the following model as the framework for understanding the influence of factors at different levels on the pathway to an ADHD diagnosis (Figure 2). The original model by Dahlgren and Whitehead illustrates the main influences on health in general. In this PhD thesis, the model was adapted to demonstrate the influences that are particularly related to the ADHD diagnosis. The model is arranged as a series of layers; one on top of the other. The structural level constitutes the overall frame. This first layer constitutes the administrative level and includes factors such as availability (resources) and access to diagnostic services and treatment as well as diagnostic culture. The next layer represents the social and community networks; these constitute the influence of school, primary healthcare for children and neighbourhood on the identification of children with ADHD. Finally, the family and child level is presented in which different characteristics of both the parents and the child may influence the help-seeking behaviour of the family. Each layer interplays with the other layers, and the factors are influenced by each other. The influence of different factors at the different levels will be explained in the following.
Figure 2. Model of influential factors at different levels (adapted from Dahlgren and Whitehead [60]).

Structural level

Access to healthcare and available resources

Different contextual factors have been associated with the geographical variations in ADHD diagnoses. Availability of diagnostic services and treatment has been suggested to influence the prevalence of ADHD diagnoses and medication use. Several studies have reported that availability of physicians in the particular area was a strong predictor of ADHD treatment; this suggests that treatment rates might be driven by supply-side forces (available resources) rather than by “demand pull” forces (the actual need for services) [43, 44, 51]. In Norway, a possible explanation for the large geographical variation in the prevalence of ADHD has been suggested to result from the decentralised Norwegian specialist health services for children, where several institutions treat very small proportions of children with different diagnoses [47]. In Germany children in large cities were more likely to be using ADHD medication; this suggests differential healthcare access depending on population density [50]. Finally, a Danish study found that prescribing rates were the highest for disadvantaged children in all Danish regions. However, the differences in socio-demographic composition explained little of the regional variation, which points to different availability of diagnostic services [48].

Cultural differences in diagnostic services

Psychiatric diagnoses are based on descriptive criteria and are influenced by the interpretation of symptoms and decision-making by the professionals; this process can be influenced by the culture in different professions (psychiatrists, psychologists, paediatricians, neurologists and other healthcare professionals) and by the prevailing cultures in different geographical areas [9, 61, 62]. US studies have found that ADHD diagnosis and medication rates were associated with the specialisation profile and age of physicians within the state [43, 44, 51]. In addition, it has been suggested that drug prescribing patterns might be a function of the professional training and the traditions of physicians and other mental healthcare providers [63]. In a recent
Danish study the authors reported that the prescribing of ADHD medication by the child and adolescent psychiatrists varied consistently between hospitals; this affected the probability that a child with an ADHD diagnosis would receive ADHD medication [64].

Community level

The school

Children referred to paediatric services for assessment of symptoms of ADHD may first be identified as problematic in an educational setting (e.g. pre-school, school). A US survey found that teachers were most likely to be the first to suggest the diagnosis of ADHD followed by parents, primary care physicians and school personnel other than teachers [65]. A UK study assessing barriers to the identification of children with ADHD demonstrated that education professionals were the first, and often the only, professionals consulted by concerned parents [66]. The presence of school-related problems has been shown to increase the help-seeking for child psychopathology [67]. Efron et al. examined the factors associated with a positive diagnosis of ADHD in children aged 4–9 years referred to ADHD assessment. They found that teacher-reported ADHD symptom severity and learning difficulties were the strongest predictors of an ADHD diagnosis [68]. In addition, a US study found that high diagnosis rates were associated with having an older teacher, whereas lower rates were associated with having a white teacher. Furthermore, in schools that were subject to strict state-level performance accountability laws, higher odds of ADHD diagnoses have been found [69].

The presented findings highlight the influence of the school setting. Teachers and other school personnel may find ADHD both time-consuming and challenging as they spend a considerable amount of time addressing concerns regarding children with ADHD symptoms. However, teachers may have little accurate knowledge about ADHD. In some cases, they may share misconceptions that are common in the public sphere, i.e. that ADHD is not a real disorder or that the ADHD symptoms are caused by the intake of too much sugar, poor parenting or a stressful family environment [10, 59]. Consequently, this may result in a lack of referral of children with ADHD symptoms to psychiatric evaluation. In a study using data from several European countries, a third of caregivers for children with ADHD reported a high degree of difficulty in obtaining an ADHD diagnosis for their child; less than half felt that sufficient resources were available, and lack of support from healthcare providers and schools were identified [70].

Primary healthcare

In Denmark and other European countries such as the UK, primary healthcare (GPs and health visitors) usually acts as the first level of health service accessed by parents. GPs traditionally have a gate-keeping role and must first be consulted before any further contact with specialist child health services. Problem recognition by the GP has been identified as an important barrier on the way to specialized help [66, 67, 71]. Studies have also suggested that the media is an important source of information about ADHD for GPs, which could result in misconceptions about ADHD [7, 8]. A qualitative study by Klasen & Goodman found that the views on ADHD of parents and GPs markedly differed. Parents generally saw severe hyperactive behaviour as a
long-lasting biological problem that would benefit from diagnosis and that needed treatment. In contrast, most of the GPs were unsure whether hyperactivity was a medical disorder that would warrant specific treatment, and many often saw it as a passing phase related to family stresses [72]. Some parents reported to worry that professionals would blame them for their child’s problem, whereas many GPs saw the parent’s wish to redeem medications for their children as a way to avoid thinking about their own shortcomings in parenting [72]. Still, one study found that parental request for referral was the strongest determinant of recognition by the GP, which suggest that the GP is indeed responsive to the parents’ requests [71]. However, the downside to this may be that an increasing pressure on clinicians will result in the provision of medication to children who are not accurately diagnosed [7].

Social networks and neighbourhood
Within the community, the availability of services and social networks that can provide referrals have shown to be of importance for referral of children with mental health problems [73]. In addition, knowledge and conceptions are probably important preconditions for the social support of the network existing in the close community. In a vignette study of American adults, Pescolido et al. found that more than half of respondents could not identify ADHD; among those who could, almost one in five did not perceive the condition as a mental illness. In comparison to ADHD, several respondents saw depression as serious and less likely to improve on its own. Lack of knowledge and information combined with diverse cultural ideas about symptoms may work as barriers in the community [10]. Cultural and socioeconomic influences related to the family residence may work as a barrier in the recognition of children with ADHD symptoms, but it could also work as a facilitating factor. This phenomenon has been demonstrated in relation to the autism diagnosis, where children living in very close proximity to a child diagnosed with autism were more likely to be later diagnosed with autism [74, 75]. The hypothesis behind this phenomenon is that the sharing of information on autism between parents in communities with high autism prevalence also increases community awareness about signs and symptoms of the disorder [74]. However, a UK study found that the clinical diagnosis of ADHD was not related to school or community factors but only to child characteristics. The authors suggest that individually assessed child and family factors may be more influential than aggregate measures of school and neighbourhood factors [76].

Family level
Parents play a central role in the utilization of mental health services for their children. Family factors such as ethnicity, parental mental health and socioeconomic status (SES) may thus have great influence on whether a family would seek help for their child. The family or parental factors can be explained in addition to a model of help-seeking behaviour. Three stages in the help-seeking pathway have been proposed: problem recognition, decision to seek help and service utilization [73]. Families respond to mental health problems and concerns within the context of the larger social environment that may both guide and push them toward or away from various types of services. Additionally, different characteristics of the family may influence the help-seeking stages differently [73].
In the first step of help-seeking it is implied that the child’s problems are recognized. Yet, ethnic and cultural groups differ on questions as basic as what is perceived to be a mental health problem [73]. In a yet unpublished study of about 4000 children from a Danish municipality, we examined the influence of non-Danish origin on child hyperactivity/inattentiveness problems as reported by the parents and teachers using the Strength and Difficulties Questionnaire (SDQ). We found that non-Danish parents were less likely to report ADHD symptoms in their children than Danish parents, even when teachers reported ADHD problems in their children [77]. Divergent results have been found, dependent on what racial or ethnic group investigated.

Studies from the US have often focused on differences between African-Americans, Hispanics and Caucasians, whereas studies from Europe have mostly focused on migrants and differentiated on whether migrants were from western or non-western countries. Studies from the US have found that African-American children were less likely than Caucasian children to receive psychiatric evaluation or to have ever used mental healthcare services, even when the parents recognized ADHD problems and adjustments for socio-demographic factors were made [78, 79]. A Canadian study demonstrated that immigrants had a significantly lower risk of receiving ADHD medication [80]. In a review addressing help-seeking for behavioural problems in children, negative associations were found between ethnic minority status and parental help-seeking. However, the association disappeared when socioeconomic variables were accounted for [67].

A German study found that boys from families with no immigration background used ADHD medication almost six times as frequently as boys with immigration background [50]. Another German study found that parents from families with a history of migration reported significantly fewer ADHD diagnoses in their children than parents without a history of migration, but the parents reported just as many ADHD symptoms in the children (using the SDQ) as non-migrant families [81]. The studies did not examine in which stage of help-seeking the barriers occurred, but the authors conclude that the inverse association of ADHD diagnosis and medication use with immigration status suggests potentially restricted access to healthcare services or the reflection of culture-specific differences in the attitudes toward symptoms of ADHD [50, 81].

**Parental mental health**

The co-occurrence of ADHD in parents and their offspring is fairly common [82-91]. It has been estimated that half of all adults with ADHD have at least one child with ADHD, and between 25% and 50% of children with ADHD have one parent who has been diagnosed with the disorder [88, 92]. Parental, especially maternal, depression has also been linked to offspring ADHD, and it has been estimated that about 40% of children with ADHD have at least one parent with a depressive disorder [82, 93]. Several studies have found that parental psychopathology increased the problem recognition of their child’s symptoms. However, it did not increase the mental health service utilization, only when the parents themselves or their relatives received mental healthcare [94-97].
Assessment guidelines on child ADHD emphasize the use of a multi-informant approach but parent-reported symptom scales often serve as the primary type of information employed by clinicians [98]. It has been suggested that parent psychopathology may affect the report of child ADHD symptoms. A positive relation has been found between maternal levels of depression and discrepancies between mother’s ratings and the ratings of other informants, such as teachers or the child’s own rating [99]. This observation has resulted in the depression-distortion hypothesis, in which it is theorized that parents with depressive symptoms hold more negative schemas for their child’s behaviour and consequently tend to over-report the severity of their child’s symptoms [100, 101]. Potential depression-related distortions in the parental perception of the child’s behaviour are important as they may lead to biased assumptions in the clinical assessment of the child [102].

Parental socioeconomic status
In the scientific literature, it is well established that family socioeconomic disadvantage is associated with childhood ADHD [45, 52, 81]. This was recently illustrated in a review reporting that children in families of low SES on average were twice as likely to be diagnosed with ADHD than their peers in families of high SES [103]. However, the influence on help-seeking behaviour is less clear. A review suggested, that the influence of SES on help-seeking seems to depend largely on the healthcare system of the country. Whereas studies conducted in the USA and Australia have found different effects of SES on help-seeking, studies in countries like France, Finland and the Netherlands, in which healthcare is readily available and no major financial constraints are linked with receiving professional help, have not found any association between SES and help-seeking [67]. However, SES also reflects the educational level of the parents. Education and knowledge may shape the conceptions and beliefs about ADHD and influence the possibility that parents will seek help for their children and accept treatment [11, 104]. In addition, higher educated parents may have better communicative skills and health literacy and, in turn, better preconditions for understanding the healthcare system and make demands [105].

Child level
Although findings suggest that parental problem recognition and help-seeking are dependent on the amount of distress or burden on the family rather than on the level of child psychopathology per se [106-108], studies have also suggested that child characteristics such as symptoms, gender and age may affect the parental perceived burden and the likelihood of the children being referred and diagnosed.

Symptoms and presentation
Factors identified in previous research to be associated with the likelihood of referral for clinical services include hyperactivity and disruptive behaviours, chronicity of ADHD symptoms and functional impairment, severity of ADHD symptoms, learning difficulties, academic problems and impact on peer relations [61, 95, 96, 109, 110].

Gender
In epidemiological studies of ADHD, a male to female ratio of 3-4:1 has often been
reported. However, in clinical samples, the ratio has been reported to be 9:1, which suggests referral bias in relation to girls with ADHD [111]. Although the presence of child psychopathology does not automatically lead to parental problem recognition, help-seeking for child psychopathology has been proposed to increase with externalizing problems and severity and persistence of problems [67, 95]. Research on gender differences suggests that girls may be consistently under-identified [112-116]. It has been suggested that the under-identification of girls may be due to gender differences in the phenotypic expression of ADHD [117]. Girls with ADHD tend to exhibit lower levels of disruptive behaviour and rule-breaking and higher levels of inattentiveness and internalizing symptoms than boys; this makes girls less likely to disrupt the classroom and more likely to be overlooked [5, 117-119]. This is consistent with a study using data from 10 European countries in which Nøvik et al. found that gender specific variations had very little influence on paediatric practise; once referred, the girls were just as frequently diagnosed as boys [116].

In a review from 2003, Zwaanswijk et al. demonstrated that the effect of the child’s gender on parental problem recognition and help-seeking was dependent on the age of the child. In childhood and early adolescence, more help is generally sought for boys. However, in late adolescence, girls seek help more often. This finding may result from the fact that externalising problems, which are more prevalent in boys than girls, tend to decrease with age, whereas internalising problems, which are more typical for girls, tend to increase with age [67].

**Age**
ADHD is most commonly diagnosed when children reach middle childhood (around the age of 8 years) [120]. Recent studies from the US, Canada and Iceland have shown that the youngest children in the class were more likely to be diagnosed and treated for ADHD [121-124]. Because of the cut-off dates of birth for entry to school, children within the same grade may be almost one year apart in age; children with birthdates just before the cut-off will be younger and may be less mature than their classmates born at a different time of the year. This phenomenon has been termed the relative-age effect, and it has been suggested that it is resulting in an unnecessary ADHD medication of children [123]. These findings could not be replicated in a Danish context [125]. The authors of the Danish study speculate that this may be due to the high proportion of relatively young children held back by one year in the Danish school system and a generally low prevalence of ADHD medication use in the country [125].
Conclusions leading to the present studies
Despite available effective treatments, studies have shown that many children with ADHD do not receive adequate help and treatment. Understanding the factors influencing the pathway to an ADHD diagnosis is of great importance as it provides insight into the challenges that children with mental health problems and their families might face.

Results from the studies on the geographic variation of the ADHD diagnosis and treatment suggest that where you live matters greatly for the possibility of being diagnosed and that the influence of structural factors, such as availability of mental health services, might be an explanation. However, most of the studies examining predictors of the variations in ADHD diagnosis and treatment at the structural level have been conducted in the US. The influence of factors at the structural level may be very different in European countries with different healthcare systems. In addition to different access to diagnostic services, the variation in ADHD diagnoses and treatment could reflect different thresholds for recognising and referring children with ADHD symptoms. Hence, factors at the community, family and child level may also play an important role in the pathway to an ADHD diagnosis. However, the studies that have examined these problems only addressed factors at a single level and often did not take into account the interplay between the levels. In the current thesis my aim was to investigate how factors at the structural, community, family and child level might influence the possibility of children receiving ADHD diagnoses.

Methodological considerations
All Danish citizens have a unique personal identification number. Thus, it is possible to link information at the individual level between nationwide health registers and other data sources, such as cohorts. This provides a unique opportunity to examine the factors involved in the pathway to an ADHD diagnosis and medical treatment [126]. The studies presented in this thesis are based on data from the Danish national health registers and the Danish National Birth Cohort (DNBC). While the registers have the advantage of population completeness, this is not the case for the DNBC. A study revealed that groups with low socioeconomic resources in terms of education, occupation, income and civil status are underrepresented in the DNBC compared to the background population [127]. Low parental SES has shown to be associated with increased childhood psychiatric disorders [103, 128]. Given these associations, childhood psychiatric diagnoses would likely be underrepresented in cohorts like the DNBC. In order to consider the external validity of the studies in this thesis, we found it relevant to investigate whether the social gradient in the willingness to participate in the DNBC might influence the representation of later childhood psychiatric diagnoses, including the ADHD diagnosis.
Aim of the thesis

The overall aim of this thesis is to investigate, in an epidemiological setting, the influence of structural, community, family and child factors on the diagnosis of Attention Deficit Hyperactivity Disorder (ADHD) in children.

The specific aims of the four studies included in this PhD dissertation are:

- To examine the geographical patterns of the distribution of ADHD diagnosis and medication use, and to explore the association with access to diagnostic services, diagnostic culture, neighbourhood socioeconomic status and municipal spending on healthcare for children (Study I).

- To estimate the relative representation of childhood psychiatric diagnoses and to explore the use of psychotropic medication in the Danish National Birth Cohort (DNBC) (Study II).

- To estimate the number of children with parent-reported ADHD behaviour at age 7 years and absence of recorded ADHD diagnosis during adolescence, and to investigate sociodemographic and mental health characteristics of this group (Study III).

- To investigate the association between maternal depression and maternal, teacher and self-reports of child hyperactivity/inattention and additional mental health problems (Study IV).
Material and methods

Data sources

Danish national health registers
The registers used in this thesis are:

The Danish Civil Registration System
The Danish Civil Registration System (CRS) was established in 1968. Since then, all persons alive and living in Denmark are registered for administrative use. The CRS includes individual information on the unique personal identification number, name, gender, date of birth, place of birth, citizenship, identity of parents and continuously updated information on vital status, place of residence and spouses [129].

The Danish Medical Birth Register
The Danish Medical Birth Register (MBR) was established in 1968 to monitor the health of the new-borns and the quality of the antenatal and delivery care services. It comprises data on all live births, stillbirths and infant deaths of women with permanent residence in Denmark, including information on gender, place of delivery, date of birth and birth weight [130].

The Danish National Patient Register
The Danish National Patient Register (NPR) was established in 1977, and it is considered to be the finest of its kind internationally. When first established, the register included information on inpatient admissions in somatic wards. The content of the register has gradually been expanded. From 1995 onwards, all outpatient activities, emergency room contacts and activities in psychiatric wards have been included in the NPR. Since 2007, the register has included information on all patients in Danish hospitals [131, 132].

The Danish Psychiatric Central Register
The Danish Psychiatric Central Register (DPCR) provides individual level data on all clinical diagnoses and admission/discharge dates for all inpatient psychiatric hospital admissions since 1969 and on all outpatient visits at psychiatric hospitals and clinics since 1995. Since 1994, the ICD-10 has been used. Before 1994 the ICD-8 was used [133].

The Danish National Prescription Registry
Individual-level data on all prescription drugs sold in Danish community pharmacies have been recorded in the Register of Medicinal Products Statistics under the Danish Medicines Agency since 1994. The register subset, termed the Danish National Prescription Registry (DNPR), contains information on dispensed prescriptions, including variables at the level of drug user, prescriber and pharmacy [134].
The Danish National Birth Cohort

The Danish National Birth Cohort (DNBC) is presently one of the largest birth cohorts in the world, including over 90,000 participants enrolled during 1996-2002. The cohort was established to explore social, environmental and lifestyle factors during pregnancy and early childhood on the development and health of the child [135]. The first Danish counties began enrolment in 1996. From 1999 to 2002, all counties in Denmark were included. The participants were recruited to the study at the first antenatal visit (between 6 and 12 weeks of gestation) at their general practitioner (GP). All Danish GPs were asked to take part in the recruitment of the pregnant women; about 60% of eligible women received an invitation and around 60% of the invited women participated.

The participation rate at enrolment was about 30% of all eligible women in Denmark [127]. Hence, about half of the non-participation was related to the recruitment by GPs and the other half by pregnant women who declined the invitation [136].

As presented in Figure 3, the first interview took place at the first antenatal visit at the GP. Once enrolled, the women were invited to participate in four computer-assisted telephone interviews: twice during pregnancy (at 16 and 30 weeks of gestation) and twice after delivery (at child age 6 and 18 months). At child age seven years, the primary caregiver, mainly the mother, filled in a follow-up questionnaire including the Strengths and Difficulties Questionnaire (SDQ) either through the Internet or by paper. In addition, at child age eleven years, the SDQ was filled in by multiple informants: the child, the mother and the child’s teacher.

Figure 3. Interview and questionnaire follow-up in the Danish National Birth Cohort
Design, study populations, measures and statistical analyses
First, an overall description of study designs, populations and measures is presented. Next, a more in-depth description will follow for each study.

All studies presented in this dissertation were nationwide population-based cohort studies using the Danish National Health Registers (Study I), the DNBC (Study IV) and the registers combined with the DNBC (Study II and III).

Study populations (Study II, III, IV)
Attrition in each of the studies using data from the DNBC is shown in Figure 4. Initially, 96 840 pregnant women were enrolled in the cohort. In study II, we included children born 1998-2002 from the DNBC. In study III, we included only children from the 7-year follow-up and excluded siblings and multiple births. In study IV, we included only children from the first interview, the 7-year follow-up and multiple informant reports from the 11-year follow-up.

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Attrition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study II</td>
<td>The Danish National Birth Cohort N=96 840</td>
<td>Loss to follow-up n=1 444</td>
</tr>
<tr>
<td></td>
<td>Interview 1: 12th week of pregnancy,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pregnanacies N=92 696</td>
<td>Loss to follow-up n=33 469</td>
</tr>
<tr>
<td></td>
<td>Pregnant women N=84 171</td>
<td>Excluded Siblings and multiple births n= 8 720</td>
</tr>
<tr>
<td>Study III</td>
<td>7-year follow-up, N=51 527</td>
<td>Loss to follow-up n=16 048</td>
</tr>
<tr>
<td>Study IV</td>
<td>Complete SDQ reported by all informants; parent,</td>
<td>Missing SDQ: Parent; n = 2 779</td>
</tr>
<tr>
<td></td>
<td>child and teacher N=12 961</td>
<td>Teacher; n = 21 679</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Self; n= 3 638</td>
</tr>
</tbody>
</table>

Figure 4. Attrition flowchart of the studies using data from the Danish National Birth Cohort

ADHD diagnoses
In studies I-III, children were followed in the NPR and the DPCR for the ICD-10 diagnoses equivalent to the DSM-IV diagnosis of ADHD. First, we defined ADHD to be present when the following ICD-10 diagnoses were registered either as the main or additional diagnosis after the age of five years: F90.0-F90.9 “Hyperkinetic disorders” or F98.8 “Other specified behavioural and emotional disorders with onset
usually occurring in childhood and adolescence” (equivalent to the ADHD inattentive subtype). Second, we used the DNPR to include ADHD patients diagnosed in private psychiatric practices in Denmark; these do not report diagnoses to the national patient registries. Children were categorized as ADHD cases when they had one prescription (Study III) or two or more prescriptions (Study I and II) of methylphenidate (N06BA04) or atomoxetine (N06BA09) in the register after the age of five years.

The Strengths and Difficulties Questionnaire (SDQ)

In Studies III and IV we used the Strengths and Difficulties Questionnaire (SDQ), which is a validated screening questionnaire developed by the English professor of child psychiatry Robert Goodman in 1998. The standard version of the questionnaire has been widely used in research studies throughout Europe and has also served as a screening and/or assessment tool by both school psychologists and clinicians in order to assess mental health problems and impairment in children aged 5-17 years [137-140].

The SDQ has been available in a Danish validated version since 2002 and is free of charge online (www.sdqinfo.com). The questionnaire is available as a parent and teacher version for 5-17 year-olds and as a self-report version for 11-17 year-olds. The questionnaire focuses on the child’s behaviour during the previous six months.

The SDQ consists of 25 questions scored on a Likert scale. The questions cover five subscales: hyperactivity/inattention (H/I), conduct problems (CD), emotional symptoms (EM), peer relationship problems and pro-social behaviour. Each of these are rated as the sum score of five items. Answer categories are: 0 (not true) 1 (somewhat true) or 2 (certainly true). Each subscale is hence scored from 0 to 10; higher scores indicate worse behaviour (except for the prosocial scale). Details of the calculations are available at the official SDQ website.

In addition, an impact supplement is provided to the informants; this supplement enquires about distress, burden and impairment of the child in different settings. The range of possible impact scores in the parent and child versions range from 0 to 10. The scale covers whether the experienced difficulties have upset or distressed the child and social impairment in four domains: home life, friendships, classroom learning and leisure activities. In the teacher version, impact scores only range from 0 to 6 as teachers are not asked to assess the difficulties regarding home life and leisure activities [138].

Computerised algorithms have been developed to predict child psychiatric disorders on the basis of symptoms and impact scores derived from multi-informants: parents, teachers and the child. The predictive algorithm generates "unlikely”, "possible" or "probable" ratings for caseness of hyperactivity-inattention disorder, conduct-oppositional disorder, anxiety-depressive disorder and any psychiatric disorder [141, 142].

The hyperactivity-inattention prediction (SDQ ADHD) is presented in Table 2 and is described briefly in the following. For each informant, a “possible” prediction requires a minimum score of 6 on the hyperactivity/inattention scale and an impact
score of 1 or more, and “probable” prediction requires a score of minimum 7 and a minimum impact score of 2. When combining scores from more informants, a prediction of “possible” ADHD requires a “possible” prediction from both the parent and the teacher or a “probable” prediction from either the parent or the teacher. A combined prediction of “probable” requires that the parent prediction is “probable” and the teacher prediction is at least “possible”. In the combined algorithm, the child’s self-report is only counting if the parent report is missing, and if so, the self-report is used as described for the parent. If either parent or teacher report is missing, the report from either one is sufficient in predicting “possible”.

Table 2. The SDQ ADHD prediction algorithms for each informant and combined

<table>
<thead>
<tr>
<th>Single-informant prediction</th>
<th>Parent</th>
<th>Teacher</th>
<th>Self report</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hyperactivity</td>
<td>Impact</td>
<td>Hyperactivity</td>
</tr>
<tr>
<td>Unlikely</td>
<td>≥0</td>
<td>≥0</td>
<td>≥0</td>
</tr>
<tr>
<td>Possible</td>
<td>≥6</td>
<td>≥1</td>
<td>≥6</td>
</tr>
<tr>
<td>Probable</td>
<td>≥7</td>
<td>≥2</td>
<td>≥7</td>
</tr>
<tr>
<td>Probable</td>
<td>≥9</td>
<td>≥1</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Combined prediction</th>
<th>Parent</th>
<th>Teacher</th>
<th>Self report</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hyperactivity</td>
<td>Impact</td>
<td>Hyperactivity</td>
</tr>
<tr>
<td>Unlikely</td>
<td>unlikely</td>
<td>OR</td>
<td>unlikely</td>
</tr>
<tr>
<td>Possible</td>
<td>probable</td>
<td>OR</td>
<td>probable</td>
</tr>
<tr>
<td>Possible</td>
<td>possible/probable</td>
<td>AND</td>
<td>possible/probable</td>
</tr>
<tr>
<td>Possible</td>
<td>possible/probable</td>
<td>AND</td>
<td>missing</td>
</tr>
<tr>
<td>Possible</td>
<td>missing</td>
<td>AND</td>
<td>possible/probable</td>
</tr>
<tr>
<td>Possible</td>
<td>probable</td>
<td>AND</td>
<td>possible/probable</td>
</tr>
</tbody>
</table>

The psychometric properties of the SDQ have generally been found to be satisfactory [143, 144]. In addition, the instrument has shown to be able to identify children with highly increased risk of later being diagnosed with ADHD in school age [145]. The SDQ ADHD predictive algorithm has an acceptable sensitivity for the ADHD diagnosis [146].

Statistical analysis
In all four studies a two sided p-value of <.05 was considered statistically significant. Analyses in Study I were performed using Stata/SE 12 (Stata Corporation, College Station, TX, USA), the Statistical Analysis Software package (SAS, version 9.3), and R (the CARBayes package, R version 3.1.2). Analyses in Study II, III and IV were performed using Stata/SE 11 (Stata Corporation, College Station, TX, USA) on a secure platform hosted by Statistics Denmark.

Exact information about study populations, measures and statistical analyses are presented for each study in the following.
Study I

In Study I, we used an ecological design to assess predictors of the variations in ADHD diagnoses at a municipality level. Data for all Danish children born between the 1 of January 1990 and 31 of December 2000 were extracted from the DMBR, and a total of 750,512 children were included. By means of the civil registration number, the children were followed in the DPR and DPCR for ADHD diagnoses and in the DNPR for ADHD medication. All children were followed from birth until first diagnosis of ADHD, first use of ADHD medication, the age of 11 years, emigration or death, whichever came first.

**Outcome**

The number of ADHD cases was aggregated at municipality level and divided by the number of children born in the municipality in the period; this resulted in an incidence proportion for each of the 98 municipalities. Four groups were created: diagnosis only, medication only, diagnosis and medication, diagnosis and/or medication.

**Explanatory variables**

To examine the access to diagnostic services, information on number and municipality of psychiatric hospitals and privately practising paediatric psychiatrists was extracted from the Danish National Register of Healthcare Provision for 2009. Reflecting the local resources in the municipalities, the information on average annual household in the municipalities and the municipal spending on healthcare were derived from Statistics Denmark for the year 2010. Incidence proportions of the ICD-10 hospital diagnoses F91 “Conduct disorders” and F92 “Mixed disorders of conduct and emotion”, registered in the DPR and DPCR, were used as a proxy for differences in diagnostic culture. A number of criteria for ADHD are also seen as a sign of conduct disorder, which is highly comorbid to ADHD and the distinction between the two diagnoses would rely heavily on the experience of the child psychiatrist [36].

**Statistical Analysis**

Four maps were constructed based on the incidence proportion of ADHD in each municipality using the indicators of ADHD: a) all children with a hospital diagnosis, b) all children redeeming medication, c) all children redeeming medication but without a hospital diagnosis, d) all children with a hospital diagnosis and/or redeeming medication.

Next, the spatial clustering was determined using the local Moran’s I. The Moran’s I statistic is a measure of spatial autocorrelation used to test whether values in a numeric variable are randomly distributed over the geographical area. The strength of spatial autocorrelation ranges from +1 (high values are proximal to other high values) to -1 (high values tend to be near low values), where a value of 0 indicates randomly distributed data. The local Moran’s I reveals whether and where any local clustering occurs, resulting in “hot spots” (clustering of high incidence) and “cold spots” (clustering of low incidence) [147, 148].
Areal data typically exhibit spatial autocorrelation as observations from areal units close together tend to have similar values. This violates the assumption of independence that is common in many regression models. A Bayesian conditional autoregressive (CAR) analysis was performed to estimate the significance of the explanatory variables when considering the spatial autocorrelation between neighbouring municipalities and non-spatial variation for each municipality that was not accounted for by the explanatory variables [149]. A detailed description of the use of the CAR model is presented in the published paper (Study I) [55].
Study II

We restricted the representation analysis of children from the DNBC and the general population to the years 1998-2002 as not all counties were represented in the first two years (1996-1997) and the last year (2003) of enrolment. This subpopulation represents about 90% of the initial cohort. The general population was identified as all live childbirths during 1998-2002 registered in the DMBR.

Measures

Linking the DNBC and the general population to the DPR and DPCR, we followed all children until the first main diagnosis of one of the diagnoses mentioned in the left column of Table 3 or end of follow-up in March 2013 when the children were 11-15 years old. In addition, information on specific medication prescribed for ADHD, anxiety and depression was obtained from the DNPR and updated until November 2011. A child was considered a case if s/he had redeemed at least two prescriptions for ADHD medication, a Selective Serotonin Reuptake Inhibitor (SSRI) product or Serotonin and Noradrenaline Reuptake Inhibitor (SNRI) product. The three groups of medication are described in the right column of Table 3.

Table 3. Description of diagnoses and medication of Study II.

<table>
<thead>
<tr>
<th>Included diagnoses</th>
<th>Included medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>F20-29: Schizophrenia, schizotypal, delusional, other non-mood psychotic disorders</td>
<td>ADHD medication:</td>
</tr>
<tr>
<td>F32-33: Depression</td>
<td>N06BA04 (methylphenidate)</td>
</tr>
<tr>
<td>F40-42: Anxiety disorders (AD) and Obsessive Compulsive Disorder (OCD)</td>
<td>N06BA09 (atomoxetine)</td>
</tr>
<tr>
<td>F84: Autism Spectrum disorders (ASD)</td>
<td>N06BA07 (modafinil)</td>
</tr>
<tr>
<td>F90 and F98.8: Hyperkinetic disorders (HKD/ADHD)</td>
<td>SSRI:</td>
</tr>
<tr>
<td>F91 Conduct disorders (CD)</td>
<td>N06AB04 (Citalopram)</td>
</tr>
<tr>
<td></td>
<td>N06AB05 (Paroxetine)</td>
</tr>
<tr>
<td></td>
<td>N06AB03 (Fluoxetine)</td>
</tr>
<tr>
<td></td>
<td>N06AB10 (Escitalopram)</td>
</tr>
<tr>
<td></td>
<td>N06AB08 (Fluvoxamin)</td>
</tr>
<tr>
<td></td>
<td>N06AB06 (Sertralin)</td>
</tr>
<tr>
<td></td>
<td>SNRI:</td>
</tr>
<tr>
<td></td>
<td>N06AX21 (Duloxetine)</td>
</tr>
<tr>
<td></td>
<td>N06AX16 (Venlafaxin)</td>
</tr>
</tbody>
</table>

Statistical analysis

The proportions of children with recorded childhood diagnosis from the general population and from the DNBC were compared by estimating a prevalence ratio (PR) for every diagnostic group. The PR \(\frac{\text{prevalence}_{\text{participants}}}{\text{prevalence}_{\text{general population}}}\) corresponds to the relative representation of the group. Confidence limits were found by using the following simple approximate formula and interpreted as 95% confidence intervals \[127\].

\[
SE(\log(\text{PR})) = \sqrt{SE(\log(\text{Prevalence}_{\text{participants}}))^2 - SE(\log(\text{Prevalence}_{\text{source}}))^2}
\]

Age at first diagnosis is presented as means with standard deviations (SD). Age in the general population and the DNBC was compared using the one sample t-test, accounting for the inter-dependency between children with diagnoses in the general population and in the DNBC.
Study III

In Study III, the population consisted of participants from the DNBC. We used information from the follow-up questionnaire in the child’s seventh year. A total of 57,282 parents participated in the 7-year follow-up. We included only singletons with complete SDQ data (n=51,527) and linked the information to the DPR, the DPCR and the DNPR in order to identify children with a diagnosis of ADHD and prescribed ADHD medication.

Measures

We identified the children who exhibited ADHD behaviour using the SDQ ADHD algorithm for probable ADHD; hyperactivity/inattention score ≥7 and impact score ≥2. Children were excluded if the impact score did not apply to more than one setting. Children diagnosed with F.84 “Pervasive developmental disorders” were excluded as difficulties corresponding to ADHD may have been recognised without a corresponding diagnosis being registered, respecting the exclusion rule in the ICD-10. Children with positive SDQ ADHD behaviour who were not registered with an ADHD diagnosis were followed in the registers for other psychiatric diagnoses.

Explanatory variables

Socioeconomic status (SES) was based on the current or most recent job within six months or the type of education and was ordered in three categories; “high”, “middle” and “low” [150]. Information on the family structure was obtained from the 7-year follow-up questionnaire and was based on the question whether the parents had been living together since the birth of their child. Maternal depression was self-reported and referred to the time from childbirth to child age 7 years. Maternal depression was positive when the mother reported: 1) to have had a psychiatric illness, and 2) to have been in contact with a physician or a psychologist because of this and 3) that the psychiatric illness was depression. Place of residence was obtained from the CRS, and each ADHD case was assigned to the region in which they were diagnosed or had redeemed medication. Children without an ADHD diagnosis were assigned to the region in which they were born.

Statistical analysis

First, descriptive characteristics are presented for the overall sample, for the ADHD cases and for the SDQ ADHD positives in the absence of an ADHD diagnosis. Second, other mental and behavioural diagnoses are presented for the latter children. To determine the possibility of gender, family status, maternal depression, place of residence and SES being associated with the SDQ ADHD positives and no ADHD diagnosis, we conducted a logistic regression model comparing these children with the ADHD diagnosed children. First, gender, family status, maternal depression, place of residence and SES were analysed separately. Next, all independent variables were included in the model. Multiple logistic regression results are presented with odds ratios (OR) and 95% confidence intervals (CI) for each variable. T-test analyses were used to compare the SDQ subscale scores between the SDQ ADHD positives in the absence of an ADHD diagnosis and the ADHD diagnosed children.
Study IV

The study population consisted of participants from the DNBC, including only those who participated in the first interview and the 7- and 11-year follow-up. We only included children who had complete SDQ reports from all informants; the mother, teacher and child. We restricted our analysis to singletons and excluded siblings.

Outcome
Mothers, teachers and the children themselves were asked about the child’s behaviour through the SDQ. We used the hyperactivity/inattention (H/I), conduct problems (CD) and emotional problems (EM) scales. In addition we used the SDQ ADHD prediction algorithms for each informant and combined.

Exposure
Maternal depression was self-reported and collected at two different time-points: in the first interview referring to the time before pregnancy and at 7-year follow-up referring to the time from childbirth to child age 7 years. Maternal depression was positive when the mother reported 1) to have had a psychiatric illness, and 2) to have been in contact with a physician or a psychologist because of this and 3) that the psychiatric illness was depression. Depression was categorised as reported either at 12 weeks of gestation, in the 7-year follow-up or reported at both time-points.

Potentially confounding variables
In the present study, we controlled for the following potential confounders: mother’s self-reported hyperactivity problems in childhood, mother’s SES, family status and older siblings. The mother’s hyperactivity problems in childhood were assessed with the following question in the 7-year follow-up: Does the following statement fit your own childhood? Was restless, “hyperactive”, had problems keeping quiet long. The question could be answered; “not true”, “partly true” and “very true”, with the latter two as an indicator of the mother’s history of hyperactivity problems.

SES was based on the current or most recent job within 6 months or the type of education and was ordered in three categories; “high”, “middle”, and “low” [150]. We obtained information on family status in the 7-year follow-up questionnaire, in which parents were asked if they had been living together since the birth of their child. We obtained information on whether the index child had older siblings from the first interview.

Statistical analyses
First, parent and child characteristics among children in the 11-year population and the subsample with multi-informant SDQ are presented and compared using the Chisquare test. The raw SDQ subscales scores are then presented with means and SD for each informant and stratified by gender. Teacher and child ratings were each compared to the maternal ratings using a paired T-test.

Next, each informant’s rating was converted into a z-score, by placing each informant’s rating on a distribution relative to the rest of the same informant’s ratings in the sample (standardized score). Resultantly, these z-scores have a distribution with a mean of 0 and a SD of 1 [151].
We examined whether maternal depression would predict hyperactivity/inattention, conduct and emotional problems reported by different informants in multiple linear regression models. We stratified the analysis by gender. The positive prediction from maternal depression to standardized SDQ scores would support the depression-distortion hypothesis if only significant in the maternal report of child problems. Finally, we examined the association between maternal depression and the SDQ ADHD prediction reported by each informant and in combination by using logistic regression models. Odds ratios (OR) and corresponding 95% confidence intervals (95% CI) are presented.

All conducted analyses were adjusted for mother's hyperactivity trait and SES, family status and older siblings.
Results

Study I: Geographic variation and municipality level factors

A total of 750,512 children were born in the period from 1990 to 2000 in Denmark; 8,218 of these had a hospital diagnosis of ADHD and/or redeemed ADHD medication (Table 4) [55].

Table 4. ADHD cases in the study population [55]

<table>
<thead>
<tr>
<th>Hospital diagnosis</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>742,294</td>
</tr>
<tr>
<td>Yes</td>
<td>1,525</td>
</tr>
</tbody>
</table>

GIS mapping

All indicators of ADHD varied considerably across municipalities; the mean incidence proportion of overall ADHD was 1.19%, and the incidence ranged from 0% to 2.87% in the municipalities. The public hospitals in the municipalities are shown as points in map (a), and the private diagnostic facilities as points in map (c) (Figure 5) [55].

Spatial autocorrelation and cluster identification

Figure 6 displays the results of the local Moran’s I analyses. We identified “hot” and “cold” spots in all four analyses. Both the “hot” and the “cold” spots were statistically significant at a 5% level. A large cluster of high incidence of ADHD diagnoses was found in the northwestern part of Region Zealand and the western part of the Capital Region of Denmark (Figure 6, map a). Low incidence of ADHD diagnoses was clustered in the North Denmark Region (Figure 6, map a). Regarding the incidence proportion of overall medication use (Figure 6, map b), we found two significant clusters of low incidence; one in the Region of Southern Denmark and one in the Central Denmark Region. We found three clusters regarding children who had redeemed medication but who did not have a hospital diagnosis (Figure 6, map c). We located “hot” spots in the North Denmark Region, in parts of the Region Zealand and in municipalities in Funen. In addition, we located a “cold” spot in a large part of southern Jutland and the western part of Jutland. The clustering of high incidence of overall ADHD (Figure 6, map d) was not much different from the clustering of high incidence of the other indicators. The clustering of low incidence of overall ADHD was located in the western part of Jutland. In municipalities with a clustering of low incidence of overall ADHD, the average population density was 54 people per square kilometres (ranging from 20 to 145 people per square kilometre). The clustering of high incidence of overall ADHD was located in municipalities with an average population density of 175 per square kilometre (ranging from 84 to 403 people per square kilometre) [55].
Figure 5. Incidence proportion (%) in children aged 0-11 years born from 1990-2000 of (a) diagnosis, (b) medication use, (c) medication use and no registered diagnosis and (d) overall ADHD by municipality. The incidence proportions are split into quartiles. Red points in map (a) and (c), respectively, show the public and private diagnostic facilities in the municipalities [55].
Figure 6. Local Moran’s I clustering of the incidence proportion of (a) diagnosis, (b) medication use, (c) medication use and no registered diagnosis, (d) overall ADHD by municipality (red=hot spots, blue=cold spots) [55].
Spatial regression analysis

When considering the spatial autocorrelation between neighbouring municipalities in the Bayesian CAR analysis, we found no statistically significant associations with any of the explanatory variables for the three outcomes (Table 5). The OR estimates ranged from 0.94 (family income and overall ADHD) to 1.36 (absence of hospital or psychiatrist and diagnosis only) with 95% CIs ranging from below one to above one [55].

Table 5. Summary statistics of parameters in the spatial regression model for outcomes ADHD, diagnosis and medication use given by odds ratio (OR) and credible interval (95% CI) (adapted from the original table in the published paper [55])

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ADHD overall</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family income</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low versus high</td>
<td>0.94</td>
<td>0.76; 1.14</td>
</tr>
<tr>
<td>Medium versus high</td>
<td>0.96</td>
<td>0.81; 1.14</td>
</tr>
<tr>
<td>Municipal spending</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low versus high</td>
<td>1.03</td>
<td>0.88; 1.22</td>
</tr>
<tr>
<td>Medium versus high</td>
<td>1.05</td>
<td>0.89; 1.23</td>
</tr>
<tr>
<td>Conduct disorder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low versus high</td>
<td>1.00</td>
<td>0.80; 1.25</td>
</tr>
<tr>
<td>Medium versus high</td>
<td>1.07</td>
<td>0.89; 1.30</td>
</tr>
<tr>
<td>Absence of hospital/child psychiatrist</td>
<td>1.14</td>
<td>0.97; 1.33</td>
</tr>
<tr>
<td><strong>Medication and no hospital diagnosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family income</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low versus high</td>
<td>0.97</td>
<td>0.70; 1.36</td>
</tr>
<tr>
<td>Medium versus high</td>
<td>1.10</td>
<td>0.83; 1.46</td>
</tr>
<tr>
<td>Municipal spending</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low versus high</td>
<td>1.01</td>
<td>0.77; 1.33</td>
</tr>
<tr>
<td>Medium versus high</td>
<td>0.99</td>
<td>0.77; 1.27</td>
</tr>
<tr>
<td>Conduct disorder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low versus high</td>
<td>1.01</td>
<td>0.68; 1.48</td>
</tr>
<tr>
<td>Medium versus high</td>
<td>1.20</td>
<td>0.87; 1.69</td>
</tr>
<tr>
<td>Absence of a child psychiatrist</td>
<td>0.94</td>
<td>0.70; 1.26</td>
</tr>
<tr>
<td><strong>ADHD diagnosis only</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family income</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low versus high</td>
<td>0.98</td>
<td>0.77; 1.23</td>
</tr>
<tr>
<td>Medium versus high</td>
<td>0.94</td>
<td>0.77; 1.13</td>
</tr>
<tr>
<td>Municipal spending</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low versus high</td>
<td>1.05</td>
<td>0.87; 1.26</td>
</tr>
<tr>
<td>Medium versus high</td>
<td>1.05</td>
<td>0.87; 1.25</td>
</tr>
<tr>
<td>Conduct disorder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low versus high</td>
<td>0.95</td>
<td>0.73; 1.22</td>
</tr>
<tr>
<td>Medium versus high</td>
<td>1.02</td>
<td>0.82; 1.25</td>
</tr>
<tr>
<td>Absence of hospital/child psychiatrist</td>
<td>1.36</td>
<td>0.80; 1.66</td>
</tr>
</tbody>
</table>
Study II: Representation of diagnoses in the DNBC

In the period 1998-2002, 344,160 children were born in Denmark. In the DNBC, mothers of 91,442 children participated in the study in the same time period (26.57%). The participation of children with the specific diagnoses in the DNBC ranged from 21% (schizophrenia and other psychotic disorders) to 28% (anxiety disorders and OCD), with an overall participation of 25% for all selected psychiatric diagnoses. The relative participation varied accordingly as PRs ranged from 0.80 (95% CI: 0.59 1.09) for schizophrenia and 0.83 (95% CI: 0.71; 0.98) for conduct disorders to 1.01 (95% CI: 0.96; 1.06) for ASD and 1.06 (95% CI: 0.97; 1.17) for anxiety disorders or OCD. Children who redeemed prescriptions for SSRI/SNRI (PR: 1.05, 95% CI: 0.90; 1.18) or ADHD medication (PR: 0.99, 95% CI: 0.95; 1.03) were equally represented in the DNBC compared to the general population (Table 6) [152].

In general more boys than girls were registered with a psychiatric diagnosis (4:1) but not for the following diagnoses: schizophrenia, depression and anxiety disorders or OCD. In addition, girls were generally underrepresented to a greater extent than boys, except in relation to diagnoses of depression (PR=1.00 vs. 0.89), anxiety disorders or OCD (PR= 1.12 vs. 1.00) and ASD (PR=1.07 vs. 0.99) (Table 6) [152].

Age at first diagnosis ranged from 7.85 years (ASD) to 12.01 years (depression) in the general population (Table 7). In the DNBC, the children with depression were on average almost 0.4 years younger at the time of diagnosis than the children in the general population (p=0.023). Similar trends were found for children with conduct disorders, although this was not statistically significant (p=0.078) (Table 7). The average age at diagnosis was 0.16 years higher for children with ASD in the DNBC than in the general population, but these figures were not statistically significant (Table 7) [152].
Table 6. The prevalence and relative representation of childhood psychiatric diagnoses and the use of medication in the general population and the DNBC, including gender distribution of the diagnoses [152]

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Prev. (%)</td>
<td>n</td>
<td>Prev. (%)</td>
<td>PR</td>
<td>95% CI</td>
</tr>
<tr>
<td>All</td>
<td>344,160</td>
<td>26.57</td>
<td>91,442</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F20-29 Schizophrenia</td>
<td>150</td>
<td>0.04</td>
<td>32</td>
<td>0.03</td>
<td>21.33</td>
<td>0.80</td>
</tr>
<tr>
<td>- Girls</td>
<td>81</td>
<td>0.023</td>
<td>16</td>
<td>0.017</td>
<td>19.75</td>
<td>0.74</td>
</tr>
<tr>
<td>- Boys</td>
<td>69</td>
<td>0.020</td>
<td>16</td>
<td>0.017</td>
<td>23.19</td>
<td>0.87</td>
</tr>
<tr>
<td>F32-33 Depression</td>
<td>445</td>
<td>0.13</td>
<td>112</td>
<td>0.12</td>
<td>25.17</td>
<td>0.95</td>
</tr>
<tr>
<td>- Girls</td>
<td>237</td>
<td>0.068</td>
<td>63</td>
<td>0.068</td>
<td>26.58</td>
<td>1.00</td>
</tr>
<tr>
<td>- Boys</td>
<td>208</td>
<td>0.060</td>
<td>49</td>
<td>0.053</td>
<td>23.56</td>
<td>0.89</td>
</tr>
<tr>
<td>F40-42 Anxiety disorders and OCD</td>
<td>1,094</td>
<td>0.32</td>
<td>309</td>
<td>0.34</td>
<td>28.24</td>
<td>1.06</td>
</tr>
<tr>
<td>- Girls</td>
<td>549</td>
<td>0.159</td>
<td>164</td>
<td>0.179</td>
<td>29.87</td>
<td>1.12</td>
</tr>
<tr>
<td>- Boys</td>
<td>545</td>
<td>0.158</td>
<td>145</td>
<td>0.158</td>
<td>26.61</td>
<td>1.00</td>
</tr>
<tr>
<td>F84 Autism Spectrum disorders</td>
<td>4,132</td>
<td>1.20</td>
<td>1,107</td>
<td>1.21</td>
<td>26.79</td>
<td>1.01</td>
</tr>
<tr>
<td>- Girls</td>
<td>798</td>
<td>0.232</td>
<td>226</td>
<td>0.247</td>
<td>28.32</td>
<td>1.07</td>
</tr>
<tr>
<td>- Boys</td>
<td>3,334</td>
<td>0.968</td>
<td>881</td>
<td>0.963</td>
<td>26.42</td>
<td>0.99</td>
</tr>
<tr>
<td>F90, F98.8 Hyperkinetic disorders</td>
<td>6,560</td>
<td>1.91</td>
<td>1,652</td>
<td>1.81</td>
<td>25.18</td>
<td>0.95</td>
</tr>
<tr>
<td>- Girls</td>
<td>1,473</td>
<td>0.427</td>
<td>341</td>
<td>0.372</td>
<td>23.15</td>
<td>0.87</td>
</tr>
<tr>
<td>- Boys</td>
<td>5,087</td>
<td>1.478</td>
<td>1,311</td>
<td>1.433</td>
<td>25.77</td>
<td>0.97</td>
</tr>
<tr>
<td>F91 Conduct disorders</td>
<td>517</td>
<td>0.15</td>
<td>114</td>
<td>0.12</td>
<td>22.05</td>
<td>0.83</td>
</tr>
<tr>
<td>- Girls</td>
<td>108</td>
<td>0.031</td>
<td>14</td>
<td>0.015</td>
<td>12.96</td>
<td>0.49</td>
</tr>
<tr>
<td>- Boys</td>
<td>409</td>
<td>0.118</td>
<td>100</td>
<td>0.109</td>
<td>24.45</td>
<td>0.92</td>
</tr>
<tr>
<td>All diagnoses</td>
<td>12,898</td>
<td>3.75</td>
<td>3,326</td>
<td>3.64</td>
<td>25.79</td>
<td>0.97</td>
</tr>
<tr>
<td>ADHD medication</td>
<td>7,488</td>
<td>2.18</td>
<td>1,965</td>
<td>2.15</td>
<td>26.24</td>
<td>0.99</td>
</tr>
<tr>
<td>- Girls</td>
<td>1,586</td>
<td>0.461</td>
<td>397</td>
<td>0.434</td>
<td>25.03</td>
<td>0.94</td>
</tr>
<tr>
<td>- Boys</td>
<td>5,902</td>
<td>1.715</td>
<td>1,568</td>
<td>1.715</td>
<td>26.57</td>
<td>0.99</td>
</tr>
<tr>
<td>SSRI &amp; SNRI</td>
<td>537</td>
<td>0.15</td>
<td>150</td>
<td>0.16</td>
<td>27.93</td>
<td>1.05</td>
</tr>
<tr>
<td>- Girls</td>
<td>223</td>
<td>0.065</td>
<td>45</td>
<td>0.049</td>
<td>20.17</td>
<td>0.76</td>
</tr>
<tr>
<td>- Boys</td>
<td>314</td>
<td>0.091</td>
<td>105</td>
<td>0.115</td>
<td>34.44</td>
<td>1.26</td>
</tr>
</tbody>
</table>

DNBC: Danish National Birth Cohort, ICD 10: International Classification of Diseases, 10th Revision, CI: Confidence Intervals, OCD: Obsessive Compulsive Disorder, SSRI: Selective Serotonin Reuptake Inhibitor, SNRI: Serotonin and Noradrenaline Reuptake Inhibitor
Table 7. Age at diagnosis in the general population and in the DNBC [152]

<table>
<thead>
<tr>
<th>ICD-10 diagnoses</th>
<th>General population</th>
<th>DNBC</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) at diagnosis (SD)</td>
<td>Age (years) at</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>diagnosis (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F20-29: Schizophrenia</td>
<td>11.60 2.46</td>
<td>11.92 3.23</td>
<td>t=0.04, df=31, p=0.416</td>
</tr>
<tr>
<td>F32-33: Depression</td>
<td>12.01 1.83</td>
<td>11.64 1.70</td>
<td>t=-2.29, df=110, p=0.023</td>
</tr>
<tr>
<td>F40-42: Anxiety disorders and OCD</td>
<td>10.61 2.25</td>
<td>10.51 2.18</td>
<td>t=-0.83, df=308, p=0.405</td>
</tr>
<tr>
<td>F84: Autism Spectrum disorders</td>
<td>7.85 3.14</td>
<td>8.01 2.98</td>
<td>t=1.88, df=1104, p=0.060</td>
</tr>
<tr>
<td>F90, F98.8: Hyperkinetic disorders</td>
<td>8.87 2.40</td>
<td>8.81 2.29</td>
<td>t=-0.74, df=1648, p=0.459</td>
</tr>
<tr>
<td>F91: Conduct disorders</td>
<td>7.88 2.97</td>
<td>7.43 2.73</td>
<td>t=-1.77, df=113, p=0.078</td>
</tr>
</tbody>
</table>
Study III: Characteristics of undiagnosed children

There were 51,527 participating children; 1,046 received an ADHD diagnosis and 998 had redeemed ADHD medication prescriptions during follow-up. A total of 1,373 children were registered as ADHD cases (2.7% of the cohort) due to an overlap of 671 children who redeemed medication and had a registered ADHD diagnosis. Of the 1,179 children with a positive SDQ ADHD prediction, 680 were not identified with an ADHD diagnosis (Table 8). Excluding children if the impact did not apply to more than one setting (n=14) and with a diagnosis of F84: Pervasive development disorder (n=13), we found that the SDQ positives in the absence of an ADHD diagnosis (n=653) represented 57% of the SDQ ADHD “probable” and 1.3% of the total cohort. Of the 1,373 ADHD diagnosed children, 727 (53%) were predicted “unlikely” of SDQ ADHD [153].

Table 8. Children with and without ADHD diagnosis and the SDQ ADHD prediction categories[153]

<table>
<thead>
<tr>
<th>ADHD diagnosed</th>
<th>SDQ ADHD prediction</th>
<th>Unlikely</th>
<th>Possible</th>
<th>Probable</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td></td>
<td>48,794</td>
<td>680</td>
<td>680</td>
<td>50,154</td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td>727</td>
<td>147</td>
<td>499</td>
<td>1,373</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>49,521</td>
<td>827</td>
<td>1,179</td>
<td>51,527</td>
</tr>
</tbody>
</table>

In Table 9, the distributions of sociodemographic variables are reported for the whole sample, the ADHD diagnosed children, and the children with SDQ ADHD behaviour and no ADHD diagnosis. Compared with the overall sample, ADHD diagnosed children were more likely to be boys (79% vs. 51.2%), less likely to live with both parents (69.4% vs. 83.8%) and more likely to belong to low SES (14.2% vs. 7.8%) (Table 9). In the group of SDQ positives without ADHD diagnosis, the gender distribution was also in favour of boys, although the difference was smaller than in the group of ADHD cases. The SDQ positives without ADHD diagnosis were more similar with the ADHD cases than the overall sample on family status, mother’s socioeconomic status and maternal depression (Table 9). The mean child age at end of follow-up did not differ between the overall sample, the ADHD cases and the SDQ ADHD positives without ADHD diagnosis (Table 9) [153].

In the group of children with SDQ ADHD and without ADHD diagnosis, 46 (7%) had other mental and behavioural disorders. Of those, the majority had a diagnosis related to disorders of psychological development (35%) or behavioural and emotional disorders (35%) [153].
Table 9. Distribution of sociodemographic variables for the overall sample, the ADHD diagnosed and the SDQ ADHD positives without ADHD diagnosis [153]

<table>
<thead>
<tr>
<th></th>
<th>Overall sample</th>
<th>ADHD diagnosed n (%)</th>
<th>SDQ ADHD positive, no ADHD diagnosis n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>51 527 (100)</td>
<td>1 373 (2.7)</td>
<td>653 (1.3)</td>
</tr>
<tr>
<td>Child’s gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boy</td>
<td>26 371 (51.2)</td>
<td>1 085 (79)</td>
<td>440 (67)</td>
</tr>
<tr>
<td>Girl</td>
<td>25 144 (48.8)</td>
<td>288 (21)</td>
<td>213 (33)</td>
</tr>
<tr>
<td>Missing data</td>
<td>12 (&lt;0.1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Family status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Living with both parents</td>
<td>43 156 (83.8)</td>
<td>953 (69.4)</td>
<td>445 (68.1)</td>
</tr>
<tr>
<td>Parents divorced</td>
<td>8 254 (16)</td>
<td>417 (30.3)</td>
<td>207 (31.7)</td>
</tr>
<tr>
<td>Missing data</td>
<td>117 (0.2)</td>
<td>3 (0.3)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Mother’s socioeconomic status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>27 243 (52.9)</td>
<td>561 (40.9)</td>
<td>236 (36.2)</td>
</tr>
<tr>
<td>Middle</td>
<td>17 938 (34.8)</td>
<td>555 (40.4)</td>
<td>268 (41.0)</td>
</tr>
<tr>
<td>Low</td>
<td>4 006 (7.8)</td>
<td>199 (14.5)</td>
<td>108 (16.5)</td>
</tr>
<tr>
<td>Missing data</td>
<td>2 340 (4.5)</td>
<td>58 (4.2)</td>
<td>41 (6.3)</td>
</tr>
<tr>
<td>Maternal depression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3 740 (7.3)</td>
<td>227 (16.5)</td>
<td>96 (14.7)</td>
</tr>
<tr>
<td>No</td>
<td>47 787 (92.7)</td>
<td>1 146 (83.5)</td>
<td>557 (85.3)</td>
</tr>
<tr>
<td>Mean child age at end of follow-up (SD)</td>
<td>12.49 (1.36)</td>
<td>12.59 (1.31)</td>
<td>12.44 (1.37)</td>
</tr>
</tbody>
</table>

The adjusted results of the logistic regression analysis showed that the SDQ ADHD without ADHD diagnosis were more likely to be girls (OR_adj: 1.83; 95% CI 1.45; 2.29), to have a mother with a low SES (OR_adj: 1.49; 95% CI 1.10; 2.02) and to live in the Region of Southern Denmark (OR_adj: 2.04; 95% CI 1.51; 2.73), with the Capital Region of Denmark serving as the reference (Figure 7).

Figure 7. Plot of the logistic regression model predicting the probability for each independent variable occurring in the group of SDQ ADHD positive without ADHD diagnosis vs. ADHD diagnosed. OR adjusted for each explanatory variable.
The SDQ ADHD positives without ADHD diagnosis had significantly higher scores on all subscales compared to the children who received an ADHD diagnosis during follow-up, except for the prosocial scale, which is a positive scale (with higher scores reflecting better prosocial behaviour). The differences between the groups were most pronounced on the hyperactivity/inattention scale (8.51 vs. 6.27) and the emotional scale (3.72 vs. 2.77) and (Table 10) [153].

Table 10. Mean scores on SDQ subscales for SDQ ADHD positive without ADHD diagnosis vs. ADHD diagnosed children [153]

<table>
<thead>
<tr>
<th>SDQ ADHD positive without ADHD diagnosis Mean (95% CI)</th>
<th>ADHD diagnosed Mean (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperactivity/inattention 8.51 (8.42; 8.59)</td>
<td>6.27 (6.12; 6.41)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Conduct problems 3.45 (3.31; 6.60)</td>
<td>2.81 (2.71; 2.91)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Emotional problems 3.72 (3.54; 3.90)</td>
<td>2.77 (2.65; 2.89)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Impact 3.19 (3.04; 3.34)</td>
<td>2.19 (1.87; 2.13)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Peer problems 3.06 (2.89; 3.24)</td>
<td>2.42 (2.30; 2.54)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Prosocial (positive)* 6.52 (6.35; 6.69)</td>
<td>7.21 (7.10; 7.33)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*The prosocial score is positive, reflecting better prosocial behaviour
Study IV: Maternal depression-related distortions

The sample participating in the first interview, and the 7-year follow-up and the 11-year follow-up consisted of 35,479 children with SDQ reports either by the mother (n=32,700), the teacher (n=13,800) or the child (n=31,841), resulting in a subsample of 12,961 children (37%) with complete SDQ by all three informants. Of the participants with multi-informant reports, 2.3% of the mothers reported depression before pregnancy, 6.6% reported depression in the period from childbirth to child age 7 years and 0.9% reported depression at both time-points (Table 1). These did not differ from the participants without multi-informant reports. Among participants with multi-informant reports, slightly more mothers reported a history of hyperactivity (10.5% vs. 9.4%), girls were more represented (51.3% vs. 49.9%) and more children were living with both parents (86.7% vs. 84.9%) than participants without multi-informant reports. Children with missing teacher SDQ report were generally reported by the mother to have significantly more problems on all SDQ subscales than participants with multi-informant reports (Table 1) [154].

On the hyperactivity/inattention and conduct scales, boys presented with higher scores, whereas girls presented with more emotional problems as reported by all informants (Table 12). Teachers reported statistically significantly higher scores on the hyperactivity/inattention and conduct scales in both boys and girls than mothers. Mothers significantly reported more emotional problems in both boys and girls than teachers (Table 12). Girls generally reported more emotional problems than mothers, whereas no difference was found between mothers and self-reports in boys. In contrast, both boys and girls reported more hyperactivity/inattention and conduct problems than the mothers (Table 12) [154].
Table 1. Parent and child characteristics among participants without and with multi-informant reports in the child population aged 11 years [154]

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Participants without multi-informant SDQ</th>
<th>Participants with multi-informant SDQ</th>
<th>Pearson chi2 P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=22,518</td>
<td>N=12,961</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Maternal depression before pregnancy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>506 (2.3)</td>
<td>296 (2.3)</td>
<td>0.819</td>
</tr>
<tr>
<td>No</td>
<td>21,988 (97.6)</td>
<td>12,647 (97.6)</td>
<td></td>
</tr>
<tr>
<td>Maternal depression at child age 0-7 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1,496 (6.6)</td>
<td>853 (6.6)</td>
<td>0.828</td>
</tr>
<tr>
<td>No</td>
<td>21,012 (93.4)</td>
<td>12,097 (93.3)</td>
<td></td>
</tr>
<tr>
<td>Maternal depression at both time-points</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>209 (0.9)</td>
<td>124 (0.9)</td>
<td>0.784</td>
</tr>
<tr>
<td>No</td>
<td>22,275 (98.9)</td>
<td>12,809 (98.8)</td>
<td></td>
</tr>
<tr>
<td>Maternal history of hyperactivity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2,374 (10.5)</td>
<td>1,214 (9.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>19,833 (88)</td>
<td>11,594 (89.4)</td>
<td></td>
</tr>
<tr>
<td>Child gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>11,275 (50.1)</td>
<td>6,318 (48.7)</td>
<td>0.016</td>
</tr>
<tr>
<td>Girls</td>
<td>11,239 (49.9)</td>
<td>6,643 (51.3)</td>
<td></td>
</tr>
<tr>
<td>Socioeconomic status of the mother</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>12,267 (54.5)</td>
<td>8,126 (62.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medium</td>
<td>8,200 (36.5)</td>
<td>3,909 (30.2)</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1,726 (7.6)</td>
<td>710 (5.5)</td>
<td></td>
</tr>
<tr>
<td>Family status, living with both parents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>19,126 (84.9)</td>
<td>11,243 (86.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>3,350 (14.9)</td>
<td>1,702 (13.1)</td>
<td></td>
</tr>
<tr>
<td>Older siblings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>11,700 (52)</td>
<td>6,764 (52.2)</td>
<td>0.678</td>
</tr>
<tr>
<td>No</td>
<td>10,818 (48)</td>
<td>6,197 (47.8)</td>
<td></td>
</tr>
<tr>
<td>Maternal SDQ report</td>
<td>Mean (SD)*</td>
<td>Mean (SD)</td>
<td>T-test P value</td>
</tr>
<tr>
<td>Hyperactivity/inattention</td>
<td>2.31 (2.20)</td>
<td>1.98 (2.04)</td>
<td>&gt;0.001</td>
</tr>
<tr>
<td>Conduct problems</td>
<td>0.93 (1.18)</td>
<td>0.78 (1.09)</td>
<td>&gt;0.001</td>
</tr>
<tr>
<td>Emotional problems</td>
<td>1.84 (1.95)</td>
<td>1.62 (1.79)</td>
<td>&gt;0.001</td>
</tr>
<tr>
<td>Impact</td>
<td>0.36 (1.11)</td>
<td>0.24 (0.91)</td>
<td>&gt;0.001</td>
</tr>
</tbody>
</table>

*Among participants without multi-informant SDQ, 2,779 children had missing maternal SDQ report
### Table 12. Raw SDQ subscale scores by informant type and child gender [154]

<table>
<thead>
<tr>
<th>SDQ scale</th>
<th>Parent M</th>
<th>Parent SD</th>
<th>Teacher M</th>
<th>Teacher SD</th>
<th>Child M</th>
<th>Child SD</th>
<th>Paired T-test PT</th>
<th>Paired T-test PC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperactivity/inattention</td>
<td>2.34</td>
<td>2.18</td>
<td>4.18</td>
<td>4.15</td>
<td>2.67</td>
<td>2.20</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Conduct problems</td>
<td>0.81</td>
<td>1.14</td>
<td>2.18</td>
<td>0.92</td>
<td>1.24</td>
<td>1.32</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Emotional problems</td>
<td>1.51</td>
<td>1.77</td>
<td>1.17</td>
<td>1.75</td>
<td>1.55</td>
<td>1.72</td>
<td>&lt;0.001</td>
<td>0.042</td>
</tr>
<tr>
<td>Impact</td>
<td>0.29</td>
<td>1.03</td>
<td>0.35</td>
<td>0.89</td>
<td>0.16</td>
<td>0.73</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Boys N=6 318**

<table>
<thead>
<tr>
<th>SDQ scale</th>
<th>Parent M</th>
<th>Parent SD</th>
<th>Teacher M</th>
<th>Teacher SD</th>
<th>Child M</th>
<th>Child SD</th>
<th>Paired T-test PT</th>
<th>Paired T-test PC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperactivity/inattention</td>
<td>1.63</td>
<td>1.84</td>
<td>3.91</td>
<td>0.89</td>
<td>2.25</td>
<td>1.98</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Conduct problems</td>
<td>0.74</td>
<td>1.03</td>
<td>2.11</td>
<td>0.66</td>
<td>1.18</td>
<td>1.21</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Emotional problems</td>
<td>1.74</td>
<td>1.81</td>
<td>1.36</td>
<td>1.84</td>
<td>2.09</td>
<td>1.90</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Impact</td>
<td>0.19</td>
<td>0.77</td>
<td>0.18</td>
<td>0.65</td>
<td>0.18</td>
<td>0.75</td>
<td>0.319</td>
<td>0.359</td>
</tr>
</tbody>
</table>

**Girls N=6 643**

M: Mean, SD: Standard deviation, PT: parent-teacher comparison, PC: parent-child comparison.

As presented in figure 8, maternal depression, when reported during pregnancy or at child age 7 years, was associated with an increase in maternal-reported hyperactivity/inattention problems in both boys and girls, while no association was found for the teacher report (adjusted results are presented). Both boys and girls reported significantly higher hyperactivity/inattention, but only when maternal depression was reported at child age 7 years (adjusted results are presented).

![Figure 8. Associations between maternal depression and child hyperactivity/inattention problems reported by the mother, teacher and child, results are shown for boys and girls.](image-url)
Similar results were found in relation to conduct problems (Figure 9). Both boys and girls reported significantly higher conduct problems, but only when maternal depression was reported at child age 7 years. For girls, teachers reported significantly fewer conduct problems when maternal depression was reported at both time-points (Figure 9).

Figure 9. Associations between maternal depression and child conduct problems reported by the mother, teacher and child, results are shown for boys and girls.

For emotional problems, agreement was present between the informants; higher emotional problems for both boys and girls when maternal depression was reported at child age 7 years (Figure 10).
The associations between maternal depression and SDQ-predicted ADHD (reported by each informant and in combination) are presented in Figure 11. We found different risk estimates (ORs), depending on the informant. Maternal depression reported at child age 7 years statistically significantly increased the risk of SDQ-predicted ADHD as reported by each informant. When combining the reports from all informants, almost twice the risk of SDQ-predicted ADHD was observed among children with depressive mothers (OR$_a$ 1.78 (1.29; 2.46)). The association between maternal depression and SDQ-predicted ADHD was stronger when the mother reported than when the teacher reported (OR$_a$ 2.04 (1.54; 2.69) vs. OR$_a$ 1.47 (1.09; 1.98)).
Figure 11. Plot of associations between maternal depression and SDQ-reported ADHD by mother, teacher, child and all combined, adjusted OR.
Discussion
The overall aim of this thesis was to explore the influence of factors at the different levels on the pathway to an ADHD diagnosis. In study I, we investigated the geographical pattern of the incidence of ADHD at municipality level, and we explored the associations between the incidence of ADHD and structural factors. In study III and IV, we examined family and child level factors associated with ADHD behaviour and ADHD diagnosis. In study III, we found a group of children who exhibited ADHD behaviour according to their parents, but who did not receive an ADHD diagnosis during follow-up. In the discussion, we will use the term “potentially undetected” for these children, although we are well aware that these children may not be within the clinical range of an ADHD diagnosis.
Study II, which focuses on the representation of childhood psychiatric diagnoses, is included when relevant and mainly in the discussion of strengths and limitations.

Main findings in relation to previous studies

Geographic variation and structural factors (Study I)
In study I, we found considerable variation in the incidence of ADHD in the Danish municipalities; from a low incidence of 0% to a high incidence of 2.87%, which is consistent with findings in other western countries [43, 47, 51]. In addition we found significant clustering of both low and high incidence rates. The clustering of low incidence was located in less populated areas, whereas the clustering of high incidence was located in densely populated areas [55]. This phenomenon has also been described in studies from other western countries, where diagnosis of ADHD and medication use were found to be less prevalent in rural than urban areas [50, 51].

The observed variations in the incidence of children with ADHD diagnoses and treated with ADHD medication may not reflect differences in the prevalence of the disorder. Rather, it may reflect differences in the interpretation and handling of behavioural problems in children, as has been suggested in previous studies [48, 52, 80]. Opposite to previous findings in US studies, we did not find significant associations between the incidence of ADHD diagnoses/medication and factors at the structural level, when taking into account the spatial correlation.

Healthcare access and availability of resources (Study I)
In less populated areas, the recruitment of specialist physicians is known to be difficult. In Denmark, the locations of private practicing child psychiatrists are highly correlated to location of psychiatric hospitals; this implies that large areas do not have diagnostic resources available [55].

Since the 1990s, 14 child psychiatric wards have existed in Denmark (two were closed in 2007). These wards have been distributed with at least one in each of the five Danish regions. Three child and adolescent psychiatric wards are located in the Capital Region of Denmark and three are located in the northern part of Region Zealand. This results in a large capacity of resources in these areas, which might explain the locations of the high ADHD incidence clusters. Conversely, with only one child and adolescent psychiatric ward in the North Denmark Region, this is the
region with the least capacity and the least resources in the area of child psychiatry. The North Denmark Region has had the lowest frequency of referrals and patients in child and adolescent psychiatry in 2001-2011 compared to the other Danish regions [155]. One commonly accepted explanation is that GPs and school psychologists have adapted to the low capacity in the psychiatric hospitals and, therefore, do not refer as many children as is the case in other geographical areas. Probably as a result of the relatively low capacity in the public child and adolescent psychiatric facility in this region, a large number of children are being treated under the auspices of private practice physicians. This is reflected in the large cluster of high incidence of medication use when no diagnoses are registered. In line with these findings, a recent review assessing how parents perceive barriers and facilitators to access treatment for mental health problems in their children found that the capacity and the waiting time to access the services and the location of service providers were recurring structural barriers [156]. However, we did not find a statistical association with availability of diagnostic services, which might suggest that there are different reasons for the variations in ADHD incidence in the regions and probably also in the municipalities [55].

Cultural differences in diagnostic services (Study I)

In the Region of Southern Denmark, there are four psychiatric hospitals, but large variations are still found between the municipalities within the region. The municipalities right next to each other vary in incidence; from the lowest quartile to the highest quartile. Similar patterns have been found in Norway [47]. The large variation may reflect differences in the diagnostic practices between hospitals. There are few child psychiatric wards and few child psychiatrists in Denmark. The opinion of one senior child psychiatrist may thus affect the entire psychiatric ward, which may result in different diagnostic and treatment cultures at different hospitals. This is consistent with a recent study that found considerable variation across hospitals in the ADHD treatment behaviour of specialist physicians [64]. We explored whether the incidence of ADHD could be affected by different diagnostic cultures by examining the variation in the incidence of the differential diagnosis conduct disorder. A number of criteria for ADHD are also seen as a sign of conduct disorder, which is highly comorbid to ADHD [36]. The idea was to examine if the variation in the incidence of conduct disorders would explain the incidence in ADHD as we hypothesized that the incidence of conduct disorders may be higher in municipalities with a lower ADHD incidence. We did not find an association, and this suggests that cultural differences in diagnostic practice are far more complex than simply distinguishing between the two diagnoses [55].

The use of two different diagnostic systems may reflect some of the national variation as some professionals may choose to use the principles of the DSM-system despite registering the diagnoses with ICD-10 codes. The inclusion criteria are far more strict in the ICD-10 with an expected prevalence of 1-3%, whereas the expected prevalence is 4-8% when using the DSM system [157]. However, even where the same diagnostic definitions are applied, differences may still be found in the thresholds applied for symptoms and impairment. For example, how severe should avoidance of tasks that require sustained attention or high levels of fidgeting be before such avoidance is considered to be clinically significant? [27]. Likewise, how
significant should the impairment in social, academic or occupational performance be to warrant the diagnosis? [14].

Community factors (Study I)

In study I, we investigated the associations between the incidence of ADHD and the available resources at municipality-level in terms of municipal spending on healthcare for children and household SES. Municipal spending on primary healthcare for children is a measure of the services provided by health visitors and school nurses. These services are available for all Danish children, but how the resources are spent and how the care is organized may differ between the municipalities [55]. Using the municipal spending on healthcare for children as a measure of the capacity of health promotion and disease prevention in children, we set up two contending hypotheses: 1) high spending would indicate greater knowledge and awareness about children with mental health challenges, which was expected to result in increased referral for diagnostic assessment, and 2) high spending could reflect greater need for services because of adverse socioeconomic composition in the municipality. However, we found no association with the municipal spending and no association between incidence of ADHD and average household SES in the municipalities. This is in contrast to an American study, which found that high-income areas had higher incidence of diagnosed ADHD [104]. In addition, a study on the geographic variation of autism diagnoses found that individuals were more likely to be diagnosed with autism when they moved into well-resourced neighbourhoods compared to individuals whose neighbourhood resources did not change [75]. However, even if local resources may influence the public attention and thereby the referral of children, it would be difficult to demonstrate this in a Danish context because of the relatively low variation in SES between the municipalities. In addition, the municipality is probably too large an areal unit for assessing community factors [55].

Study I was clearly not designed to assess whether the variations in ADHD diagnoses and medication use were caused by different thresholds in problem recognition by parents or teachers or barriers related to referral or healthcare utilization. However, in study III, we found that the potentially undetected children were more likely to live in the Region of Southern Denmark in municipalities with an ADHD incidence in the lowest quartile. These results suggest that low ADHD incidence might not be due to lack of problem recognition by parents, but rather is caused by barriers related to either the school or the GP in the referral process. This is an example of how factors at different levels are interdependent. If the diagnostic resources are not available at the structural level the increased parental problem recognition may not lead to an increased ADHD diagnosis prevalence.

A study found that ADHD diagnosis rates ranged significantly between school district boundaries, which suggests that variation occurs at even smaller units than the municipality level [158]. Unfortunately, we were not able to examine the role of the schools or the GPs in the studies. School-related problems have been found to play an important role in the help-seeking process and to influence both parental help-seeking and problem recognition by the GP. The findings from a recent study suggest that teachers may lack information about the causes, nature and outcomes of
ADHD and may have difficulty identifying symptoms in a particular student [159]. Therefore, future research should focus on the role of school personnel in the detection, referral, and provision of help for child and adolescent psychopathology. Likewise, the potential the effects on mental health service use should be explored [67].

Family factors (Study III and IV)

Parental mental health (Study III and IV)

Consistent with other studies, we found that the proportion of ADHD diagnosed children with a mother who had depression (at some point during the first seven years of the child’s life) was more than twice as high as in the overall population (16.5% vs. 7.3%) (Study III). The proportion was slightly smaller in the potentially undetected group of children (14.7%). Greater family stress has been found to influence help-seeking. However, while parental psychopathology seems to increase problem recognition, it does not seem to increase service utilization [67]. This might suggest that mentally vulnerable parents experience barriers in the access to the healthcare system and/or that they perceive the child’s problematic behaviour as worse than it really is. The latter mechanism has been confirmed in clinical [98, 160-162] and population-based studies [163-168] and has been referred to as the depression-distortion hypothesis [101].

In study IV, we investigated the influence of maternal depression on the report of child behaviour problems in a Danish population sample of 11-year-old children. We found that maternal depression, both before pregnancy and during the first seven years of the child’s life, was associated with increased child hyperactivity/inattention and with conduct problems when reported by the mother but not when reported by the teacher. The child’s self-report of behaviour problems was only associated with maternal depression when present during the child’s first seven years of life. These results could point to bias in the maternal report of child behaviour, which could be caused by depression-related distortions. However, an alternative explanation for our findings is the possibility that children of depressed mothers in fact show higher levels of behaviour problems at home than at school. Cross-situational differences in the behaviour of the child could be a plausible explanation as children may behave differently at home because of potential negative parenting prompted by the mother’s depressive symptoms [163, 168].

In Study IV, we used the SDQ ADHD prediction to assess the influence of maternal depression on clinically relevant ADHD behaviour. We found that risk estimates of maternal depression as predictor of SDQ ADHD differed by informant, with the highest risk when reported by the mother. These results suggest that relying on different informants (and with different characteristics) may lead to identifying different children in a given population as children meeting criteria for the disorder [169]. In the assessment of child ADHD, multi-informant methods are preferred. However, the results suggest that, when combined categories are generated, thus identifying ADHD problems if present according to either one of the informants, bias by maternal reports cannot be ruled out [164].

In clinical practice, parent reports are often readily available and are sometimes used
in the absence of a teacher report. In situations that also call for a teacher report, such report is typically acquired with some effort on the part of the clinician and parent. Using only a parent report leaves some uncertainty as to whether the child indeed satisfies the diagnostic criteria for ADHD. Obtaining a teacher report in addition to that of a parent is likely to delay making a diagnosis and initiate appropriate treatment [170]. However, on indication of psychopathology in a parent, clinicians should focus on involving the ratings of other informants, e.g., the other parent or the teacher. Furthermore, it would also seem reasonable to include an evaluation of the mother’s emotional state in the clinical assessment of the child [162].

**SES (Study III)**

Similar with other studies, we found that socioeconomic disadvantage was more common in children diagnosed with ADHD (Study III) [45, 52]. In addition, we found that the potentially undetected children were even more likely than the children diagnosed with ADHD during follow-up to have mothers with low SES. This is consistent with findings from several other studies showing that socioeconomic disadvantage may be a predictor of non-treatment [112, 171]. As low SES generally reflects a low level of education, the association with undetected ADHD in the children could reflect that these mothers do not necessarily have any preconditions for understanding the healthcare system and make demands because of a poorer communicative and health literacy [105]. A recent review found that lack of knowledge about where to go to ask for help and how to go about as well as a poor understanding of the healthcare system acted as important barriers for parents’ help-seeking [156].

Lone parenthood may affect the SES in the family, and family status has been associated with mental disorders in children. A large UK study found that the prevalence rates of mental disorders were greater among children in lone parents compared with two-parent families and in reconstituted families compared to intact families [58]. A Swedish study found similar results [52]. In line with this, we found that among the ADHD diagnosed children about 70% were living with both parents compared to about 84% in the overall sample, which was similar in the group of potentially undetected children.

Unfortunately, we were not able to investigate the influence of ethnicity in the current studies.

**Child factors (Study III)**

**Symptoms and presentation (Study III)**

In study III, we compared the mean parent-reported SDQ subscale scores for children at age 7 years with an ADHD diagnosis during follow-up and potentially undetected children. Surprisingly, we found that the latter group of children had significantly higher scores on both the internalizing (emotional and peer problems) and externalizing (hyperactivity/ inattention and conduct problems) scales. In previous studies, externalizing behaviour has been found to increase problem recognition and help-seeking by the parents [95]. The fact that these children do not have a diagnosis (although a small part have another diagnosis of mental health
disorders) could either point to barriers in the access to treatment or reluctance by the parents to seek help.

**Gender (Study III)**
In study III, we found a gender ratio of about 1:4 (girls:boys) among the ADHD diagnosed children, whereas the gender ratio among the potentially undetected children was 1:2. After adjusting for the other covariates, the potentially undetected children were about 80% more likely to be girls compared with the children who received an ADHD diagnosis during follow-up. It has been suggested that the under-identification of girls may be due to gender differences in the phenotypic expression of ADHD as girls tend to present with less disruptive behaviour, which may result in less problem recognition by parents and teachers [117]. Though studies have concluded that the symptoms of hyperactivity and impulsivity are indeed present in girls with ADHD, girls generally have a lower intensity of these symptoms than do boys, and girls are more likely to have the inattentive subtype of ADHD [115]. Only two questions in the SDQ assess inattention, and the SDQ ADHD prediction requires a score of 7 on the hyperactivity/inattention scale, which suggests that these girls would indeed have some hyperactivity/impulsivity symptoms.

**Strengths and limitations**
There are several strengths in the four studies included in the current thesis. A major strength is the use of the national registers, which hold data on all Danish citizens. The use of registers implies that only migration or death could cause attrition, which minimises the risk of bias. In addition, we used information from the DNBC, which is one of the largest cohorts in the world with extensive information about factors during pregnancy, the birth and the later life course of the child. Although cohorts lack the advantage of complete follow-up, they generally provide more detailed information about the population, including perceptions of the child’s behaviour. Strengths and limitations are further discussed in the following in relation to selection and information bias and confounding.

**Selection bias**
Selection bias is a systematic error in a study that derives from the procedures used to select subjects to a study and from factors that influence study participation. The phenomenon will occur when the studied association differs for those who participate and those who do not participate in the study [172]. Selection problems are common in cohort studies, and the DNBC is no exception. Even though the relatively low participation rate in the DNBC was mainly due to unwillingness of GPs to participate, a study revealed an underrepresentation of groups with low socioeconomic resources in terms of education, occupation, income and civil status [127]. Because of this, we investigated the representation of childhood psychiatric diagnoses and prescribed psychotropic medication in the DNBC compared to the background population (Study II). We found that most of the specific diagnoses were modestly underrepresented in the DNBC compared to the general population. However, the prevalence of prescribed ADHD medication did not differ from the general population. The ADHD diagnosis was underrepresented by about 5% more for girls than for boys, which was similar to the findings recently reported for the
large Norwegian Mother and Child Cohort (MoBa) [173]. The results suggest that social selection may have had an influence on the prevalence of later diagnosed ADHD in the DNBC. We found that the children in the DNBC on average were diagnosed earlier with depression, which suggest earlier identification. However, no significant age differences were found for first ADHD diagnosis or for other psychiatric diagnoses.

Selection bias can also occur from loss to follow-up. This is particularly relevant for study III and IV in which a significant number of losses to follow-up was observed. In a study of loss to follow-up in the DNBC from the first interview to the 11-year follow-up, we found that loss to follow-up was associated with a low SES, maternal psychopathology, being a young mother (<20 years) and child ADHD diagnosis [174]. In Study III, this might have resulted in an underestimation of ADHD diagnosed children and consequently in an overestimation of potentially undetected children. However, the relatively poor representativeness of low SES groups in the DNBC may have caused an underestimation of children with positive SDQ ADHD. In study IV, loss to follow-up was associated with both exposure (maternal depression before pregnancy) and outcome (child behaviour problems). This could have caused selection bias, which may have resulted in an underestimation of the association between maternal depression and child behaviour problems reported by the teacher.

In Study III, we were not able to follow all children for an equal amount of time because the cohort was born between 1996 and 2003. This problem could cause misclassification as some more recently born children may receive a diagnosis after the end of follow-up. However, the mean age at the end of follow-up was the same in the overall sample, the ADHD diagnosed group and the group of children with a positive SDQ ADHD and no ADHD diagnosis. In addition, a Danish study found that most children have been diagnosed and received treatment by the age of 12 years [175].

Information bias
Systematic errors can also arise when the information collected from or about the study subjects is incorrect. Such information is often referred to as misclassification if the variable is measured on a categorical scale and the error leads to a person being placed in an incorrect category. Misclassification can be differential or non-differential, with the latter being unrelated to other study variables. In contrast, differential misclassification occurs when the misclassification differs according to other variables. Non-differential misclassification will always bias an association (if there is one) toward the null, whereas differential misclassification can exaggerate or underestimate an association [172].

The ADHD diagnosis (Study I, II, III)
Unlike parental reports of diagnosis, the register-based information on diagnoses and prescriptions are clinically confirmed. Previous validation studies of the diagnosis of hyperkinetic disorders in the Danish Psychiatric Central Research Register have shown an agreement on the diagnosis of 83-87% [176, 177]. Although
only few records were examined, this suggests that registered ADHD diagnoses are valid measures [55].

We used the prescribed central stimulants as a proxy measure for ADHD diagnosis made by privately practising psychiatrists. However, we might assume that not all children diagnosed with ADHD in private clinics are prescribed medications, and this could result in misclassification caused by an underestimation of ADHD diagnosed children. In addition, ADHD medications can be prescribed to children treated for narcolepsy. As this number is presumed to be negligibly low in Denmark, such misclassification is unlikely to have affected the presented results [145].

In Study I, misclassification would cause bias in the geographic analyses if the underestimation of ADHD diagnoses was related to particular private clinics that tended not to prescribe ADHD medication. This would in turn result in an underestimation of the association between ADHD incidence and available diagnostic services.

In Study II, misclassification of ADHD diagnoses would only affect the prevalence ratio if children from the DNBC were more or less likely to receive an ADHD diagnosis in private clinics without receiving ADHD medication.

In Study III, the implications of a possible underestimation of ADHD diagnoses would depend on whether the misclassification was associated with a positive ADHD behaviour reported by the parents. If this is the case, it would result in an overestimation of potentially undetected children.

Child ADHD behaviour measured with the Strength and Difficulties Questionnaire (Study III and IV)

In Studies III and IV, we used the SDQ as a measure of child behaviour problems. Furthermore we used the SDQ ADHD prediction as a measure of clinically relevant ADHD behaviour. Goodman described the psychometric properties in a study of about 10 000 British 5-15 year-olds. For the specific hyperactivity/inattention subscale, he found a specificity of 92% and a sensitivity of 74% in predicting ADHD when reported only by the parent [139]. Since then, the psychometric properties of the SDQ have been studied in the Nordic countries, and sensitivity and specificity estimates of 45-52% and 98-99.6%, respectively, have been reported [145, 146, 178]

In study III, we used the SDQ ADHD prediction with only one informant (the mother) to estimate the number of potentially undetected children. Impairment in multiple contexts is an important precondition in the ADHD diagnosis. Therefore, we excluded children in whom the impact score was only related to one setting to avoid false-positives. However, when the SDQ is used in a community sample, it has been argued that some children with clinical range SDQ will actually be typically developing (i.e., false positives) due to low prevalence rates in the general population. In contrast, when the SDQ is used in a clinical sample, where prevalence rates are usually higher, fewer children will be false positives [179]. Other possible explanations for the finding of the large number of children with a positive SDQ ADHD without ADHD diagnosis could be that the difficulties reported by the
parents for some children were transient; and despite difficulties in impulse-control and hyperactivity, symptoms would not exceed the threshold for an ADHD diagnosis. When using screening instruments like the SDQ without further clinical evaluation of the children, we cannot be certain that these children do in fact have ADHD. Hence, in study III, the number of potentially undetected children could be overestimated. However, some issues may also point to an underestimation of potentially undetected children. A Norwegian study found a low sensitivity of the SDQ ADHD in predicting the inattentive subtype [146]. Given the extant literature suggesting diagnostic underrepresentation of especially girls with the inattentive subtype, this could point to a higher number of potentially undetected children.

Maternal psychopathology
The questions assessing maternal depression and the history of hyperactivity were not standardized nor clinically confirmed. This could increase the risk of misclassification of the exposure in Study IV. However, the misclassification is not likely to be differential in relation to the reporting of maternal depression before pregnancy as maternal depression would not be affected by the outcome since the child is not yet born. However, it is possible that maternal depression when reported at child age 7 years is associated with child behaviour. Our results point to different mechanisms in relation to the time-point of the mother’s depressive episodes. When reported by the mother, maternal depression was associated with increased ADHD behaviour in both boys and girls when maternal depression was present either before pregnancy or during the first seven years of the child’s life. However, when self-reported by boys and girls, the associations were only significant when maternal depression had been present during the first seven years of the child’s life. When depression was present during this time period, maternal depression could be influenced by the child’s behaviour problems as parents of children with ADHD tend to suffer from high levels of psychiatric distress, which may antedate and interact with the child’s ADHD symptoms [180]. Depression before pregnancy would only be related to the mother since the child is not yet born, whereas, depression reported at both time-points would suggest a far more severe psychiatric condition. Only few mothers reported depression at both time-points and the analyses with this as exposure did not show a clear pattern.

We did not have information on depression status at the time-point of the SDQ reports. Hence, we do not know how current depressive symptoms would affect the associations. We would speculate that the further apart the maternal depressive incident would be from the reporting at child age 11 years, the lesser influence it would have. However, our findings suggest that the mother may be biased in the reporting on child behaviour even though depression occurred more than 11 years earlier.

Confounding
A central issue for the epidemiologic study design is confounding, which can be defined as confusion of effects. Confounding may occur when the effect of the exposure is mixed with the effect of another variable leading to bias. Theoretically, a confounding variable should be a cause of the outcome and must also be differently distributed across exposure categories [172]. Whenever possible, confounding was
handled by multivariate adjustment and stratification in the current studies. However, there will always be the risk of unmeasured confounding.

In Study III, we examined how the explanatory variables each predicted potential underdetection of ADHD symptoms in children. We analysed SES, maternal depression, family status, gender, and place of residence separately. Taking into account the possible confounding from each variable in the final analysis, we adjusted for all variables. We did not have adequate information on the parent’s psychopathology, besides maternal depression. This could have had an influence since parental psychopathology has been associated with a higher degree of problem recognition, but not to help-seeking or utilisation of mental health services.

In Study IV, potential confounders were chosen a priori based on previous studies on associations between maternal depression and child behaviour problems. Low parental SES has been associated with child behaviour problems and parental psychopathology as have history of hyperactivity and family status. We adjusted for older siblings because the maternal perceptions of child behaviour may be influenced by comparisons with older siblings. In addition, we stratified the analysis by gender because studies have suggested that the gender of the child may affect the maternal reports of child behaviour.
Conclusion

This thesis explored the influence of factors at different levels in the pathway to an ADHD diagnosis using Danish national health registers and cohort information.

We found a large geographical variation in the incidence of ADHD diagnosis and prescribed ADHD medication in the municipalities. Clustering of low incidence was present in less populated municipalities with limited diagnostic resources. Conversely, clustering of high incidence was seen in densely populated municipalities with greater diagnostic resources. This may point to some difference in the access to psychiatric services, although, this was not statistically significant. The variation in ADHD diagnoses and medication use was not random, but we found no associations with availability of diagnostic services, municipal spending on healthcare for children, household SES or differences in diagnostic practises. Although the municipality is the smallest administrative areal unit, it might be too large to fully capture the different mechanisms that influence ADHD diagnostics throughout the country.

We identified a considerable number of children with parent-reported ADHD behaviour at age 7 years and no registered diagnosis during a long follow-up. Our results correspond with previous studies, which suggest that a number of children with ADHD symptoms might go undetected and that these children might have considerable associated mental health problems. In addition, the results demonstrated that the potentially undetected children were more likely to be girls, more likely to have mothers with a low SES and to be living in regions with predominantly low incidence of ADHD diagnoses.

Consistent with previous findings in both clinical and population-based samples, we found discrepancies in the reporting of child behaviour problems when reported by different informants. Maternal depression was associated with child hyperactivity/inattention and conduct problems when reported by the mother and child (only when depression was reported at child age 7 years), but not when reported by the teacher. These findings emphasize the importance of considering the ratings by each of the informants when obtaining observations from multiple sources in both epidemiological studies and in clinical practice.

The mechanisms involved in the pathway to an ADHD diagnosis are complex and diverse. This thesis contributes to the understanding of the influence of factors at different levels in the pathway to an ADHD diagnosis. The results suggest that access to healthcare services, place of residence, maternal socioeconomic status and mental health, child gender and symptoms are all factors that might affect the probability of a child being referred for diagnostic assessment and receiving an ADHD diagnosis.
Perspectives

As evident from our studies, the prevalence of ADHD diagnoses and prescribed ADHD medication in Denmark lies below the estimated worldwide prevalence of the disorder, which suggests under-diagnosis of the disorder [33]. Studies have presented examples of both over- and under-diagnosis, but the studies have mainly been conducted in the US, where diagnosis rates have been reported to be much higher than in the Nordic countries [112, 181, 182].

In Study III, we identified a number of children with parent-reported ADHD behaviour but no ADHD diagnosis during follow-up (1.3% of the population). This points to a high number of children with potentially undetected ADHD problems. Even though the children may not exceed the threshold of a diagnosis according to the ICD-10 or the DSM-V, these children may indeed still exhibit problems with functioning that may lead to limitations in their everyday lives. The potentially undetected children showed markedly impairments on all SDQ subscales, suggesting that they may be in need of special care. Indeed, children with subthreshold symptoms are at heightened risk of adverse outcomes although they typically do not qualify for special care or educational interventions [183].

Early identification and interventions are important in child psychiatric disorders like ADHD. Delays in initiation of appropriate treatment may lead to a poor outcome [64, 184]. A study by Dalsgaard et al. demonstrated that risk of premature death was associated with ADHD; the risk increased with age at diagnosis, and the mortality was higher in girls and women than boys and men. The excess mortality in ADHD was mainly driven by deaths from unnatural causes, especially accidents [184].

Several therapeutic interventions have been developed and some, including medical interventions, have been shown effective to improve both the daily functioning and the long-term outcomes for children and adolescents with ADHD [64, 185-187]. Children with impairing mental health problems should ideally be recognised and receive treatment. However, factors at different levels clearly affect the detecting and diagnosing of ADHD, which seems to result in under-detection and under-diagnosis.

In the clinical guidelines drawn up by the National Institute for Health and Care Excellence (NICE) in the UK, it is stated that the ability to recognise ADHD in children and youths is limited and that the way in which services are provided and organised for this group is inconsistent. In addition, referral pathways can be complicated, and are subject to considerable variation in the local organisation of mental health services for children and young people [27]. When considering the results of the current thesis this is probably also a phenomenon occurring in Denmark. Furthermore, studies suggest that the identification of affected children is unsystematic and driven largely by the extent to which parents are knowledgeable about ADHD or recognise that their child might have hyperactive behaviour [66, 71]. Finally, there may be difficulties with awareness and recognition of the symptoms by healthcare professionals in schools and primary/secondary care and by other professionals who come into contact with these children [27].
The recurring problem involved at all levels is probably related to the knowledge and the conceptions about ADHD. The public values, beliefs and attitudes toward ADHD shape the healthcare policies. Likewise, the willingness of children, young people and their families to seek help can be compromised by stigma associated with mental health issues [188].

So how do we move forward? In a commentary to Dalsgaard’s paper on increased mortality from ADHD, Faraone wrote:

“For too long, the validity of ADHD as a medical disorder has been challenged. Policy makers should take heed of these data and allocate a fair share of healthcare and research resources to people with ADHD. For clinicians, early identification and treatment should become the rule rather than the exception” [189]. This statement indeed sounds reasonable as the allocation of resources to psychiatric care have been given low priority for many years, including in Denmark. However, the allocation of resources to psychiatric hospitals may not enhance the chances of children with ADHD symptoms being identified in a school or primary care setting. Fortunately, in Denmark, the first steps have been taken to improve the identification of children with mental health problems. In a collaboration between several municipalities and Aarhus University, the web site Skolesundhed.dk (Schoolhealth.eu) was developed. This web site is an interdisciplinary monitoring tool that supports the municipalities in their efforts to develop and target interventions for children with special needs. It is based on questionnaires targeting teachers, parents, children and young people to establish a foundation for a dialogue about the particular child, class or school. The knowledge gathered through Skolesundhed.dk makes it possible to create innovative interventions and to allocate resources strategically by targeting children and young people with special needs. In addition, our research group Mindhood have taken the lead on developing a postgraduate course on child mental health to teachers, other school personnel and school health nurses. The purpose of the course is to increase the knowledge and identification of mental health problems in children and to present available classroom management techniques to use in classes with children who have special needs.
Danish summary

Baggrund
Attention Deficit Hyperactivity Disorder (ADHD) er en adfærdsmæssig lidelse, som er karakteriseret ved uopmærksomhed, hyperaktivitet og impulsivitet. ADHD er en af de mest almindelige børnepsykiatriske lidelser med en prævalens på 3-5% blandt børn og unge. I de seneste år har vi set en stigning i forekomsten af børn og unge med en ADHD-diagnose. En stor geografisk spredning i forekomsten af diagnosen giver dog anledning til at undersøge, hvad der påvirker diagnosticeringen af ADHD.

Formål
Det overordnede formål med denne ph.d-afhandling var at undersøge betydningen af strukturelle, samfundsmæssige, familiemæssige og individuelle faktorer for ADHD-diagnosen.

Metode
De anvendte datakilder var nationale sundhedsregistre og den danske nationale fødselskohorte, Bedre Sundhed for Mor og Barn (BSMB). Følgende blev undersøgt ved hjælp af befolkningsbaserede observationelle studier: den geografiske variation i forekomsten af ADHD diagnoser og strukturelle faktorer forbundet med variationen, repræsentationen af børnepsykiatriske diagnoser i BSMB, karakteristika hos ikke-diagnostiserede børn med forældre rapporteret ADHD-adfærd og bias i rapporteringen af adfærdsproblemer hos barnet relateret til depression hos moderen.

Resultater
Vi fandt stor variation i forekomsten af ADHD i de danske kommuner. Den laveste forekomst var 0% og den højeste var 2,87%. Klynger af lav forekomst var centrerede omkring tyndt befolkede områder, mens klynger med høj forekomst var centrerede omkring tætbefolkede områder. Vi fandt ingen associationer mellem forekomsten af ADHD-diagnoser og tilgængelighed til diagnostiske ydelser, kommunale udgifter til den primære sundhedsstjeneste til børn, gennemsnitlig husstands indkomst i kommunerne eller forskelle i anvendte diagnostiske metoder.

Den relative repræsentation af de udvalgte børnepsykiatriske diagnoser varierede fra en underrepræsentation på 20% (skizofreni) til en overrepræsentation på 7% (angst og tvangspræget adfærdsforstyrrelse), hvilket resulterede i en underrepræsentation af alle udvalgte diagnoser på 3%. ADHD-diagnosen var underrepræsenteret med 5%, hvilket var mere udtalt for piger end for drenge.

Resultaterne viser, at mere end halvdelen af børnene med forældre-rapporteret ADHD-adfærd i 7-års alderen ikke blev diagnosticeret med ADHD under opfølgningen (potentiel uopdaget), hvilket svarer til 1,3% af den samlede population. Børn med potentiet uopdaget ADHD var i højere grad piger, havde i højere grad mødre med lav socioøkonomisk status, boede i højere grad i bestemte regioner i landet og havde signifikant højere scorer på SDQ subskalaerne end børn med en ADHD diagnose.
Vi fandt diskrepans i rapporteringen af adfærdsproblemer hos barnet ved forskellige informanter (moder, lærer og barnet selv). Depression hos moderen var forbundet med hyperaktivitet, uopmærksomhed og adfærdsproblemer hos barnet, når analyserne var baseret på moderens eller barnets rapportering (kun når depression blev rapporteret i løbet af de syv første år af barnets liv), men ikke når analyserne var baseret på lærerens rapportering.

**Konklusion**

Denne afhandling bidrager til en bedre forståelse af hvad forskellige faktorer betyder for ADHD-diagnosen. Resultaterne tyder på, at adgang til sundhedsydelser, bopæl, moderens socioøkonomiske status og mentale helbred, barnets køn og symptomer kan påvirke sandsynligheden for, at et barn bliver henvist til diagnostisk vurdering og får en ADHD-diagnose.
English summary

Background
Attention Deficit Hyperactivity Disorder (ADHD) is a behavioural disorder characterised by inattentiveness, hyperactivity and impulsiveness. ADHD is one of the most common psychiatric disorders in childhood with a current estimated prevalence of 3–5% among children and adolescents. During the past decades we have seen a rise in the prevalence of ADHD diagnosis. Yet, reports of geographically different occurrence have given rise to questions about what might influence receiving an ADHD diagnosis.

Aim
The overall aim of this thesis was to investigate, in an epidemiological setting, the influence of structural, community, family and child factors on the diagnosis of Attention Deficit Hyperactivity Disorder in children.

Methods
The data sources utilised were Danish national health registers and the Danish National Birth Cohort (DNBC). The following were studied using population-based observational designs: the geographical variation in the incidence of ADHD diagnoses and structural factors associated with the variation, the representation of childhood psychiatric diagnoses in the DNBC, characteristics of undiagnosed children with parent-reported ADHD behaviour, and maternal depression-related distortions in the report of child behaviour problems.

Results
We found considerable variation in the incidence of ADHD in the Danish municipalities; from a low incidence of 0% to a high incidence of 2.87%. The clustering of low incidence was located in less populated areas. In contrast, the clustering of high incidence was located in densely populated areas. No associations were found between the incidence of ADHD diagnoses and availability of diagnostic services, municipal spending on healthcare for children, average household SES and different diagnostic practices.

The relative representation in the DNBC of the selected childhood psychiatric diagnoses ranged from an underrepresentation of 20% (schizophrenia) to an overrepresentation of 7% (anxiety disorders or OCD), resulting in an underrepresentation of all selected diagnoses of 3%. The ADHD diagnosis was underrepresented by 5%, this trend was more pronounced in girls than boys.

We found that more than half of the children with parent-reported ADHD behaviour at age 7 years were not diagnosed with ADHD during follow-up (potentially undetected), which corresponds to 1.3% of the total cohort. The potentially undetected children were more likely to be girls, to have mothers with low SES, to live in certain regions of the country and had significantly higher scores on the SDQ subscales than children with an ADHD diagnosis.
We found discrepancies in the reporting of child behaviour problems when reported by different informants. Maternal depression was associated with child hyperactivity/inattention and conduct problems when reported by the mother and child (only when depression was reported during the child’s life), but this association was not found when reported by the teacher.

Conclusions
This thesis contributes to the understanding of the influence of factors at different levels in the pathway to an ADHD diagnosis. The results suggest that access to healthcare services, place of residence, maternal socioeconomic status and mental health, child gender and symptoms might affect the probability of a child being referred for diagnostic assessment and receiving an ADHD diagnosis.
References


17. National Collaborating Centre for Mental Health. Attention Deficit Hyperactivity Disorder: Diagnosis and Management of ADHD in Children, Young People and Adults.
2009, Leicester (UK): The British Psychological Society & The Royal College of Psychiatrists.


27. National Collaborating Centre for Mental Health, Attention Deficit Hyperactivity Disorder; Diagnosis and management of ADHD in children, young people and adults, 2009: London.

28. Sundhedsstyrelsen, National klinisk retningslinje for udredning og behandling af ADHD hos børn og unge - med fokus på diagnosterne ”Forstyrrelse af aktivitet og opmærksomhed” og ”Opmærksomhedsforstyrrelse uden hyperaktivitet” i henhold til ICD-10 [National clinical guidelines to the management of ADHD in children and adolescents - with focus on the diagnoses “Hyperkinetic disorder” and “Other specified behavioural and emotional disorders with onset usually occurring in childhood and adolescence” according to the ICD-10], 2014, Sundhedsstyrelsen [the National Health Authority]: København.


54. Sundhedsloven [The Danish Health Act], Lov nr. 546 af 24 juni 2005.


169. Caye, A., et al., Attention-Deficit/Hyperactivity Disorder Trajectories From Childhood to Young Adulthood: Evidence From a Birth Cohort Supporting a Late-onset Syndrome. JAMA Psychiatry, 2016.


174. Mikkelsen SH; Madsen KB; Olsen J; Liew Zeyan; Hammer BH., Selection bias caused by non-participation in the follow-up questionnaire including the Strength and Difficulties Questionnaire (SDQ) among 11 years old children in the DNBC. Manuscript in progress, 2017.


Appendices

Table A. The DSM-5 diagnostic criteria for attention deficit hyperactivity disorder [18].

(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 6 months to a degree that is maladaptive and inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:

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

(2) Six or more of the following symptoms of hyperactivity-impulsivity have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:

   a) Often fidgets with hands or feet or squirms in seat
   b) Often leaves seat in classroom or in other situations in which remaining seated is expected
   c) Often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)
   d) Often has difficulty playing or engaging in leisure activities quietly
   e) Is often “on the go” or often acts as if “driven by a motor”
   f) Often talks excessively
   g) Often blurts out answers before questions have been completed
   h) Often has difficulty awaiting turn
   i) Often interrupts or intrudes on others (e.g., butts into conversations or games)

(B) Several inattentive or hyperactive-impulsive symptoms were present prior to age 12 years.
(C) Several inattentive or hyperactive-impulsive symptoms are present in two or more settings.
(D) There is clear evidence that the symptoms interfere with, or reduce the quality of, social, academic, or occupational functioning.
(E) The symptoms do not occur exclusively during the course of a Pervasive Developmental Disorder, Schizophrenia, or other Psychotic Disorder and are not better accounted for by another mental disorder (e.g., Mood Disorder, Anxiety Disorder, Dissociative Disorders, or a Personality Disorder).
Table B. The ICD-10 diagnostic criteria for Hyperkinetic Disorders [21]

G1. Demonstrable abnormality of attention, activity and impulsivity at home, for the age and developmental level of the child, as evidenced by (1), (2) and (3):

(1) At least three of the following attention problems:
   (a) Short duration of spontaneous activities;
   (b) Often leaving play activities unfinished;
   (c) Over-frequent changes between activities;
   (d) Undue lack of persistence at tasks set by adults;
   (e) Unduly high distractibility during study e.g. homework or reading assignment;

(2) Plus at least three of the following activity problems:
   (a) Very often runs about or climbs excessively in situations where it is inappropriate; seems unable to remain still;
   (b) Markedly excessive fidgeting & wriggling during spontaneous activities;
   (c) Markedly excessive activity in situations expecting relative stillness (e.g. mealtimes, travel, visiting, church);
   (d) Often leaves seat in classroom or other situations when remaining seated is expected;
   (e) Often has difficulty playing quietly.

(3) Plus at least one of the following impulsivity problems:
   (a) Often has difficulty awaiting turns in games or group situations;
   (b) Often interrupts or intrudes on others (e.g. butts in to others’ conversations or games);
   (c) Often blurts out answers to questions before questions have been completed.

G2. Demonstrable abnormality of attention and activity at school or nursery (if applicable), for the age and developmental level of the child, as evidenced by both (1) and (2):

(1) At least two of the following attention problems:
   (a) Undue lack of persistence at tasks;
   (b) Unduly high distractibility, i.e. often orienting towards extrinsic stimuli;
   (c) Over-frequent changes between activities when choice is allowed;
   (d) Excessively short duration of play activities;

(2) And by at least three of the following activity problems:
   (a) Continuous (or almost continuous) and excessive motor restlessness (running, jumping, etc.) in situations allowing free activity;
   (b) Markedly excessive fidgeting and wriggling in structured situations;
   (c) Excessive levels of off-task activity during tasks;
   (d) Unduly often out of seat when required to be sitting;
   (e) Often has difficulty playing quietly.

G3. Directly observed abnormality of attention or activity. This must be excessive for the child’s age and developmental level. The evidence may be any of the following:

(1) Direct observation of the criteria in G1 or G2 above, i.e. not solely the report of parent or teacher;
(2) Observation of abnormal levels of motor activity, or off-task behaviour, or lack of persistence in Activities, in a setting outside home or school (e.g. clinic or laboratory);
(3) Significant impairment of performance on psychometric tests of attention.

G4. Does not meet criteria for pervasive developmental disorder (F84), mania (F30), depressive (F32) or anxiety disorder (F41).
G5. Onset before the age of seven years.
G6. Duration of at least six months.
G7. IQ above 50.
Papers for Studies I-IV

Study I

Study II
In review

Study III
In review

Study IV
Madsen KB, MikkelSEN SH, Rask CU, Niclasen J, Olsen J, Simonsen M, Obel C. Depression-related distortions in maternal reports of child hyperactivity/inattention problems.
Submitted
Study I

Geographic analysis of the variation in the incidence of ADHD in a country with free access to healthcare: a Danish cohort study

Kathrine Bang Madsen1*, Annette Kjær Ersbøll2, Jørn Olsen1, Erik Parner1 and Carsten Obel1

Abstract

Background: The prevalence of citizens diagnosed with Attention Deficit Hyperactivity Disorder (ADHD) has risen dramatically over the past decades in many countries, however, with large variations. Countries such as Denmark with centrally organized welfare systems, free access to health services and individual tracking based on unique personal identification may in particular contribute to our understanding of the reasons for this increase. Based on Danish registers we aimed to examine the geographical patterns of the distribution of ADHD diagnosis and medication use and explore the association with access to diagnostic services, diagnostic culture, neighbourhood socioeconomic status and municipal spending on health care for children.

Methods: We combined information on registered diagnosis of ICD-10 Hyperkinetic Disorder and ADHD medication use in a Danish register-based cohort of children born between 1990 and 2000. We mapped incidence proportions of diagnoses and medication use within the 98 Danish Municipalities. Global and local clustering of ADHD was identified using spatial analysis. Information on contextual factors in the municipalities was obtained from national registers. The associations between the incidence of ADHD and contextual factors were analysed using Bayesian spatial regression models.

Results: We found a considerable variation in the incidence of ADHD across the municipalities. Significant clustering of both high and low incidence of ADHD was identified and mapped using the local Moran’s I. Clustering of low incidence of diagnosis and medication use was observed in less populated areas with limited diagnostic resources and in contrast clustering of high incidence in densely populated areas and greater diagnostic resources. When considering the spatial autocorrelation between neighbouring municipalities, no significant associations were found between ADHD and access to diagnostic services, different diagnostic culture, socioeconomic status at municipality level or the municipal spending on health care for children.

Conclusions: A large geographical variation of ADHD in the municipalities was observed despite tax-financed and free access to healthcare. Although not statistically significant, results indicate that accessibility to diagnostic resources might explain some of the variation in ADHD incidence. In contrast to US studies the observed variation was not statistically associated to contextual factors in terms of SES, municipal spending on health care for children or differences in diagnostic practices.

Keywords: Attention deficit hyperactivity disorder, Incidence proportion, GIS, Spatial analysis, Geographic variation, Diagnostic resources

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Background

Attention Deficit Hyperactivity Disorder (ADHD) is a behavioural disorder characterised by inattentiveness, hyperactivity and impulsiveness. In most countries it is the most commonly diagnosed childhood behavioural disorder with an estimated prevalence of 3–5% among 6 to 12-year-old children [1, 2]. The causal pathways of ADHD are complex as both inherited and non-inherited factors contribute and their effects are interdependent [3]. ADHD is a clinically heterogeneous disorder that is associated with a considerable economic burden to society, stress to the affected families, and adverse academic and vocational outcomes to some of the affected children [4]. The recorded prevalence of ADHD has been increasing for the last decades in a number of countries including Denmark; the same tendency has been observed for many other paediatric psychiatric conditions such as Autism Spectrum Disorders (ASD), Obsessive–Compulsive Disorder and Tourette’s syndrome [5, 6]. However, the increase in prevalence of ADHD is not homogenous within countries or regions. In Norway, the diagnostic prevalence of ADHD by county among children aged 6–12 years ranged from 1.1 to 3.4%, similar differences are found in Sweden and large variations between regions and states are found in the USA [7–12]. Some studies report that residing in rural and semi-rural areas is associated with reduced prevalence of ADHD diagnosis and health service use [13–15].

It has been debated whether this increase in diagnosis and treatment of childhood psychiatric disorders reflects a true increase in the incidence of mental health problems in children, changes in their impact or simply an increase in recognition and help-seeking behaviour. This increase in diagnosis and treatment of psychiatric disorders may be related to contextual changes in society and an improved understanding of the relative contribution of these factors has become of major public interest. A recent study found a reduction over time in parent and teacher perceived levels of behavioural problems in preadolescent children in Great Britain concurrent with the increase in diagnosis and treatment; this suggests that the increased prevalence may be due to contextual factors rather than an increase in behavioural problems [16].

Contextual factors causing an increase in diagnosis and treatment could be related to changes in access to diagnostic facilities/number of specialists, diagnostic culture, community resources such as socioeconomic status (SES) and spending on primary health care for children; these factors have been suggested to be associated with geographical differences [8, 17–19]. Examining these contextual factors in relation to the geographical distribution of ADHD may provide a clue to the causal pathway of the increasing prevalence of ADHD. Denmark and other Nordic countries are unique for examining this because it is possible to do a complete follow-up on diagnosis and residence of all citizens as they are registered with a personal identification number.

Studies of factors related to access to diagnostic facilities have found that having a diagnosis of ADHD or taking medication for ADHD was associated with the number, age, and specialisation profile of physicians within states and counties in the US [8, 17]. In Norway, the considerable geographical variation in prevalence of ADHD could be explained by the very decentralised Norwegian specialist health services for children where many institutions treat a very small number of children in each diagnostic group [7].

Psychiatric diagnoses are based on descriptive criteria, interviews and observations; any diagnosis in psychiatry includes an interpretation and decision-making by a professional [20]. A recent Danish study found that the behaviour of specialist physicians varied considerably across hospitals and that the prescribing behaviour affected the probability that a child would receive ADHD medication [21]. Danish hospitals use the WHO’s International Classification of Diseases (ICD-10) while the concept of ADHD is from the American diagnosis system DSM-IV (now DSM-5) [22, 23]. The inclusion criteria are far more narrow within the former system, reflected in comparison studies reporting an ICD-10 Hyperkinetic Disorder (HKD) prevalence of 1–3% and a DSM-IV ADHD prevalence of 4–8% [24]. Changes in diagnostic practices with a more pronounced clinical use of the DSM criteria in countries like the UK and Germany may very well account for part of the observed increase [25]. The relative use of the two diagnostic systems may also explain some of the variation observed within countries.

An association between family socioeconomic disadvantage and childhood ADHD has been established at the individual level [12, 18, 19], and one study found that the geographical variation in treatment prevalence to some extent was attributable to measured socioeconomic differences at the population level [17]. Hence, SES of a geographical area might be important when considering the risk of being diagnosed with ADHD. The impact of SES for a diagnosis of ADHD is consistent with findings on a wide range of health outcomes. US studies have found that children residing in fortunate SES areas had an increased risk of being diagnosed with autism [26, 27]. The mechanisms underlying the associations between SES and health outcomes are unknown, but SES is probably a good proxy for local resources and the availability of health-related information [27].

Most studies addressing the rise and geographical variation in prevalence of ADHD have been conducted in the US; few have addressed European contexts. The
associations between ADHD and access to diagnostic facilities, diagnostic culture and community SES may be very different in a country with free access to qualified health care and economic equality.

In the present study we performed exploratory spatial analysis to examine if the following contextual factors were associated with the risk of ADHD diagnosis or treatment: access to paediatric psychiatrists and psychiatric hospitals, average SES in the community, spending on primary health care for children and diagnostic culture in the public psychiatric hospitals. We used administrative data from Denmark to identify spatial patterns of ADHD that may drive the increase in recorded incidence.

**Results**

**Incidence of ADHD**

The total number of children with ADHD was 8218 of which 6798 children had a hospital diagnosis, 6693 children redeemed medication, and 1420 children redeemed medication but did not have a registered diagnosis (treated by private practicing paediatric psychiatrists). In all of 750,512 children were born in the period from 1990 to 2000 in Denmark (Table 1).

The incidence has been steadily increasing with each birth year. The incidence proportion increased from 0.36 % (95 % CI 0.31; 0.41) in the 1990 birth cohort to 2.58 % (95 % CI 2.46; 2.70) in the 2000 birth cohort (Table 2).

The average national incidence proportions were computed for the children born in the period 1998–2000 and in the period 1990–1992. The average national incidence proportion in the 1998–2000 birth cohort was 4.4 times higher (95 % CI 4.1; 4.8) than the incidence proportion in the 1990–1992 birth cohort resulting in a significant national increase in incidence. Figure 1 displays the geographical areas in which the incidence proportion has increased below or above national average increase when comparing the 1990–1992 and 1998–2000 birth cohorts. Three municipalities have experienced a decrease in incidence proportion when comparing the two birth cohorts.

All indicators of ADHD vary considerably across municipalities. The mean incidence proportion of overall ADHD was 1.19 %, ranging from 0 to 2.87 % in the municipalities (Table 3).

**GIS mapping**

Four maps were constructed based on the incidence proportion of ADHD in each municipality using the previously mentioned indicators of ADHD: (a) all children with a diagnosis, (b) all children redeeming medication, (c) children redeeming medication but without a registered diagnosis, (d) all children with a diagnosis and/or redeeming medication (Fig. 2). The public diagnostic facilities in the municipalities are shown as points in map (a), and the private diagnostic facilities are shown in map (c).

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**Table 1 ADHD cases in the study population**

<table>
<thead>
<tr>
<th>Hospital diagnosis</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>742,294</td>
<td>1420</td>
</tr>
<tr>
<td>1525</td>
<td>5273</td>
</tr>
</tbody>
</table>

**Table 2 Incidence proportions in the study population by birth year**

<table>
<thead>
<tr>
<th>Birth cohort</th>
<th>ADHD cases</th>
<th>Births</th>
<th>Incidence proportion (%)</th>
<th>95 % CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990</td>
<td>242</td>
<td>66,623</td>
<td>0.36</td>
<td>0.31; 0.41</td>
</tr>
<tr>
<td>1991</td>
<td>327</td>
<td>66,791</td>
<td>0.49</td>
<td>0.44; 0.55</td>
</tr>
<tr>
<td>1992</td>
<td>371</td>
<td>69,669</td>
<td>0.53</td>
<td>0.48; 0.59</td>
</tr>
<tr>
<td>1993</td>
<td>451</td>
<td>68,808</td>
<td>0.66</td>
<td>0.59; 0.72</td>
</tr>
<tr>
<td>1994</td>
<td>557</td>
<td>70,999</td>
<td>0.79</td>
<td>0.72; 0.85</td>
</tr>
<tr>
<td>1995</td>
<td>662</td>
<td>70,522</td>
<td>0.94</td>
<td>0.87; 1.01</td>
</tr>
<tr>
<td>1996</td>
<td>730</td>
<td>67,595</td>
<td>1.08</td>
<td>1.00; 1.16</td>
</tr>
<tr>
<td>1997</td>
<td>819</td>
<td>67,134</td>
<td>1.22</td>
<td>1.14; 1.31</td>
</tr>
<tr>
<td>1998</td>
<td>1028</td>
<td>65,092</td>
<td>1.58</td>
<td>1.49; 1.68</td>
</tr>
<tr>
<td>1999</td>
<td>1366</td>
<td>64,341</td>
<td>2.12</td>
<td>2.01; 2.24</td>
</tr>
<tr>
<td>2000</td>
<td>1665</td>
<td>64,630</td>
<td>2.58</td>
<td>2.46; 2.70</td>
</tr>
</tbody>
</table>
Within 98 municipalities in Denmark, 12 paediatric psychiatric wards are placed in 12 different municipalities and 16 private paediatric psychiatrists are practicing in 12 different municipalities. In all, diagnostic facilities are available in 18 municipalities (Fig. 2 map a and c).

Spatial autocorrelation and cluster identification
Global Moran’s I values indicated that with all four indicators of ADHD the data was not randomly distributed geographically. The analyses suggested significant presence of general tendencies to cluster for all four indicators of ADHD, however, values were very small (Table 4).

Figure 3 displays the results of the local Moran’s I analyses. In all four analyses both “hot” and “cold” spots were identified. These clustered spots were statistically significant at a 5 % level. Regarding the incidence proportion of diagnosis (map a) a large cluster of high values was found in the northwestern part of the Zealand Region.

Table 3  Summary statistics of ADHD incidence proportion and contextual factors

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence proportion of hospital diagnosis (%)</td>
<td>0.98</td>
<td>0.49</td>
<td>0</td>
<td>2.74</td>
</tr>
<tr>
<td>Incidence proportion of medication use (%)</td>
<td>0.96</td>
<td>0.44</td>
<td>0</td>
<td>2.47</td>
</tr>
<tr>
<td>Incidence proportion of medication use and no hospital diagnosis (%)</td>
<td>0.20</td>
<td>0.14</td>
<td>0</td>
<td>0.77</td>
</tr>
<tr>
<td>Incidence proportion of overall ADHD (%)</td>
<td>1.19</td>
<td>0.52</td>
<td>0</td>
<td>2.87</td>
</tr>
<tr>
<td>Average household income (1000 DKK)</td>
<td>480</td>
<td>80</td>
<td>369</td>
<td>788</td>
</tr>
<tr>
<td>Municipal spending on health care for children (1000 DKK/child)</td>
<td>0.77</td>
<td>0.18</td>
<td>0.54</td>
<td>1.34</td>
</tr>
<tr>
<td>Incidence proportion of conduct disorder F91 (%)</td>
<td>0.18</td>
<td>0.14</td>
<td>0</td>
<td>0.86</td>
</tr>
<tr>
<td>Incidence proportion of conduct disorder F92 (%)</td>
<td>0.16</td>
<td>0.13</td>
<td>0</td>
<td>0.59</td>
</tr>
</tbody>
</table>

Fig. 2  Incidence proportion (%) in children aged 0–11 years old born from 1990 to 2000 of a diagnosis, b medication use, c medication use and no registered diagnosis, d overall ADHD by municipality. The incidence proportions are split into quartiles. Red points in map a and c respectively show the public and private diagnostic facilities in the municipalities.
expanding to the western part of the Capital Region. A cluster of low values covered a large part of the North Denmark Region. Looking at the incidence proportion of overall medication use (map b) different clusters of low values emerged. Two "cold" spots were identified, one in the Region of Southern Denmark and one in the Central Denmark Region, both in the western part of Denmark. However, the pattern of clustering of high values was not considerably different from the pattern of the diagnostic incidence proportion. If we only look at the children who use medication but do not have a registered diagnosis (map c) three clusters are significant. Hot spots are found in the North Denmark Region covering almost the entire region and in the northwestern part of the Zealand Region and also in a small part of Funen. One "cold" spot covers almost the entire part of southern Jutland moving upwards covering the western part of Jutland. Looking at all the cases (diagnosis and/or medication) (map d) the clustering of high values only varies a little and the clustering of low values remains in the western part of Jutland. The area with clustering of low incidence has on average a population density of 54 people per km\(^2\) (ranging from 20 to 145 people per km\(^2\) in the municipalities) and the clustering of high incidence is covering an area with an average population density of 175 per km\(^2\) (ranging from 84 to 403 people per km\(^2\)).

**Non-spatial and spatial regression analysis**

The non-spatial logistic regression analysis of overall ADHD, diagnosis, and medication use without diagnosis

<table>
<thead>
<tr>
<th>Variables</th>
<th>I</th>
<th>E (I)</th>
<th>Sd (I)</th>
<th>Z</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnoses</td>
<td>0.058</td>
<td>−0.010</td>
<td>0.017</td>
<td>3.945</td>
<td>0.000</td>
</tr>
<tr>
<td>Medication</td>
<td>0.049</td>
<td>−0.010</td>
<td>0.017</td>
<td>3.426</td>
<td>0.000</td>
</tr>
<tr>
<td>Medication no diagnoses</td>
<td>0.090</td>
<td>−0.010</td>
<td>0.017</td>
<td>5.855</td>
<td>0.000</td>
</tr>
<tr>
<td>Overall ADHD</td>
<td>0.062</td>
<td>−0.010</td>
<td>0.017</td>
<td>4.172</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Fig. 3 Local Moran’s I clustering of the incidence proportion of a diagnosis, b medication use, c medication use and no registered diagnosis, d overall ADHD by municipality (red hot spots, blue cold spots)
showed considerable overdispersion with 12.7, 15.0 and 6.4, respectively. The initial non-spatial analysis without adjustment for overdispersion was highly significant for the explanatory variables for each of the three outcomes (Table 5). Adjustment for overdispersion does not affect the parameter estimates (odds ratio (OR)), but results in larger standard errors and wider confidence intervals of the parameter estimates. The analysis adjusted for overdispersion resulted in non-significance of the explanatory variables for the three outcomes except municipal spending for the outcome overall ADHD with \( p \) value = 0.045 (Table 5).

The Bayesian CAR analysis showed no significant effect of any of the explanatory variables for the three outcomes (Table 5).

**Discussion**

We found considerable differences in the incidence of documented ADHD in the Danish municipalities ranging from 0 to 2.87 %. This variation is consistent with findings in other western countries [7–9, 12]. The clustering of low incidence proportions is located in less populated areas and in contrast clustering of high incidence proportions is located in densely populated areas. This is not exclusively a Danish phenomenon but is also described in studies from other western countries where diagnosis of ADHD and medication use is less prevalent in rural areas [9, 15].

The recruitment of doctors to less populated areas is known to be difficult and lower incidence of ADHD in rural regions may point to differential healthcare access. Our results indicate that accessibility to diagnostic services is of some importance to the variation in incidence, though not statistically significant (Fig. 2 map a). The locations of privately practicing paediatric psychiatrists are highly correlated with location of psychiatric hospitals; this results in long distances to diagnostic resources in some areas. Since the nineties, there have been 14 paediatric psychiatric wards distributed with at least one in each of the five Danish regions. There are three paediatric and adolescent psychiatric wards in the northern part of the Zealand Region as well as in the Capital Region. The relatively large capacity in the area of paediatric and adolescent psychiatry might explain the clustering of high incidence proportions in these geographical areas. In the western part of Jutland we find clustering of low incidence proportion of both diagnosis and medication use. A few municipalities in this area have even experienced a decrease in incidence of ADHD, which is opposite to the rest of the country. Very few public and no private diagnostic resources are available in the western part of Jutland. Hence, even in a country with free access to healthcare population density and access to diagnostic services might explain the clustering of both high and low incidence of ADHD. In Norway, which is similar to Denmark considering health care and well fare, similar results are found although there are much greater geographical distances [7]. The results are also consistent with findings in US studies despite very different well fare systems [8, 17]. However, considering the incidence of ADHD in all the municipalities, we did not find a statistically significant association to access to diagnostic services when considering the spatial correlation. This is perhaps a result of the relatively low statistical power due to the number of municipalities with diagnostic services (18 out of 98 municipalities). It is possible that access to diagnostic services is of greater importance in the parts where we found clustering than in the rest of the country.

It could also be argued that the large variation in incidence of ADHD between municipalities is a reflection of both under- and over-diagnosing resulting from different diagnostic cultures. A scientific and public debate is ongoing discussing whether ADHD is overdiagnosed in children. Previous studies have suggested that both under-diagnosis and over-diagnosis occur routinely in ADHD [28–30]. Hyperactivity is common, but its diagnosis is still controversial, with two contending approaches: ADHD from DSM IV and hyperkinesis from ICD-10. The concept of ADHD predicts higher rates, but its use may lead to overmedication. Hyperkinesis usefully indicates benefits from medication, but clinics may lead to detection of far fewer cases and thus the possibility of under-diagnosis. It has never been shown whether this lower rate results from hyperkinesis criteria or from the difference in methods used to detect hyperactivity [31]. The validity of the ADHD diagnosis in the Danish Psychiatric Central Register has previously been investigated. However, very few [23] records were examined, of which 89 % were in agreement with a full diagnosis of ADHD according to the DSM-IV; the remaining 11 % lacked one symptom to meet the diagnostic criteria [32]. Although the predictive value of diagnoses in hospitals may be high, it does not clarify the problem of undetected cases in the population.

We explored whether the incidence of ADHD could be affected by different diagnostic cultures by examining the variation in the incidence of the differential diagnosis conduct disorder but we did not find an association; this could be due to an inadequate measure of differences in diagnostic practices. A recent Danish study found considerable variation across hospitals in treatment behaviour of specialist physicians within ADHD [21]. Diagnostic practice is probably far more complex than just distinguishing between the two diagnoses ADHD and conduct disorder. Also, decisions to identify and treat children with ADHD often involve not just the opinion of doctors.
Table 5 Summary statistics of parameters in the non-spatial and spatial regression model for outcomes ADHD, diagnosis and medication use given by odds ratio (OR), 95 % confidence interval (95 % CI) for the non-spatial analysis and 95 % credible interval (95 % CI) for the spatial analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>No adjustment for overdispersion</th>
<th>Adjustment for overdispersion</th>
<th>Spatial</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-spatial</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td>95 % CI</td>
<td>p value</td>
</tr>
<tr>
<td>ADHD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family income</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low versus high</td>
<td>0.94</td>
<td>0.88; 0.99</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medium versus high</td>
<td>0.87</td>
<td>0.81; 0.92</td>
<td>0.70; 1.07</td>
</tr>
<tr>
<td>Municipal spending</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low versus high</td>
<td>1.15</td>
<td>1.08; 1.22</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medium versus high</td>
<td>1.29</td>
<td>1.22; 1.36</td>
<td>1.06; 1.56</td>
</tr>
<tr>
<td>Conduct disorder</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low versus high</td>
<td>0.97</td>
<td>0.92; 1.03</td>
<td>0.80; 1.18</td>
</tr>
<tr>
<td>Medium versus high</td>
<td>1.07</td>
<td>1.00; 1.14</td>
<td>0.85; 1.34</td>
</tr>
<tr>
<td>Absence of hospital/child psychiatrist</td>
<td>0.97</td>
<td>0.92; 1.03</td>
<td>0.80; 1.18</td>
</tr>
<tr>
<td>Dispersion parameter</td>
<td>1.14</td>
<td>1.08; 1.20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Spatial correlation, $\rho$</td>
<td>1.14</td>
<td>1.08; 1.20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Spatial variation, $\tau^2$</td>
<td>1.14</td>
<td>1.08; 1.20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medication no hospital diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family income</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low versus high</td>
<td>1.15</td>
<td>0.98; 1.34</td>
<td>0.77; 1.70</td>
</tr>
<tr>
<td>Medium versus high</td>
<td>0.98</td>
<td>0.84; 1.13</td>
<td>0.67; 1.43</td>
</tr>
<tr>
<td>Municipal spending</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low versus high</td>
<td>1.11</td>
<td>0.95; 1.30</td>
<td>0.74; 1.64</td>
</tr>
<tr>
<td>Medium versus high</td>
<td>1.22</td>
<td>1.06; 1.40</td>
<td>0.86; 1.74</td>
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<tr>
<td>Conduct disorder</td>
<td></td>
<td></td>
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<tr>
<td>Low versus high</td>
<td>1.00</td>
<td>0.86; 1.15</td>
<td>0.69; 1.45</td>
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<td>1.20</td>
<td>1.02; 1.42</td>
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<tr>
<td>Absence of a child psychiatrist</td>
<td>0.82</td>
<td>0.71; 0.94</td>
<td>0.57; 1.17</td>
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<tr>
<td>Dispersion parameter</td>
<td>0.82</td>
<td>0.71; 0.94</td>
<td>0.57; 1.17</td>
</tr>
<tr>
<td>Spatial correlation, $\rho$</td>
<td>0.82</td>
<td>0.71; 0.94</td>
<td>0.57; 1.17</td>
</tr>
<tr>
<td>Spatial variation, $\tau^2$</td>
<td>0.82</td>
<td>0.71; 0.94</td>
<td>0.57; 1.17</td>
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<tr>
<td>Diagnosis</td>
<td></td>
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<tr>
<td>Family income</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low versus high</td>
<td>0.92</td>
<td>0.86; 0.99</td>
<td>&lt;0.001</td>
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<tr>
<td>Medium versus high</td>
<td>0.86</td>
<td>0.80; 0.92</td>
<td>0.67; 1.10</td>
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<td>Municipal spending</td>
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<td>Low versus high</td>
<td>1.17</td>
<td>1.09; 1.25</td>
<td>&lt;0.001</td>
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<td>Medium versus high</td>
<td>1.28</td>
<td>1.21; 1.36</td>
<td>1.01; 1.63</td>
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<td>Conduct disorder</td>
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<tr>
<td>Low versus high</td>
<td>0.95</td>
<td>0.90; 1.01</td>
<td>0.75; 1.20</td>
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<tr>
<td>Medium versus high</td>
<td>1.02</td>
<td>0.95; 1.09</td>
<td>0.78; 1.33</td>
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and patients but also teachers, school psychologists, and parents. Differences in the knowledge and values of other stakeholders may influence prevalence of ADHD [17]. Studies suggest that schoolteachers play an important role in the identification of children with ADHD [33, 34]. It has even been suggested that regional variations in the prescribing of medication for ADHD may be due at least in part to variations in the likelihood of a teacher suggesting the diagnosis of ADHD [33].

Cultural influences related to family's residence could also affect ADHD prevalence as seen in ASD. The hypothesis is that in geographical areas with high ASD prevalence, the sharing of information on autism between parents increases community awareness about signs and symptoms. This results in children living in very close proximity to a child previously diagnosed with ASD are more likely to be diagnosed with ASD [35]. Parents' willingness to accept stimulant treatment of their children may also vary geographically, reflecting different beliefs and values about medical treatment or behavioural disorders.

We found no associations with municipality level resources in terms of SES and spending on health care for children. This is in contrast to a study from the US reporting that children living in high-income household areas had a higher incidence of physician-diagnosed ADHD [36]. Another American study on the geographical variation in the diagnosing of autism found that individuals were more likely to be diagnosed with autism when they moved into well-resourced neighbourhoods [27]. An important difference is that the health care system in Denmark is tax financed allowing free and equal access to diagnostic services and thereby the individual household income would be of less importance. However, a Danish study similarly found an association with greater levels of urbanicity and risk of ASD and an increased risk of ASD in children who moved to a higher level of urbanicity after birth [37]. This could reflect that local resources have some influence on the public attention and health information in the municipalities or that migration is influenced by available treatment options. Our study could not demonstrate this in relation to ADHD diagnosis and treatment although a greater incidence was observed in densely populated areas.

With the possibility of environmental factors influencing the risk of ADHD, children living in different areas would also have different risk exposure of ADHD. However, one problem in evaluating the geographical distribution of ADHD for aetiological purposes lies in difficulties disentangling the geographical distribution of other factors associated with diagnosis. Some factors might promote the recognition of ADHD but not necessarily the occurrence of ADHD.

We cannot, however, rule out the possibility that environmental toxicants have contributed to the geographical variation, but it is unknown if the diagnostic pattern resembles the true occurrence. Also, looking at environmental risk factors, pre- and post-natal exposures to lead and low birth weight/prematurity have been identified as consistent risk indicators, but none are yet known to be definitely causal. ADHD has even been associated to the geospatial factor sunlight [38]. However, Denmark is a rather small country with very little variation in both sunlight and altitude and therefore these factors are probably not important in a Danish context. There is a large amount of literature documenting associations between ADHD and a wide variety of putative environmental risks that can, at present, only be regarded as correlates or potential causes [3]. Therefore, it seems somewhat unlikely that the geographical variation is due to life style or environmental factors alone.

In contrast to studies from the US, we found no statistically significant associations with contextual factors in terms of SES, municipal spending on health care for children or differences in the diagnostic practices. These indicators may, however, be too broad to capture the drivers of diagnostics and treatment. The differences between study results could also be due to different definitions of

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<td>Absence of a hospital</td>
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<td>Spatial correlation, $\rho$</td>
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<td>Spatial variation, $\sigma^2$</td>
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Family income: average yearly total family income. Municipal spending: average municipal spending on primary health care for children. Conduct disorder: percent of children with ICD-10 F91 and F92 diagnoses. All three explanatory variables are categorized into three groups of equal size (33.3 %), low, medium and high.
neighbourhoods. The municipality is the smallest administrative unit in Denmark, but it may be too large to capture the spatial variation of social inequality and too small to capture the regionally organised healthcare system. However, a major strength of this study is the complete follow-up of all citizens; this is a particular strength within health geographies and must be taken into consideration when comparing with studies from countries with incomplete registration where loss to follow-up is likely to provide considerable bias.

Large overdispersion was seen in the non-spatial logistic regression analysis. Overdispersion can be due to clustering (lack of independence) of the incidence proportion of the different indicators of ADHD between municipalities. Significant spatial clustering (by Moran’s I) between municipalities was seen. Overdispersion can also be due to lack of important explanatory variables. This study shows that the variation in ADHD diagnoses and medication use in Denmark is not random as the incidence is highly correlated in the municipalities. One possible cause is confounding if an important spatially correlated covariate is either not measured or unknown [39].

This study used aggregated data at municipal level since we hypothesized that the variation is due to structural factors at this level.

Conclusions
This exploratory analysis produced maps of the incidence proportions of ADHD by municipality using different indicators. Large variations in the incidence were observed as well as considerable differences in the increase in incidence across municipalities. Significant clustering of both high and low values was identified and mapped using the local Moran’s I. The clustering of low incidence proportions was located in less populated areas with limited diagnostic resources and in contrast clustering of high incidence proportions in densely populated areas with greater diagnostic resources. A large geographical variation of ADHD in the municipalities was observed despite tax-financed and free access to healthcare. Although not statistically significant, results indicate that accessibility to diagnostic resources might explain some of the variation in ADHD incidence. In contrast to US studies the observed variation was not statistically associated to contextual factors in terms of SES, municipal spending on health care for children or differences in diagnostic practices.

With complete follow-up of a whole country’s citizens this study shows that the variation in ADHD diagnosis and medication use is not random and the reasons for the increased incidence of ADHD are probably complex and diverse.

There are likely unknown factors related to diagnostic processes, besides accessibility to diagnostic services that drive the diagnostic occurrence of ADHD.

Methods
Study design
We included all children born in Denmark from 1 January 1990 to 31 December 2000. This cohort was extracted from the Danish Medical Birth Registry and consisted of 750,512 children. The Danish Medical Birth Registry comprises data on all live births and stillbirths among women with permanent residence in Denmark [40]. All live born children in Denmark are assigned a unique civil registration number at birth. This makes it possible to link data from the Danish Medical Birth Registry, the Danish Psychiatric Central Register and the Danish National Hospital Register. The registries include information on all inpatient admissions from 1980 and all outpatient contacts to psychiatric hospitals, wards, and clinics in Denmark from 1995 [41, 42]. Inpatient hospital admission corresponds to overnight hospital stays or daily hospital appointments during an extended period for diagnostic evaluation and treatment. Outpatient contacts correspond to less regular appointments. Children with suspected ADHD are generally referred by general practitioners or school psychologists to a paediatric psychiatric ward to undergo diagnostic evaluation and receive treatment. In some cases paediatricians and neurologists take part of the diagnostic evaluation. The Danish Psychiatric Central Register and the Danish National Hospital Register include data on clinical diagnoses, dates of admission and discharge, and reasons for admission, and the International Classification of Diseases, 10th Revision (ICD-10) diagnostic code criteria, which have been used since 1994.

All children were followed from birth until the first diagnosis of ADHD, first use of ADHD medication, death, emigration, the age of 11 years, or 31 December 2011, whichever came first. All children were followed up to the age of 11 years to ensure the same follow-up time of all children as the geographic analysis rely on binomial regression. The last birth cohort in our analyses was born in 2000 as we were able to do a follow-up in 2011. A child was considered to have ADHD if receiving a confirmed diagnosis of ADHD after the age of 5 years or redeeming a prescription for ADHD medication. ADHD can be difficult to diagnose before the age of five therefore the child was only considered a case if registered with a hospital admission related to the diagnosis or redeemed medication after the age of 5 years. Information on ADHD medication was obtained from the Register of Medicinal Product Statistics [43]. A child was considered
a case if he/she had redeemed at least two prescriptions for ADHD medication. The ADHD medication included N06BA04 (methylphenidate), N06BA09 (atomoxetine), or N06BA07 (modafinil).

In Denmark, citizens have the right to use privately practicing specialists free of charge if waiting time at public hospital services exceeds 1 month. However, privately practicing psychiatrists are not obligated to report diagnoses to the registries. Thus, we used ADHD medication prescriptions as a proxy for those children who did not have a hospital diagnosis of ADHD. In Denmark, only specialists in paediatric psychiatry are allowed to prescribe ADHD medication to children.

Data were available at individual level. We assigned the cases to the municipality in which they were diagnosed or redeemed prescriptions, whichever came first, while the rest of the study population was assigned to their birth municipality. We performed a sensitivity analysis assigning all children to their birth municipality. The results did not differ from the initial analyses. For the purposes of this analysis we aggregated data and performed the analyses at municipality level. The aggregation was calculated as the incidence proportion for each municipality. The number of cases was divided by the number of children born in the municipality from 1990 to 2000.

The study was approved by the Danish Data Protection Agency.

Danish health care system

Health care in Denmark is primarily tax-financed and free of charge at the point of service. Danish health care is divided into three political and administrative levels: government level, regional level and municipal level. There are five regions and 98 municipalities in Denmark. The responsibility for running the public health care services is decentralised and divided between the regions and municipalities. The running of secondary care (hospitals) is the responsibility of the five regions. The 98 municipalities are responsible for primary care, public health care, school health service, child dental treatment, prevention and rehabilitation. Costs of most prescriptive medication, including ADHD medication can be reimbursed.

Spatial autocorrelation

The first phase of the spatial data analysis included mapping the distribution of the different indicators of ADHD incidence proportion; diagnosis, medication use, medication use in children without a registered diagnosis, and overall ADHD (both diagnosis and/or redeeming medication). The next phase included the use of two spatial statistics to determine the spatial clustering: the global and local Moran’s I. The global Moran’s I statistic is a global measure of spatial autocorrelation used to test whether values in a numeric variable are randomly distributed over the geographical area or whether neighbouring values tend to be more similar than non-neighbouring. Moran’s I shows the strength of spatial autocorrelation on a scale ranging from +1 to −1. A value of +1 indicates positive spatial autocorrelation where high values are proximal to other high values. Conversely, a value of −1 represents negative spatial autocorrelation where high values tend to be near low values. A value of zero indicates no spatial autocorrelation, i.e. data are randomly distributed within the studied geographical area. Since global indices of spatial autocorrelation summarize the phenomenon of interest in a single value, they are intended not so much for identifying spatial clusters, as for detecting the presence of a general tendency to clustering within the study area. The local Moran’s I statistic reveals whether and where any local clustering occurs. The local Moran’s I identifies individual clusters, or small regions of clusters that may not be evident within the global pattern [44].

An analytic tool in STATA developed by Maurizio Pisati was used to calculate both the global and the local Moran’s I statistic and associated Z-score. This tool tests whether the homogeneity (or heterogeneity) in values between a municipality and its neighbouring municipalities is higher than would be expected by chance. A municipality with a high Moran’s I statistic indicates that its incidence proportion values are close in magnitude to those of the neighbouring municipality. We used the tool to draw cluster maps visualising what is also called "hot spots" (correlation of municipalities with high incidence proportion values) and "cold spots" (correlation of municipalities with low incidence proportion values) [45].

The analysis of spatial autocorrelation requires a measurement of the degree of spatial proximity among the spatial objects of interest. Typically, the degree of spatial proximity among a given set of spatial objects is represented by a matrix called spatial weights matrix (W) [44]. We used the common variant of W the row-standardized spatial weights matrix \( W_{std} \). The distance band was chosen to be 200 km as the median distance between the centroids in the municipalities was 141 km and the 3rd quartile distance was 200 km. We performed a sensitivity analysis with distance bands of 150 and 300 km; this did not significantly change the clusters. The only changes were the appearance of one municipality and the disappearance of another in clusters with low incidence proportions. A two sided p value of <0.05 was considered statistically significant.
Municipality-level contextual factors
To examine access to diagnostic services, information on number and municipality of privately practicing paediatric psychiatrists was extracted from a national register on provision of privately practicing physicians in 2009. The variables concerning economic characteristics in the municipalities were derived from Statistics Denmark for 2010 providing information aggregated at municipality level. The measures of SES in the municipalities and the municipal spending on health care for children reflect the local resources spent in the municipalities. The municipal spending on primary health care for children is a measure of the services provided by health visitors and school nurses. These services are available for all Danish children and can be used as a measure of the capacity of paediatric health promotion and disease prevention at municipality level. The average annual household income was used as a proxy for municipality level SES and calculated as the sum of the main source of income. The average municipal spending on primary health care for children was calculated as the net operating costs per child aged 0–16 years per year including the average costs of primary care including school nurse and health visitor services. Differences in diagnostic culture were examined by studying variation in the incidence proportion of conduct disorders. A number of criteria for ADHD are also considered a sign of conduct disorder and there might be a difference in attitude to diagnosing. If the paediatric psychiatrist diagnose a child with ADHD he accepts at the same time that the cause is primarily genetically causing biological dysfunctions in the brain and therefore the treatment is primarily medical. If instead the psychiatrist believes that the child’s problems are mainly environmental he would think that the child is suffering from behavioral problems such as conduct disorder. We hypothesised that the incidence proportion of conduct disorders may be higher in municipalities with a lower ADHD incidence proportion reflecting the difference in the professional’s beliefs and decision-making. The distribution of the incidence proportions of the ICD-10 hospital diagnoses F.91 conduct disorders and F.92 mixed disorders of conduct and emotions served as a proxy for diagnostic culture.

Non-spatial regression of incidence proportions
A non-spatial logistic regression analysis was initially performed to examine the associations between incidence proportions of children with diagnosis, medication use without a registered hospital diagnosis and overall ADHD and resources. The number of children with a diagnosis, medication use without a registered diagnosis and overall ADHD (both diagnosis and/or medication) were analysed separately. The number of children with diagnosis, medication use and ADHD, respectively, were outcomes. Absence of a hospital or paediatric psychiatrist in the municipality (yes, no), household income, average municipal spending on primary health care for children and incidence proportion of conduct disorders (100 × (count F91 + count F92/N)) were included as fixed effects (explanatory variables). Pearson correlation analysis was performed to check multicolinearity of the explanatory variables. The assumption about linearity between each outcome and the explanatory variables of average yearly total household income, average municipal spending on primary health care for children and proportion of children with a conduct disorder diagnosis was evaluated by categorising the explanatory variables and examining if the estimates of the categorised variable indicated linearity. The explanatory variables were categorised in three and four groups, respectively. Furthermore, linearity was evaluated by including the explanatory variable as a continuous variable as linear and quadratic terms in the analysis. If the quadratic term was significant it indicated that the assumption about linearity was not confirmed. The assumption about linearity for the three outcomes was not confirmed and the three explanatory variables were each categorised into three equally sized groups (low, medium, high).

The logistic regression model used was:

\[
\logit(\pi_i) = \mu + I_i + R_j + B_k + P_l
\]

where \( \pi_i \) is the proportion of children with diagnosis, medication use without a registered diagnosis or overall ADHD in municipality \( i, i = 1,\ldots, n \), and \( n = 98 \).

\( \mu \) is the intercept.

\( I_i \) is the fixed effect of municipal average of yearly total household income, \( i = low, medium, high \).

\( R_j \) is the fixed effect of the municipal spending, \( j = low, medium, high \).

\( B_k \) is the fixed effect of municipal incidence proportion of conduct disorder \( k = low, medium, high \).

\( P_l \) is the fixed effect of municipal absence of hospital or paediatric psychiatrist, \( l = yes, no \).

Significance of explanatory variables was evaluated using a likelihood ratio test. Model fit was evaluated using Pearson dispersion parameter. Adjustment for over-dispersion was performed based on Pearson goodness-of-fit statistics. Overdispersion is the presence of greater variability in a data set than would be expected based on the statistical model.

The logistic regression analyses were performed in Statistical Analysis Software package (SAS, version 9.3).

Bayesian conditional autoregressive analysis of the incidence proportions
Areal data typically exhibit spatial autocorrelation with observations from areal units close together tending to
have similar values. A proportion of this spatial autocorrelation may be modelled by including known covariate risk factors in a regression model. It is, however, common for spatial structure to remain in the residuals after accounting for these covariate effects. This residual spatial autocorrelation can be induced by a number of factors, and violates the assumption of independence common in many regression models. Bayesian modelling produces parameter estimates for each individual analysis unit by borrowing information from all other analysis units [39]. A Bayesian conditional autoregressive (CAR) analysis was performed to evaluate the significance of the explanatory variables when considering the spatial autocorrelation between neighbouring municipalities and non-spatial variation for each municipality not accounted for by the explanatory variables [39]. A Bayesian CAR model with a binomial distribution of number of children with diagnosis, medication use without a registered diagnosis and overall ADHD were analysed separately. Presence of a hospital or paediatric psychiatrist in the municipality (yes, no), household income, average municipal spending on primary health care for children and incidence proportion of conduct disorders were included as fixed effects (explanatory variables). The CAR model suggested by Leroux was used [46]. The CAR analysis models overdispersion and spatial autocorrelation in data present after adjusting for the explanatory variables. Spatial correlation between neighbouring municipalities is modelled by a $98 \times 98$ neighbourhood (adjacency) matrix, whose $jk$th element is 1 if the municipalities $j$ and $k$ are sharing a common border, otherwise 0.

The Bayesian CAR model used was:

$$\logit(\pi_i) = \mu + I_i + R_j + B_k + P_i + \psi_i$$

where $\pi_i$, $\mu$, $I_i$, $R_j$, $B_k$, $P_i$ are defined as above.

$\psi_i$ is the random effect of municipality $i$, $i = 1, \ldots, n$, and $n = 98$.

A weakly informative independent Gaussian prior ($\mathcal{N}(0, 10^2)$) was specified for parameters of the explanatory variables.

The spatial autocorrelation was modelled using Leroux model as the CAR prior given by

$$\psi_i \sim \mathcal{N}\left(\frac{\rho \sum_{j=1}^{n} w_{ij} \psi_j}{\rho \sum_{j=1}^{n} w_{ij} + \tau^2}, \frac{\tau^2}{\rho \sum_{j=1}^{n} w_{ij} + \tau^2}\right)$$

when conditioning on all other municipalities, where $\rho$ is the spatial correlation between neighbouring municipalities.

$\sum \psi_i$ is the sum of the random effects of neighbouring municipalities.

$w_{ij}$ is 1 if municipalities $i$ and $j$ are neighbours (i.e. share a common border) and 0 otherwise.

$r^2$ is the random variation not accounted for by the explanatory variables.

The variance parameter $r^2$ was assigned a uniform prior $U(0,1000)$ and the spatial autocorrelation parameter $\rho$ was assigned a uniform prior $U(0,1)$.

Inference (parameter estimation) for this model was based on Markov chain Monte-Carlo (MCMC) simulation, using a combination of Gibbs sampling and Metropolis steps. A single chain was applied. Each model was estimated with 100,000 iterations for burn-in and 1,000,000 iterations with thinning $= 100$.

Significance was assessed as non-zero parameter estimates using 95% credible intervals.

Residuals of the final model for each outcome were mapped to evaluate how well the models performed. Convergence was evaluated by plotting the samples of selected parameters. The spatial regression analyses were performed in R using the CARBayes package (R version 3.1.2).

**Abbreviations**


**Authors’ contributions**

All authors have made substantial contributions to conception and design of the study and to analysis and interpretation of data. All authors agree to be accountable for all aspects of the work. All authors read and approved the final manuscript.

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**Compliance with ethical guidelines**

**Competing interests**

The authors declare that they have no competing interests.

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**References**


Study II

Madsen KB, Hohwü L, Zhu JL, Olsen J, Obel C.
Social selection in cohort studies of childhood psychiatric diagnoses: the Danish National Birth Cohort.

In review
Social selection in cohort studies of childhood psychiatric diagnoses – the Danish National Birth Cohort

Short title: Representation of child psychiatric diagnoses in the DNBC

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Abstract

Aim: To estimate the relative representation of childhood psychiatric diagnoses and use of psychotropic medication in the Danish National Birth Cohort (DNBC) compared with the general population.

Methods: The general population was identified as all childbirths in Denmark during 1998-2002 (N=344,160). Linking the DNBC (N=91,442) and the general population to the Danish national health registries, all children were followed until they received an ICD-10 psychiatric diagnosis, had a prescription of psychotropic medication or to the end of follow up in 2013. The Prevalence ratios (PRs) with corresponding 95% confidence intervals (CI) were estimated for each psychiatric diagnosis and by gender. Age at first diagnosis presented as means were compared using the one sample t-test.

Results: In the DNBC, the selected childhood psychiatric diagnoses were underrepresented by 3% (PR 0.97, 95% CI 0.94; 0.99), ranging from a 20% underrepresentation for schizophrenia (PR 0.80, 95% CI 0.59; 1.09) to a 6% overrepresentation for anxiety disorder or obsessive-compulsive disorder (OCD) (PR 1.06, 95% CI 0.97; 1.17). The majority of the specific diagnoses were modestly underrepresented in the DNBC compared to the general population, while use of psychotropic medication had similar representation. Girls were generally more underrepresented than boys. Depression was on average diagnosed 0.4 years earlier in the DNBC than in the general population (p=0.023).

Conclusion: These findings suggest that the social selection may influence the prevalence of diagnosed childhood psychiatric disorders in the DNBC.

Keywords: representation, participation, childhood psychiatric diagnoses, the Danish National Birth Cohort
Introduction

Decreasing participation-rates in population-based studies may increasingly challenge the interpretation of results in epidemiological studies. Possible differences between participants and non-participants in the distribution of the exposure and outcome variables being studied will raise the question of external validity. The decision to participate may correlate with social, educational and health conditions, which may correlate with risk factors for the outcome of interest [1, 2]. Estimates of prevalence will typically be affected by this selection, while measures of risk will only be biased if the association between exposure and outcome among participants differs from the association among non-participants [3]. Having in mind the fundamental epidemiological aim of generalization of study results to the background population, low participation rates in population-based studies could pose a challenge to the external validity of studies.

Bias due to low participation at recruitment has also been discussed concerning the Danish National Birth Cohort (DNBC) [1, 2]. The DNBC is at present one of the largest birth cohorts in the world including about 100,000 participants enrolled during 1996-2002. It is a nationwide cohort of pregnancies and children aiming to study pregnancy complications and diseases in offspring in relation to factors operating in early life [4]. Today, the DNBC has up to 18 years of follow up time. It is estimated, that the participation rate in the DNBC is about 30% of all eligible women [1] and even though this low participation rate was mainly due to unwillingness of general practitioners (GP) to participate, concern about selection bias is relevant. A study revealed that groups with low socioeconomic resources in terms of education, occupation, income and civil status are underrepresented in the DNBC compared to the background-population [2]. Socioeconomic factors are likely to be associated with childhood psychiatric disorders, recently illustrated by a review, including studies from Europe, USA and Asia, that found children in families of low socioeconomic status (SES) on average to be twice as likely to be diagnosed with Attention Deficit Hyperactivity Disorder (ADHD) than their peers in high SES families [5]. Given these associations childhood psychiatric diagnoses would likely be underrepresented in cohorts like the DNBC. Similar to the social gradient in participation in the DNBC participants in the Norwegian Mother and Child cohort study (MoBa) have been found to be better educated than the rest of the Norwegian population [6]. Recently a study assessed the representativeness of child ADHD in the MoBa. Self-selection was found to affect the proportions of ADHD, but authors conclude that MoBa may have reasonable generalizability to the general child population as the differences from the general population were small [7].

There is an on-going interest in examining associations to childhood psychiatric disorders in large cohorts such as the DNBC and results may have considerable impact in the scientific field. Thus, it is relevant to investigate whether the social gradient in the willingness to participate in the DNBC has influenced the representation of later childhood psychiatric diagnoses to consider the external validity in studies.
Aim of the study

Our aim was to estimate the relative representation of selected registered childhood psychiatric diagnoses and use of medication for Attention Deficit Hyperactivity Disorder, anxiety and depression in the Danish National Birth Cohort compared with the general child population.

Material and methods

The Danish National Birth Cohort

The DNBC initially enrolled about 100,000 pregnant women. The first Danish counties began enrolment in 1996 and from 1999 to 2002 all counties in Denmark were included. The participants were recruited to the study at the first antenatal visit to their GPs (between 6 and 12 weeks of gestation). All Danish GPs were asked to take part in the recruitment of the pregnant women; however, only about 60% of eligible women received an invitation and around 60% of the invited women participated. Overall, the participation rate at enrolment was about 30% of all eligible women in Denmark [2]. Hence, about half of nonparticipation was caused by the GPs and the other half by pregnant women who declined the invitation [1]. The analysis was restricted to the years 1998-2002 as not all counties were represented in the first two years (1996-1997) and the last year (2003) of enrolment. This subpopulation represents about 90% of the initial cohort.

The general population

Participation in the DNBC has previously been calculated as participating pregnant women divided by eligible pregnant women [1]. The present study estimated participation as participating children divided by number of children born in the recruitment period. Independently of the DNBC, the general population was identified as all live childbirths during the central recruitment period (1998-2002) registered in the Danish Medical Birth Register (DMBR) [8]. The DMBR comprises data on all live births and stillbirths among women with permanent residence in Denmark.

Childhood psychiatric diagnoses and medication

The same method for identifying childhood psychiatric diagnoses was applied in the DNBC as in the general population. All live born children and residents in Denmark are assigned a unique civil registration number. This makes it possible to link data from the DMBR and the Danish National Hospital Register. This register includes information on all inpatient admissions from 1980 and onwards and all outpatient contacts to psychiatric hospitals, wards, and clinics in Denmark.
from 1995. The Danish National Hospital Register include data on clinical diagnoses, dates of admission and discharge, and reasons for admission, and the International Classification of Diseases, 10th Revision (ICD-10) diagnostic code criteria [9, 10]. Linking the DNBC and the general population to the Danish Health registries, all children were followed until the first main diagnosis of any of the selected psychiatric disorders and specific estimates were calculated for; F20-29 schizophrenia, schizotypal, delusional, other non-mood psychotic disorders, F32-33 depression, F40-42 anxiety disorders and Obsessive Compulsive Disorder (OCD), F84 autism spectrum disorders (ASD), F90 and F98.8 Hyperkinetic disorders (HKD/ADHD) and F91 conduct disorders or end of follow-up in March 2013, where the children were between 11-15 years old.

Children with psychiatric problems are in Denmark diagnosed and treated in the hospital system and by specialized medical doctors with a private practice. Diagnoses given in private practices are not registered so as a proxy measure for this we used specific medication prescribed for ADHD, anxiety or depression. A child was considered a case if he/she had redeemed at least two prescriptions for ADHD medication, a Selective Serotonin Reuptake Inhibitor (SSRI) or Serotonin and Noradrenaline Reuptake Inhibitor (SNRI) product. The ADHD medication included N06BA04 (methylphenidate), N06BA09 (atomoxetine), or N06BA07 (modafinil). The SSRI included N06AB04 (Citalopram), N06AB05 (Paroxetine), N06AB03 (Fluoxetine), N06AB10 (Escitalopram), N06AB08 (Fluvoxamin), or N06AB06 (Sertralin) and the SNRI included N06AX21 (Duloxetine) or N06AX16 (Venlafaxin). Information on medication was obtained from the Register of Medicinal Product Statistics and updated until November 2011.

Statistical Analysis

The prevalence of the selected childhood diagnoses in the general population and the DNBC, including the gender distribution, are given as number of participants and proportions (%). The proportions of children with an administrative childhood diagnosis from the general population and from the DNBC were compared by estimating a prevalence ratio (PR) for every diagnostic group. The PR (prevalence_{participants}/prevalence_{general population}) corresponds to the relative representation of the group. Because an estimate based on a total sample and the corresponding estimate obtained in a subsample are inherently positively correlated, standard methods do not apply [2]. Confidence limits were therefore found by using the following simple approximate formula and interpreted as 95% confidence intervals [2].

\[
SE(\log(PR)) = \sqrt{SE(\log(\text{Prevalence}_{\text{participants}}))^2 - SE(\log(\text{Prevalence}_{\text{source}}))^2}
\]
Age at first diagnosis is presented as means with standard deviations (SD). The general population and the DNBC were compared using the one sample t-test, accounting for the inter-dependency between children with diagnoses in the general population and the DNBC.

Statistical analyses were performed using Stata/IC 11.2 for Windows (Stata Corp, College Station, TX).

**Results**

According to the DMBR 344,160 children were born in the period 1998-2002 in Denmark. In the DNBC mothers to 91,442 children participated in the same time period (26.57%). With a prevalence of 3.75% for the total selected childhood psychiatric diagnoses in the general population, the prevalence of the specific diagnoses ranged from 0.04% (schizophrenia and other psychotic disorders) to 1.91% (HKD) (Table 1).

The representation of children with the specific diagnoses in the DNBC ranged from 21% (schizophrenia and other psychotic disorders) to 28% (anxiety disorders and OCD) with an overall participation of 26% for all selected psychiatric diagnoses. The relative representation varied accordingly with PRs ranging from 0.80 (95% CI: 0.59 1.09) for schizophrenia and 0.83 (95% CI: 0.71; 0.98) for conduct disorder to 1.01 (95% CI: 0.96; 1.06) for ASD and 1.06 (95% CI: 0.97; 1.17) for anxiety disorders or OCD. Children using SSRI/SNRI (PR: 1.05, 95% CI: 0.92; 1.20) were overrepresented and children who had prescribed ADHD medication (PR: 0.99, 95% CI: 0.95; 1.03) were present in the DNBC to the same extent as in the general population (Table 1).

In general more boys than girls were registered with a psychiatric diagnosis (4:1), although this was not the case for schizophrenia, depression and anxiety disorders or OCD. In the DNBC girls were generally underrepresented to a greater extent than boys except for the diagnoses; depression (PR=1.00 vs. 0.89), anxiety or OCD (PR= 1.12 vs. 1.00) and ASD (PR=1.07 vs. 0.99) (Table 1).

Table 1.

Age at first diagnosis ranged from 7.85 years (ASD) to 12.01 years (depression) in the general population (Table 2). In the DNBC the children with depression were on average almost 0.4 years younger at time of diagnosis than in the general population (p=0.023) and likewise for children with conduct disorder, although this was not statistically significant (P=0.078) (Table 2). The average age at diagnosis was 0.16 years higher for children with ASD in the DNBC than in the general population, but this was not statistically significant (Table 2).

Table 2.
Discussion

The present study addressed the representativeness of registered childhood psychiatric diagnoses in a large population-based cohort study. Previous studies that have estimated bias due to non-participation in the DNBC found a social gradient in the participation [1, 2]. Our study adds to the already existing literature on representativeness in the DNBC by investigating whether the social gradient in participation influenced later representation of childhood psychiatric diagnoses. The time specific prevalence of all selected childhood psychiatric diagnoses in the general population was estimated for the birth-cohorts from 1998-2002 when followed until 2013 (3.75%). The estimated prevalence of the specific diagnoses and medications corresponds to what has previously been reported in the Nordic countries [11, 12]. However, the estimates are much lower than reported in a recently published meta-analysis of worldwide prevalence of mental disorders [13]. Meanwhile, we would expect that the administrative prevalence of psychiatric disorders would be lower than the actual prevalence due to the fact that many children with mental health problems go undetected and untreated [14]. Studies have estimated that only about 20-25% of children with psychiatric disorders are in contact with mental health services [14, 15].

In the DNBC the relative representation of the selected childhood psychiatric diagnoses ranged from an underrepresentation of 20% (Schizophrenia) to an overrepresentation of 6% (anxiety disorders or OCD) resulting in an underrepresentation of all selected diagnoses of 3%. The majority of the specific diagnoses were modestly underrepresented in the DNBC compared to the general population. The ADHD diagnosis was underrepresented by 5%, more for girls than for boys, which was similar to findings recently reported for the large Norwegian Mother and Child cohort (MoBa) [7].

Socio-economic disadvantage and childhood psychiatric disorders

The study by Jacobsen et al. showed an underrepresentation in the DNBC of mothers with no or unknown level of education by 72%, with only compulsory school as highest level of education by 43%, unemployed by 18%, women with an income in the lowest quartile by 22%, and with a civil status of being single by 28% [2].

Due to the social gradient in the cohort participation we expected an underrepresentation of all the examined psychiatric diagnoses. Previous studies have showed that several markers of socioeconomic disadvantage are associated with emotional problems such as depression, anxiety disorders as well as conduct disorders in children [16, 17]. Children with conduct disorder were underrepresented by 17% in the DNBC compared to the general population, and even more for girls alone (51%). Anxiety and OCD diagnoses and SSRI/SNRI medication use were overrepresented in the DNBC compared to the general population. Depression was modestly underrepresented (by 5%) mainly due to an
underrepresentation among boys, however the use of SSRI/SNRI was more prevalent among boys than girls. Children with a diagnosis of depression were on average 0.4 years younger at time of diagnosis from the DNBC than the general population and similar results were found for conduct disorder. Taking into account the overrepresentation of high SES families in the DNBC, earlier diagnosis can be a result of better communicative- and health literacy in higher educated women [18] who would then have better preconditions for understanding the healthcare system and make demands. Earlier diagnosis may be an indicator of how social selection can influence later representation of health outcomes such as psychiatric diagnoses, that in turn lead to problems with the generalizability of study results.

Studies from the United States have during the past years reported a positive correlation between high socioeconomic status in the family and risk of ASD diagnosis [19, 20]. This is in line with our findings that ASD was present to the same extent in the DNBC as in the general population. However, it is debatable whether the association found in previous studies merely is the expression of an unequal access to health care as the opposite has been observed in countries with different health care systems [21, 22]. A Swedish study found that low socioeconomic status was associated with an increased risk of ASD [22], and a Danish study found an association between low parental income and ASD [21]. Another study reported that children with ASD of highly educated parents were diagnosed earlier than children of poorly educated parents [20]. In our study we found that children with ASD from the DNBC were older at time of diagnosis than the children with ASD in the general population. However, the difference was small and only borderline statistically significant.

It is well known that ADHD is more prevalent among low socioeconomic groups [5, 23], and as expected we found that the diagnosis was modestly underrepresented in the DNBC (5%). However, when looking at the gender distribution, the underrepresentation of the ADHD diagnosis was mainly due to an underrepresentation of girls and the use of ADHD medication was only underrepresented by 1% or could even be overrepresented (95% CI: 0.95; 1.03). The underrepresentation of ADHD in girls may be due to gender differences in the phenotypic expression of ADHD as girls tend to present with less disruptive behaviour [24]. Girls from more resourceful homes may be better at compensating for their difficulties, which may result in less problem recognition by parents and teachers. Though studies have concluded that the symptoms of hyperactivity and impulsivity are indeed present in girls with ADHD, girls generally have a lower intensity of these symptoms than do boys, and girls are more likely to have the inattentive subtype of ADHD [25].

**Strengths and limitations**

The major strength of this study is the use of the national health registries, in which all Danish citizens are potentially registered. This makes it possible to estimate prevalence of clinical childhood psychiatric diagnoses on the same premises in the general population and in the DNBC. Using registers, only death and migration cause attrition and unlike
parental reports of diagnosis, the register-based information on diagnoses has been clinically reviewed and confirmed by the medical records. Previous validation studies of the diagnosis of hyperkinetic disorders in the Danish Psychiatric Central Research Register have shown an agreement on the diagnosis of 83-87% [26, 27]. Meanwhile, only few records were examined.

Using the national registers may, however, also be a limitation of the study. Although the predictive value of diagnoses in patient registers may be relatively high, it does not rule out the problem of undetected cases in the population nor the bias due to access to specialist care or different referral and diagnostic practices in the country [28]. In a previous Danish study the incidence of the ADHD diagnosis has been reported to vary geographically, depending on accessibility to diagnostic facilities and different diagnostic cultures [28]. However, we would not expect that the geographic variation in diagnoses would be any different in the DNBC than in the general population.

Finally, we could not test directly whether the social gradient in participation has affected the later representation of childhood psychiatric diagnoses, hence, we cannot rule out that the underrepresentation may be due to alternative factors. In conclusion we found an underrepresentation of most of the examined childhood psychiatric diagnoses in the DNBC, however only to a small extent, compared to the general population. This is in line with the social gradient in participation as socio-economic factors are associated with most childhood psychiatric disorders. Therefore we cannot rule out the possibility that social selection has had an influence on the prevalence of later diagnosed childhood psychiatric disorders in the DNBC.

Abbreviations:
ADHD: Attention Deficit Hyperactivity Disorder
ASD: Autism spectrum disorders
CD: Conduct disorders
DNBC: Danish National Birth Cohort
GP: General practitioner
HKD: Hyperkinetic disorders
ICD-10: International Classification of Diseases, 10th Revision
OCD: Obsessive Compulsive Disorder
PR: Prevalence ratio
SES: Socioeconomic Status
SNRI: Serotonin and Noradrenaline Reuptake Inhibitor
SSRI: Selective Serotonin Reuptake Inhibitor

Ethical approval
The study was based on already existing data and did not involve any contact with the participants. The Danish Data Protection Board and the DNBC steering committee approved the study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee
and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards [29]. For this type of study formal consent is not required.

Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Acknowledgment

The Danish National Research Foundation has established the Danish Epidemiology Science Centre that initiated and created the Danish National Birth Cohort. The cohort is furthermore a result of a major grant from this Foundation. Additional support for the Danish National Birth Cohort is obtained from the Pharmacy Foundation, the Egmont Foundation, the March of Dimes Birth Defects Foundation, the Augustinus Foundation, and the Health Foundation

REFERENCES


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DNBC: Danish National Birth Cohort, ICD 10: International Classification of Diseases, 10th Revision (ICD-10), CI: Confidence Intervals, OCD: Obsessive Compulsive Disorder, SSRI: Selective Serotonin Reuptake Inhibitor, SNRI: Serotonin and Noradrenaline Reuptake Inhibitor
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Study III

Madsen KB, Ravn MH, Arnfred J, Rask CU, Olsen J, Obel C. Characteristics of undiagnosed children with parent-reported ADHD behaviour. In review
Characteristics of undiagnosed children with parent-reported ADHD behaviour

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Abstract

There is an ongoing public debate on the diagnosis of Attention Deficit Hyperactivity Disorder (ADHD) in which critics have claimed that the disorder is over-diagnosed, while the potential under-diagnosis of children with ADHD has received little attention. In this study we estimate the number of children with parent-reported ADHD behaviour at age 7 and absence of recorded ADHD diagnosis through adolescence, and investigate whether socio-demographic characteristics of this group differed from the children diagnosed with ADHD during follow-up. Our study was based on data from the Danish National Birth Cohort (DNBC), where parents of 51 527 children completed questionnaires, including the Strength and Difficulties Questionnaire (SDQ). ADHD diagnosis was identified through Danish registers and parent-reported ADHD behaviour by the specific SDQ subscale. Socio-demographic predictors of positive parent-reported SDQ ADHD behaviour and absence of recorded ADHD diagnosis in their children were examined using logistic regression analyses. Children with parent-reported ADHD behaviour and no ADHD diagnosis (1.3%) were more likely to be girls (OR: 1.83; 95% CI: 1.45; 2.29), more likely to have mothers with a low socioeconomic status (OR: high vs. low 1.49; 95% CI: 1.10; 2.02) and to live in certain regions of the country (OR: Capital vs. Southern: 2.04; 95% CI: 1.51; 2.73) than children with an ADHD diagnosis. The children showed markedly impairments on all the SDQ subscales. The results demonstrate a considerable number of children with ADHD symptoms who potentially go undetected and underline the influence of socio-demographic factors in the pathway to a diagnosis of ADHD.

KEYWORDS: Attention Deficit Hyperactivity Disorder (ADHD); Strength and Difficulties Questionnaire (SDQ); cohort study; diagnosis; socio-demographic factors
Introduction

Attention deficit hyperactivity disorder (ADHD) is a developmental disorder with a substantial, lifelong impact on the individual’s social, academic and occupational performance depending on ADHD severity, comorbidity and treatment [1]. The consequences of ADHD also bear heavily on the healthcare system and society in general [2, 3]. ADHD is characterised by attention problems and/or impulsivity and hyperactivity, causing impairment in daily life. The disorder is linked to psychosocial, environmental, genetic and biological factors; yet, no specific causality is implied [4]. ADHD affects a substantial part of the population and worldwide its prevalence was recently estimated at 2.6-4.5% [5]. The past two decades have seen a rise in the prevalence of ADHD diagnoses among schoolchildren, making it the most commonly diagnosed childhood disorder in most countries [6, 7]. However, the rise is not homogeneous within countries or between countries, which may reflect different thresholds for recognising and referring children as well as different access to diagnostic facilities [8-10].

It is a common conception that ADHD is over-diagnosed probably due to the attention from the public media and the popular press in which concerns about over-medicating children has been raised [11]. However, the current scientific debate about ADHD has been equally concerned with the existence of under-diagnosis of ADHD, especially in girls [12-16].

Ideally, children fulfilling the diagnostic criteria should be diagnosed, but social factors may affect detection and diagnosing of ADHD resulting in under-detection and under-diagnosis. It has been suggested that individual factors like the child’s gender, the family status, parental mental health, where the child lives and the parents’ socioeconomic status (SES) influence the child’s probability of getting an ADHD diagnosis [10-12, 16-20]. In a population sample of 10 367 US children Cuffe et al. (2005) found that 1.59% of boys and 0.81% of girls were positive for significant parent-reported ADHD symptoms measured with the Strengths and Difficulties Questionnaire (SDQ) but did not have a clinical diagnosis of ADHD. Furthermore, these children had substantially higher proportions of elevated scores on other SDQ subscales compared to the overall population [21]. Froehlich et al. found that less than half of the children in a sample survey of 3 907 US children who met the ADHD criteria from the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV) had received the diagnosis [12]. Furthermore, the results suggested that poor children were more likely to meet criteria for ADHD yet were least likely to receive treatment [12]. Under-treatment and low rates of clinical referral to child mental health services of children who were impaired by their ADHD symptoms was also one of the main findings in a Dutch community sample of 283 9-year-old children [22]. Research on gender differences suggests that girls may be consistently under-identified [12-16]. Girls with ADHD tend to exhibit lower
levels of disruptive behavior and higher levels of inattentiveness, and internalizing symptoms than do boys, which make them less likely to disrupt the classroom and may be more readily overlooked [11, 23]. Furthermore, it has been suggested that as ADHD is more frequent in males, a boy might be seen as a more prototypical child with ADHD and might therefore receive an ADHD diagnosis more readily than a girl would [24]. Using case vignettes in a sample of therapists, Bruchmüller found that the therapists diagnosed ADHD twice as much in boys than in girls even though the only difference in the vignettes was the gender [24].

Early identification and interventions are important in child psychiatric disorders like ADHD and delay in initiation of appropriate treatment may lead to a poor outcome [25, 26]. Several therapeutic interventions have been developed and some, including medical interventions, have been shown to be effective in improving the daily function of and long-term outcomes for children and adolescents with ADHD [25, 27-29].

Until now, only few studies have addressed the potential problem with under-diagnosis of ADHD and related issues in a large population-based sample and in a European context.

In the current study our aim was twofold; first to estimate the number of children with positive parent-reported SDQ ADHD behaviour at age 7 and absence of recorded ADHD diagnosis up till adolescence, and second to investigate whether socio-demographic and other SDQ characteristics of this group differed from the children diagnosed with ADHD during follow-up.

**Method**

**Procedure and sample**

The present cohort study was part of the Danish National Birth Cohort (DNBC), which is a nationwide cohort including more than 90,000 Danish women [30, 31]. The recruitment of participants took place at the first antenatal visit to the general practitioners throughout 1996-2003. In the present study, we used information from the follow-up questionnaire, which was completed by the primary caregivers, either through the Internet or on paper, in the child’s seventh year. The questionnaire addressed the child’s health and development and included a parent-version of the Strength and Difficulties Questionnaire (SDQ-Den) (www.sdq.info.com). A total of 57,282 parents participated in the 7-year follow-up. We included only singletons with complete SDQ data and excluded younger siblings (n=51,527). We linked the information obtained in the DNBC study to the Danish National Patient Register [32], the Danish Psychiatric Central Research Register [33] and the Danish National Prescription Registry [34] in order to identify children with diagnosed and treated ADHD or other psychiatric diagnoses.
**Psychiatric diagnoses**

ADHD diagnosed children were identified through two different approaches. First, we used the Danish patient registries [32, 33] where diagnoses are classified according to the International Classification of Diseases, 10th Revision (ICD-10) [35]. These registers hold information on all inpatient hospital admissions and outpatient hospital visits. We defined that ADHD was diagnosed when ICD-10 diagnoses F90.0-F90.9 (Hyperkinetic disorders) or F.98.8 (Other specified behavioural and emotional disorders with onset usually occurring in childhood and adolescence) were registered either as the main diagnosis or an additional diagnosis after the age of 5. Second, we used the Danish National Prescription Registry, which registers information about prescribed ADHD medication in Denmark [34]. This was done to include ADHD patients diagnosed in private psychiatric practices in Denmark, which are not obliged to report the diagnoses to the national patient registers. Children were categorised as ADHD cases when they had redeemed one or more prescriptions of methylphenidate (N06BA04) or atomoxetine (N06BA09) after the age of 5 years. The registers were updated until March 2013; hence the children were followed until the age of 10-17 years. All children were followed until a diagnosis of ADHD, an ADHD medication prescription, death, emigration or end of registry follow-up, whichever came first. Information on death and emigration was obtained from the Civil Registration System. Henceforth, children who had either an ADHD diagnosis or had redeemed ADHD medication are referred to as ADHD cases or ADHD diagnosed children.

**The Strengths and Difficulties Questionnaire (SDQ)**

The SDQ is a brief screening tool for emotional and behavioural problems [36]. The SDQ consists of 25 questions scored 0–1–2 on a Likert scale (‘not true’–‘somewhat true’–‘certainly true’). The questions cover five subscales: hyperactivity/inattention, conduct problems, emotional symptoms, peer relationship problems and pro-social behaviour, each rated as the sum score of five items. In addition, an impact supplement is provided to the informants, inquiring about the child’s impairment interfering with home life, friendship, classroom learning, and leisure activities. The instrument is a multi-informant questionnaire available as a parent and teacher version of 5-16 years old and as a self-report version for 11-17 year olds [37]. A computerised algorithm has been developed that combines teacher, parent and child reports to predict child hyperactivity-inattention disorders (SDQ ADHD). The SDQ ADHD algorithm generates “unlikely”, “possible” or “probable” ratings for hyperactivity disorders [38, 39]. A program for scoring the algorithm is
available at the SDQ website www.sdqinfo.com. The psychometric properties of the SDQ have been found to be satisfactory [40, 41].

Goodman described the psychometric properties in a study of about 10,000 British 5-15-year-olds. For the specific hyperactivity/inattention subscale he found a specificity of 92% and a sensitivity of 74% in predicting ADHD when reported only by the parent [42]. In a general population study of 2,315 Danish children, the instrument identified children with highly increased risk of later ADHD diagnosed in school age (hazard ratio of 20.65 and a sensitivity of 45% and a specificity of 99.6%). The predictive algorithm for hyperactivity-inattention disorders (SDQ ADHD) was calculated with SDQ reports from both parents and teachers [43]. In another population study of 6,233 Norwegian children, the SDQ predictive algorithm using both parent and teacher reports identified 74% of children with ADHD of the combined type; the study found a sensitivity of 52% and specificity of 98% [44].

In our study, we used the hyperactivity/inattention (H/I) scale with the prediction algorithm (SDQ ADHD) with only one informant (the parent). The mothers completed 99.1% of the reported SDQ questionnaires, while the rest were completed by fathers or other primary caregivers.

*The children positive for SDQ ADHD and absence of registered ADHD diagnosis*

We identified the children who exhibited ADHD behaviour using the SDQ ADHD algorithm for probable ADHD. Ideally, the SDQ ADHD prediction should include information from both a parent and a teacher. However, with only one informant (parent) available, we based the analyses on the most strict prediction algorithm to reduce false positives; H/I score ≥7 and impact score ≥2. In addition, children were excluded if the impact score did not apply to more than one setting. Children diagnosed with F.84 (pervasive developmental disorders) were excluded as difficulties corresponding to ADHD may have been recognised without a corresponding diagnosis being registered, respecting the exclusion rule in the ICD-10. Children with positive SDQ ADHD behaviour who were not registered with an ADHD diagnosis were followed in the registers for other psychiatric diagnoses.

*Independent variables; Socio-demographic factors*

Socioeconomic information was derived from national registers at Statistics Denmark and based on the current or most recent job within 6 months or the type of education. The category ‘high’ included working in management or in jobs requiring higher education. Office workers, service workers, skilled manual workers and working in the military constituted the ‘middle’ category, while unskilled workers and the unemployed were classified into the ‘low’ category.
Women who could not be classified in this way (4.1%) were categorised according to their husband’s SES, defined as above [45]. Information on the family status was obtained from the 7-year follow-up questionnaire and based on the question whether the parents had been living together since the birth of their child.

We included maternal depression in the analysis because maternal levels of depression has been suggested to be associated with an over-report of the child’s behaviour problems [46]. Maternal depression was self-reported and collected at 7-year follow-up referring to the time from childbirth to child age 7 years. Maternal depression was positive when the mother reported 1) to have had a psychiatric illness, and 2) to have been in contact with a physician or a psychologist because of this, and 3) that the psychiatric illness was depression.

Place of residence was obtained from the Civil Registration System and each ADHD case was assigned to the region in which they were diagnosed or had redeemed medication. Children without an ADHD diagnosis were assigned to the region in which they were born.

Statistical analysis

First descriptive characteristics are presented for the overall sample, the ADHD diagnosed children and the SDQ ADHD positives in the absence of an ADHD diagnosis. Second other mental and behavioural diagnoses are presented for the latter children.

To determine the possibility of gender, family status, maternal depression, place of residence and SES status being associated with the SDQ ADHD positives and no ADHD diagnosis, we conducted a logistic regression model comparing these children with the ADHD diagnosed children. First, gender, family status, maternal depression, place of residence and SES were analysed separately. Next, all the independent variables were included in the model. Multiple logistic regression results are presented with odds ratios (OR) and 95% confidence intervals (CI) for each variable. T-test analyses were used to compare the SDQ subscale scores between the SDQ ADHD positives in the absence of an ADHD diagnosis and the ADHD cases.

The statistical analyses were conducted using STATA 11.1. A two-sided significance level of 0.05 was used in all analyses.

Results

Of the 51 527 children 1 046 received an ADHD diagnosis and 998 had redeemed ADHD medication prescriptions during follow-up. A total of 1 373 children were registered as ADHD cases (2.7% of the cohort) because of an overlap
of 671 children between medication and diagnosis. In Table 1, the number of children with and without recognised ADHD was tabulated with the number of children with a ‘probable’, ‘possible’ or ‘unlikely’ SDQ ADHD. Table 1 shows that out of the 1 179 children with a positive SDQ ADHD prediction, 680 were not identified with an ADHD diagnosis. Excluding children if the impact did not apply to more than one setting (n=14) and with a diagnosis of F.84 Pervasive development disorder (n=13), we found that the SDQ positives in the absence of an ADHD diagnosis (n=653) represented 57% of the SDQ ADHD ‘probables’ and 1.3% of the total cohort. Of the 1 373 ADHD diagnosed children 727 (53%) were predicted ‘unlikely’ of SDQ ADHD.

In Table 2, the distributions of socio-demographic variables are reported for the whole sample, the ADHD diagnosed children and the children with SDQ ADHD behaviour and no ADHD diagnosis. Compared with the overall sample, ADHD diagnosed children were more likely to be boys (79 % vs. 51.2 %), less likely to live with both parents (69.4% vs. 83.8%) and more likely to belong to low SES (14.2% vs. 7.8%) (Table 2). In the group of SDQ positives and absent ADHD diagnosis the gender distribution was also in favour of boys, although the difference was smaller than in the group of ADHD cases. The SDQ positives in absence of an ADHD diagnosis were more similar with the ADHD cases than the overall sample on family status, mother’s socioeconomic status and maternal depression (Table 2). The mean child age at end of follow-up did not differ between the overall sample, the ADHD cases and the SDQ ADHD positives and absence of ADHD diagnosis.

In the group of children with a positive SDQ ADHD in absence of an ADHD diagnosis, 46 (7%) had other mental and behavioural disorders (see Table 3). The majority had a diagnosis related to disorders of psychological development (35%) or behavioural and emotional disorders (35%).

The results of the logistic regression analyses estimating the association between the predictors and not receiving a diagnosis of ADHD during childhood or adolescence while exhibiting ADHD behaviour at age 7 years compared to children with an ADHD diagnosis are shown in Table 4. The SDQ positives in absence of an ADHD diagnosis were more likely to be girls (OR_{adj} 1.83; 95% CI 1.45; 2.29), more likely to have mother’s with a low SES (OR_{adj} 1.49; 95% CI 1.10; 2.02) and more likely to live either in the Zealand Region (OR_{adj} 1.47; 95% CI 1.05; 2.05) or the Southern Region (OR_{adj} 2.04; 95% CI 1.51; 2.73) of Denmark with the Capital Region serving as the reference (Table 4).
Associated mental health problems were measured with the SDQ subscales and in Table 5 the differences in mean scores on the subscales are presented. The SDQ positives in absence of ADHD diagnoses had significantly higher scores on all subscales compared to the children who received an ADHD diagnosis during follow-up except for the prosocial scale, which is a positive scale with higher score reflecting better prosocial behaviour. The differences between the groups were most pronounced on the emotional scale (3.72 vs. 2.77), besides the hyperactivity/inattention scale (Table 5).

**Discussion**

We found that more than half of the children with parent-reported ADHD behaviour at age 7 were not diagnosed with ADHD during follow-up, which corresponds to 1.3% of the total cohort. Our results are consistent with previous studies and the prevalence estimates of children with ADHD behaviour and no diagnosis were in fact quite similar [12, 21]. We further investigated what characterised the children with parent-reported ADHD behaviour and no ADHD diagnosis. We found that 7% of the children were diagnosed with other mental or behavioural disorders, particularly disorders of psychological development and behavioural and emotional disorders during follow-up. We also found that the children in this group were more likely to be girls, to have mothers with low SES and to live in certain regions of the country. Compared to the children who received an ADHD diagnosis during follow-up the children with ADHD behaviour and no diagnosis had significantly higher scores on the SDQ subscales, which is consistent with findings from the study by Cuffe et al. (2005) [21].

The number of children who were identified with parent-reported ADHD behaviour but were not identified as ADHD cases (57%) during follow-up point to a high number of children with potential undetected ADHD problems. However, it has been argued that when the SDQ is used in a community sample, quite a few children with clinical range SDQ results will actually be typically developing, i.e., false positives, due to low prevalence rates in the general population. In contrast, when the SDQ is used in a clinical sample, where prevalence rates are higher, fewer children will be false positives [47]. However, the children showed markedly and significantly worse impairments on all SDQ subscales compared to the children who had or received an ADHD diagnosis during follow-up. Even if these children would not exceed the threshold for a clinical diagnosis they would probably be in need of special care.

Barriers to receive an ADHD diagnosis may occur at multiple levels, including identification and referral by school personnel, parents’ help-seeking behavior, access to diagnostic services, diagnosis by the professionals, treatment decisions, and acceptance of treatment [48].
Previous national studies suggest that contextual factors like access to psychiatric services and the diagnostic approach of the specialist physicians vary considerably across Denmark; and this affects the probability that a given child is referred to diagnostic facilities and diagnosed with ADHD [10, 25]. This is in line with our results showing that the SDQ ADHD positives and absent ADHD diagnosis children were more likely to be living in particular regions (the Zealand and Southern regions) of the country where the incidence of the ADHD diagnosis has previously been estimated to be lower than in other parts of the country [10]. The study by Madsen et al. demonstrated that in the Southern region several municipalities had an incidence of ADHD diagnosis below the national average and two municipalities even experienced a decrease in incidence between 1990 and 2000 [10]. Our finding supports the notion that these children may in fact be undetected cases and may indicate a difference in identification and referral of children with ADHD as well as an unequal access to diagnostic services.

Similar with other studies, we found that socioeconomic disadvantage was more common in children diagnosed with ADHD [49, 50]. In addition, we found that the children with a positive SDQ ADHD in the absence of an ADHD diagnosis were even more likely than the children diagnosed with ADHD during follow-up to have mothers with a low SES. This is consistent with findings from several other studies showing that socioeconomic disadvantage may be a predictor of non-treatment [12, 51]. The influence of socio-demographic factors such as SES, income and educational level on parent’s help-seeking behaviour may depend largely on a country’s healthcare system. Studies in several European countries in which healthcare is readily available and where there are no major financial constraints to receiving professional help, have not found any association between SES and help seeking, opposite to studies conducted in the US [52]. As low SES reflects low level of education, the association with SDQ positives and absent diagnosis could reflect that these mothers do not necessarily have any preconditions for understanding the healthcare system and make demands because of a poorer communicative and health literacy [53].

There has been surprisingly little attention in the public media about the issue of possible under-diagnosis. Impact of negative media publicity on ADHD medication may play a vital role in influencing children with ADHD, their parents, teachers and professionals [54]. Studies have suggested that the media is an important source of information about ADHD for primary care physicians [55, 56]. Like physicians, school personnel find ADHD both challenging and time-consuming. Teachers and school counselors spend a great amount of time addressing concerns regarding children who exhibit ADHD symptoms; however, educators may have little accurate knowledge about ADHD and may, in some cases, share misperceptions common among parents, i.e., that ADHD is not a real disorder, or that the symptoms are caused by too much sugar, poor parenting, or a stressful family environment [48, 57]. Consequently this may result in a
lack of referral of children with ADHD symptoms to psychiatric evaluation. In a study using data from several European countries a third of caregivers for children with ADHD reported a high degree of difficulty in obtaining an ADHD diagnosis for their child, less than half felt that that sufficient resources were available, and gaps in support from health care providers and schools were identified [58].

The problem of undetected ADHD in society is supported in the literature, especially in girls [12-16, 21]. We found that the children with an SDQ ADHD and absent ADHD diagnosis were about 80% more likely to be girls compared with the children who received an ADHD diagnosis during follow-up. It has been suggested that the under-identification of girls may be due to gender differences in the phenotypic expression of ADHD with girls presenting with less disruptive behaviour resulting in less problem recognition by parents and teachers [23]. This is consistent with a study using data from 10 European countries where Nøvik et al. (2006) found that gender specific variations had very little influence on paediatric practise suggesting that girls with ADHD might be under-referred [16]. Meanwhile gender differences have also been suggested to play a role in the assessment of children in clinical practise [24]. It goes beyond the current study to answer this, but future research efforts should elucidate which factors might contribute to the under-identification of girls with ADHD at different levels in the pathway to an ADHD diagnosis.

Other possible explanations for the finding of the large number of children with a positive SDQ ADHD in the absence of an ADHD diagnosis could be that the difficulties reported by the parents for some children were transient; and despite difficulties in impulse-control and hyperactivity, symptoms would not exceed the threshold for an ADHD diagnosis. Using screening instruments like the SDQ without further clinical evaluation of the children, we cannot be certain that these children in fact have ADHD symptoms. Even though the children may be under the threshold of a diagnosis according to the ICD-10 or DSM-5 these children may indeed still exhibit problems with functioning and limitations in their everyday lives. Alternatively, the difficulties could be interpreted as part of a different psychiatric disorder, which was the case for about 7% of the children. Finally, some parents may have opposing views on proposed (medical) treatment of their children and would have resisted further evaluation.

We found a considerable number of children with an ‘unlikely’ SDQ ADHD prediction who had or later received an ADHD diagnosis during follow-up (n=727). According to the study by Goodman (2001) up to 26% (and even more according to other studies [43, 44]) of children with ADHD in the sample may screen negative for ADHD by the SDQ [42]. Second, there may be some children with parent-reported ADHD who are treated and thus have fewer symptoms and finally, there is a possibility of a later onset of ADHD symptoms.

Strengths and limitations
The major strength of this study was the use of data from Danish registers on clinical diagnoses and prescription of central stimulants. Using registers, only death and migration cause attrition. Unlike parental reports of diagnosis, the register-based information on diagnoses and prescriptions is clinically confirmed. Although ADHD is a disorder most often occurring early in childhood, the follow-up time allowed for a delay in the referral of children and the diagnostic processes. A considerable amount of time may pass from when parents or teachers raise concern about a child with ADHD-like behaviour until referral and confirmed diagnosis [16]. The study by Nøvik et al. demonstrated that the mean time interval between first awareness of child symptoms to seeking treatments was about 2.5 years and 1.5 years from seeking treatment to an ADHD diagnosis [16]. In contrast to a cross-sectional design, the follow-up design used here allowed us to include information on diagnostic status until the children were between 10-17 years old.

The present study is based on the DNBC cohort, which is a large general-population-based sample of Danish children recruited in early pregnancy throughout Denmark during 1996-2002. A previous study found that the cohort is not representative in terms of socioeconomic factors [59]. However, in an analysis of the representativeness of childhood psychiatric diagnoses, we found that children with a registered ADHD diagnosis are only modestly underrepresented (between 1-9%), whereas children using ADHD medication are present in the DNBC to the same extent as in the general population (Madsen KB, Hohwü L, Zhu J.L, Olsen J, Obel C. Childhood psychiatric diagnoses in the Danish National Birth Cohort. In review. 2017). However, the relatively poor representativeness of low SES groups in the DNBC may have caused an underestimation of children with positive SDQ ADHD in the current study.

Some important limitations of the present study have to do with the use of the SDQ for measuring ADHD behaviour. First, we only have parent-provided ratings of the SDQ, which could be a problem since the manifestation of ADHD symptoms in multiple contexts is important. The performance of SDQ in predicting ADHD is reported to be somewhat better when both a parent and a teacher report [42-44]. We therefore decided to include only children with a hyperactivity/inattention score above 7 and an impact score above 2 (from more than one setting), trying to reduce misclassification. However, the impact score might refer to the other domains of the SDQ resulting in misclassification. We were not able to follow all children for an equal amount of time because the cohort was born between 1996 and 2003. This problem could cause misclassification as some more recently born children may receive a diagnosis after the end of follow-up. However, the mean age at the end of follow-up was the same in the overall sample, the ADHD diagnosed group and the group of children with a positive SDQ ADHD and no ADHD diagnosis. In addition, a Danish study found that most children have been diagnosed and received treatment by the age of 12 years [60]. Additionally, we do not have information on children diagnosed in private practices who have not redeemed prescribed medication.
The lack of information could have led to an overestimation of children with a positive SDQ ADHD and negative ADHD diagnosis.

We did not have adequate information on the parent’s psychopathology, besides maternal depression. This could have had an influence, since parental psychopathology has been associated to a higher degree of problem-recognition but not help-seeking or utilisation of mental health services [52].

Finally, the use of prescribed central stimulants as a proxy measure for ADHD can cause misclassification regarding children being treated because of narcolepsy. However, this number is presumed to be negligibly low in Denmark and such misclassification would probably not have an impact on the presented results [43].

In conclusion (and noting the limitations above), our study identified a considerable number of children with parent-reported ADHD behaviour at age 7 and no registered diagnosis during a long follow-up. Our results correspond with previous studies suggesting that a number of children with ADHD symptoms might go undetected and that these children might have considerable associated mental health problems. In addition, our study demonstrated that the children exhibiting ADHD behaviour in the absence of an ADHD diagnosis were more likely to be girls, more likely to have mothers with a low SES and to be living in certain regions of the country. These results may point to socio-demographic factors as important drivers in the pathway to an ADHD diagnosis.

Ethical approval

The Danish Data Protection Agency and the DNBC Steering Committee approved the study.

Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

References

Table 1. Children with and without ADHD diagnosis and the SDQ ADHD prediction categories

<table>
<thead>
<tr>
<th>ADHD diagnosed</th>
<th>SDQ ADHD prediction</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unlikely</td>
<td>Possible</td>
</tr>
<tr>
<td>No</td>
<td>48 794</td>
<td>680</td>
</tr>
<tr>
<td>Yes</td>
<td>727</td>
<td>147</td>
</tr>
<tr>
<td>Total</td>
<td>49 521</td>
<td>827</td>
</tr>
</tbody>
</table>

Table 2. Distribution of socio-demographic variables for the overall sample, the ADHD diagnosed and the SDQ ADHD positive without an ADHD diagnosis

<table>
<thead>
<tr>
<th>Overall sample</th>
<th>ADHD diagnosed</th>
<th>SDQ ADHD positive, no ADHD diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>All</td>
<td>51 527 (100)b</td>
<td>1 373 (2.7)b</td>
</tr>
<tr>
<td>Child’s gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boy</td>
<td>26 371 (51.2)</td>
<td>1 085 (79)</td>
</tr>
<tr>
<td>Girl</td>
<td>25 144 (48.8)</td>
<td>288 (21)</td>
</tr>
<tr>
<td>Missing</td>
<td>12 (&lt;0.1)</td>
<td>0</td>
</tr>
<tr>
<td>Family status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Living with both parents</td>
<td>43 156 (83.8)</td>
<td>953 (69.4)</td>
</tr>
<tr>
<td>Parents divorced</td>
<td>8 254 (16)</td>
<td>417 (30.3)</td>
</tr>
<tr>
<td>Missing</td>
<td>117 (0.2)</td>
<td>3 (0.3)</td>
</tr>
<tr>
<td>Mother’s socioeconomic status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>27 243 (52.9)</td>
<td>561 (40.9)</td>
</tr>
<tr>
<td>Middle</td>
<td>17 938 (34.8)</td>
<td>555 (40.4)</td>
</tr>
<tr>
<td>Low</td>
<td>4 006 (7.8)</td>
<td>199 (14.5)</td>
</tr>
<tr>
<td>Missing</td>
<td>2 340 (4.5)</td>
<td>58 (4.2)</td>
</tr>
<tr>
<td>Maternal depression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3 740 (7.3)</td>
<td>227 (16.5)</td>
</tr>
<tr>
<td>No</td>
<td>47 787 (92.7)</td>
<td>1 146 (83.5)</td>
</tr>
<tr>
<td>Mean child age at end of follow-up (sd)</td>
<td>12.49 (1.36)</td>
<td>12.59 (1.31)</td>
</tr>
</tbody>
</table>

*a*Includes children diagnosed in both private and public practice (medication and/or registered diagnosis).

*b*The percentage is compared with the overall sample. Otherwise, percentage is within the group.
Table 3. Mental and behavioural disorders in the group of SDQ ADHD positive without an ADHD diagnosis

<table>
<thead>
<tr>
<th>ICD-10 Mental and behavioural disorders</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F40-48 Neurotic, stress-related and somatoform disorders</td>
<td>2 (4)</td>
</tr>
<tr>
<td>F50-59 Behavioural syndromes associated with physiological disturbances and physical factors</td>
<td>1 (2)</td>
</tr>
<tr>
<td>F70-79 Mental retardation</td>
<td>11 (24)</td>
</tr>
<tr>
<td>F80-89 Disorders of psychological development*</td>
<td>16 (35)</td>
</tr>
<tr>
<td>F91-98 Behavioural and emotional disorders with onset usually occurring in childhood and adolescence**</td>
<td>16 (35)</td>
</tr>
<tr>
<td>In all</td>
<td>46 (100)</td>
</tr>
</tbody>
</table>

ICD-10 International Classification of Diseases 10th Edition

* The F.84 diagnosis was excluded
** Not F.98.8

Table 4. Results of the logistic regression model predicting the probability for each independent variable occurring in the group of SDQ ADHD positive without an ADHD diagnosis vs. ADHD diagnosed

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>OR adjusted</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boy</td>
<td>ref.</td>
<td></td>
<td>ref.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Girl</td>
<td>1.82</td>
<td>1.48; 2.24</td>
<td>1.83</td>
<td>1.45; 2.29</td>
<td>&gt; 0.001</td>
</tr>
<tr>
<td>Socio-economic status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>ref.</td>
<td></td>
<td>ref.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle</td>
<td>1.27</td>
<td>1.01; 1.59</td>
<td>1.25</td>
<td>0.99; 1.58</td>
<td>0.056</td>
</tr>
<tr>
<td>Low</td>
<td>1.54</td>
<td>1.15; 2.06</td>
<td>1.49</td>
<td>1.10; 2.02</td>
<td>0.010</td>
</tr>
<tr>
<td>Parents living together</td>
<td>0.95</td>
<td>0.77; 1.18</td>
<td>0.97</td>
<td>0.77; 1.23</td>
<td>0.123</td>
</tr>
<tr>
<td>Maternal depression</td>
<td>0.93</td>
<td>0.71; 1.22</td>
<td>0.82</td>
<td>0.62; 1.09</td>
<td>0.184</td>
</tr>
<tr>
<td>Place of residence</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capital Region</td>
<td>ref.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central Region</td>
<td>1.07</td>
<td>0.81; 1.41</td>
<td>1.03</td>
<td>0.77; 1.38</td>
<td>0.839</td>
</tr>
<tr>
<td>Northern Region</td>
<td>1.17</td>
<td>0.81; 1.67</td>
<td>1.15</td>
<td>0.79; 1.67</td>
<td>0.475</td>
</tr>
<tr>
<td>Zealand Region</td>
<td>1.45</td>
<td>1.05; 2.01</td>
<td>1.47</td>
<td>1.05; 2.05</td>
<td>0.027</td>
</tr>
<tr>
<td>Southern Region</td>
<td>2.08</td>
<td>1.56; 2.76</td>
<td>2.04</td>
<td>1.51; 2.73</td>
<td>&gt; 0.001</td>
</tr>
</tbody>
</table>

OR Odds Ratio, CI confidence Interval

1 OR adjusted for each independent variable in the table.

Table 5. Mean scores on the SDQ subscales for the SDQ ADHD positive and absent ADHD diagnosis vs. ADHD diagnosed children

<table>
<thead>
<tr>
<th></th>
<th>SDQ ADHD positive absence of ADHD diagnosis Mean (95% CI)</th>
<th>ADHD diagnosed Mean (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperactivity/inattention</td>
<td>8.51 (8.42; 8.59)</td>
<td>6.27 (6.12; 6.41)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Conduct problems</td>
<td>3.45 (3.31; 3.60)</td>
<td>2.81 (2.71; 2.91)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Emotional problems</td>
<td>3.72 (3.54; 3.90)</td>
<td>2.77 (2.65; 2.89)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Impact</td>
<td>3.19 (3.04; 3.34)</td>
<td>2 (1.87; 2.13)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Peer problems</td>
<td>3.06 (2.89; 3.24)</td>
<td>2.42 (2.30; 2.54)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Prosocial (positive)*</td>
<td>6.52 (6.35; 6.69)</td>
<td>7.21 (7.10; 7.33)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*The prosocial score is positive, reflecting better prosocial behaviour
Study IV

Madsen KB, Mikkelsen SH, Rask CU, Niclasson J, Olsen J, Simonsen M, Obel C. Depression-related distortions in maternal reports of child hyperactivity/inattention problems. Submitted
Depression-related distortions in maternal reports of child hyperactivity/inattention problems

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Word count: 3 448
Abstract

Associations between maternal depression and child behavior problems may be biased due to depression-related distortions in the maternal reports of child behavior. We examined the association between maternal depression and child hyperactivity/inattention and associated problems reported by the mother, teacher and child in a large population-based sample of 11-year-old children. Our study was based on the Danish National Birth Cohort (DNBC). Maternal depression was reported in pregnancy (time 1) and again at child age 7 years (time 2). At the 11-year follow-up mothers, teachers and children completed the Strengths and Difficulties Questionnaire (SDQ) measuring child behavioral problems with the SDQ subscales; hyperactivity/inattention, conduct and emotional problems. Associations were analyzed using multiple linear regression models stratified by gender. Logistic regression models were conducted examining maternal depression and the risk of SDQ ADHD predicted by the different informants. We adjusted the analyses for maternal history of hyperactivity, SES, family status and older siblings. Maternal depression was associated with child hyperactivity/inattention and conduct problems in both boys and girls when reported by the mother and the by child (only depression at time 2) but not when reported by the teacher. In addition we found that risk estimates of maternal depression as predictor of SDQ ADHD differed significantly by informants, yielding the highest risk when reported by the mother. Findings suggest the need to consider the influence of different informants on the report of child behavior problems in research and in the clinical setting.
**Introduction**

Attention Deficit Hyperactivity Disorder (ADHD) is a behavioral disorder characterized by inattentiveness, hyperactivity and impulsiveness. ADHD is one of the most common psychiatric disorders in childhood with a current estimated prevalence of 3–5% among children and adolescents [1-3]. There is robust evidence from a wide range of study designs that the development of ADHD has a strong genetic component with heritability estimates suggested to be about 80% [4]. ADHD shows a high level of comorbidity with a wide variety of psychiatric disorders such as depression, which has increased focus on the association between parental depression and offspring ADHD [5-7]. Studies have suggested that maternal depression may increase the risk of both externalizing and internalizing problems among children with ADHD [8-14].

Our knowledge about the association between maternal depression and offspring mental health is mainly based on maternal reports of child problems [15, 16]. However, a positive relation has been found between maternal depression and discrepancies between mother’s ratings and the ratings of other informants, such as the teacher’s or the child’s own rating [17]. This observation has led to the depression-distortion hypothesis, theorizing that parents with depressive symptoms hold more negative schemas for their child’s behavior [18, 19]. The maternal distortion may lead to a more negative response towards the child, who may in turn respond with a more externalizing behavior. Hence, maternal depression may predict higher ratings of problematic behavior, caused both by actual increases in the child’s problematic behavior and by negative distortion or bias in maternal ratings [20].

Clinical studies [20-23] and population-based studies [16, 24-28] have investigated the contribution of maternal depressive symptomatology on cross-informant discrepancies in reports of ADHD symptoms and general behavior problems. These studies found that maternal depressive symptoms predicted negative biases in the reports of child behavior, which lead to an over-report of child
behavior problems [16, 20-28].

Both the clinical and population studies have been conducted using the Child Behaviour Checklist (CBCL), assumed as the “gold standard” in assessing childhood problems [29]. Recently, attention for an early and a more accessible identification of childhood psychopathology has increased, which has created room for other questionnaires to be used as screening instruments, such as the Strengths and Difficulties Questionnaire (SDQ) [30, 31]. The SDQ is a brief multi-informant screening tool for psychiatric disorders and has been widely used in both clinical practice and research [29]. Algorithms have been developed to predict child hyperactivity/inattention disorders (SDQ ADHD) [32].

Potential depression-related distortions in the perceptions of the child’s behavior is important from a clinical as well as conceptual point of view. Not taking knowledge about depression-related distortions into account may cause bias in epidemiological studies as well as in the clinical assessments of children [33]. In the present study we examined the association between self-reported maternal depression and maternal, teacher and child self-reports of hyperactivity/inattention, conduct and emotional problems measured with the SDQ in a population-based sample of 11-year-old children. We hypothesized that maternal depression would be associated with discrepancies in the reports by parent, teacher and child with depressive mothers reporting higher levels of offspring behavioral and emotional problems.

Material and methods

Study population

We used data from the Danish National Birth cohort (DNBC), which is a nationwide cohort of pregnant women and their offspring. From 1996 to 2003 almost 90 000 pregnant women were recruited through their general practitioner (GP) at the first prenatal visit, which usually occurred
between gestational weeks 6 and 12 [34]. All Danish GPs were asked to take part in the recruitment of the pregnant women; however, only about 60% of eligible women received an invitation and around 60% of the invited women participated. Overall, the participation rate at enrolment was about 30% of all eligible women in Denmark in the study period [35]. Once enrolled, the women were offered 4 computer-assisted telephone interviews; twice during pregnancy (at approximately 15 and 30 weeks of gestation) and twice after delivery (at approximately 6 and 18 months of the child). Further follow-ups were completed at child age 7 and 11 years, including the Strengths and Difficulties Questionnaire (SDQ) [www.sdqinfo.com]. At the 7-year follow-up the SDQ was completed by the primary caregiver (mainly mothers 99%) and at 11-year follow-up the SDQ was completed by the mother, the child’s teacher and the child. We restricted the study population to women who participated in the first pregnancy interview, the 7- and 11-year follow-up, and women who had singleton pregnancies and excluded siblings to the index child. This left us with a final sample size of 12 961 (15% of the overall population) mother-child pairs with complete data on SDQ from all three informants.

Exposure: maternal self-reported depression

Maternal depression was self-reported and collected at two different time-points: in the first pregnancy interview referring to the time before pregnancy and at 7-year follow-up referring to the time from childbirth to child age 7 years. Maternal depression was present when the mother reported positively on the following questions: 1) to have had a psychiatric illness, and 2) to have been in contact with a physician or a psychologist because of this and 3) that the psychiatric illness was depression. Depression was categorized as reported either during pregnancy, in the 7-year follow-up or at both time-points.
**Outcome: multi-informant reports of child behavior problems at age 11 years**

The SDQ is a standardized screening tool for children and adolescents aged 5-16 years that assesses five domains; hyperactivity/inattention, emotional symptoms, conduct problems, peer relation problems, and pro-social behavior and an impact supplement [30]. The questionnaire consists of 25 questions addressing the five domains. Responses are made on a three-point Likert scale; “not true”, “somewhat true” and “certainly true”. All scales yield a sum-score of 0-10, with higher scores indicating worse behavior (except for pro-social behavior). There are five questions concerning the impairment (impact) of the child inquiring if the difficulties (related to the five subscales) upset or distress the child in four domains: home life, friendships, classroom learning, and leisure activities. Teachers are not asked to assess the difficulties regarding home life and leisure activities [31]. The psychometric properties of the Danish version of the SDQ has been evaluated and results support the usefulness of the instrument as a screening tool in the general population [36, 37].

Computerized algorithms have been developed to predict child hyperactivity/inattention disorders (SDQ ADHD) reported by each informant and in combination [32, 38]. The SDQ ADHD prediction consists of algorithms combining the hyperactivity/inattention and the impact scale and generates “unlikely”, “possible” or “probable” ratings. We used the hyperactivity/inattention, conduct, and emotional problem scales to measure the association between maternal depression and child behavior reported by the mother, teacher and child. In addition, we used the SDQ ADHD predictions to assess the association between maternal depression and clinically relevant ADHD symptoms (possible/probable prediction of ADHD) when reported by the different informants.

**Potentially confounding variables**

Potential confounders were chosen a priori based on previous studies on associations between maternal depressions and child behavior problems [17, 33, 39]. We controlled for the following
potential confounders: mother’s self-reported hyperactivity problems in childhood, mother’s socio-economic status (SES), family status and if the child had older siblings.

Maternal hyperactivity problems in childhood were assessed with the following question in the 7-year follow-up: *Does the following statement fit your own childhood? Was restless, “hyperactive”, had problems keeping quiet long.* The question was answered; “not true”, “partly true” and “very true”, with the latter two chosen as an indicator of the mother’s hyperactivity problems.

The information on the mother’s SES was reported at the time of birth of the child. The variable was constructed based on information on the current or most recent job or education within 6 months. The category ‘high’ included women in management or in jobs requiring higher education. Office workers, service workers, skilled manual workers, and women in the military constituted the ‘middle’ category, while unskilled workers and the unemployed were classified into the ‘low’ category. Women who could not be classified in this way were categorized according to their husband’s socio-occupational status [40]. We obtained information on family status in the 7-year follow-up questionnaire, in which parents were asked if they had been living together since the birth of their child. We obtained information on whether the index child had older siblings from the first pregnancy interview.

Statistical analysis

First, we present a flowchart of the attrition in the current study. Second, parent and child characteristics among children with and without multi-informant SDQ are presented and compared using the Chi-square test. Third, the SDQ subscale scores are presented with means and SD for parents, teachers and self-report and stratified by gender. Teacher and child ratings were compared to the maternal ratings, respectively, using a paired T-test.

Next, each informant’s rating were converted into a z score, by placing each informant’s rating on a distribution relative to the rest of the same informants’ ratings in the sample (standardized score).
Resultantly, these z-scores have a distribution with a mean of 0 and a standard deviation of 1. The advantage of the standardized scores over raw scores is that all informants’ scores are placed on the same metric, which eases the interpretation of the scores [41].

We examined whether maternal depression would predict hyperactivity/inattention, conduct and emotional problems reported by different informants in multiple linear regression models. To test for interaction the associations were stratified by gender. If we only observe an association between maternal depression and hyperactivity/inattention problems when reported by the mother, the depression-distortion hypothesis cannot be rejected.

Finally, we examined the association between maternal depression and the SDQ ADHD prediction reported by each informant and in combination using logistic regression models to assess the influence of maternal depression on clinically relevant child behavior problems (possible/probable ADHD). Odds ratios (OR) and corresponding 95% confidence intervals (95% CI) are presented.

We adjusted the analyses for maternal history of hyperactivity, SES, family status and older siblings.

The statistical analyses were performed using Stata/IC 11.2 for Windows (Stata Corp, College Station, TX).

The Danish Data Protection Agency and the DNBC Steering Committee approved the study.

Results

In Figure 1, attrition to the study is shown. Initially, 84 171 pregnant women participated in the first interview. Due to loss to follow-up and exclusion of multiple births and younger siblings, the 7-year follow-up consisted of 51 527 mother-child pairs.

The sample participating in the first interview and the 7- and 11-year follow-up consisted of 35 479 children with SDQ reports either by the mother (n=32 700), the teacher (n=13 800) or the child
(n=31,841), resulting in a subsample from the 11-year follow-up of 12,961 children (37%) with complete SDQ by all three informants. Of the participants with multi-informant reports, 2.3% of the mothers reported depression before pregnancy, 6.6% reported depression in the period from childbirth to child age 7 years and 0.9% reported depression at both time-points (Table 1). This did not differ from the participants without multi-informant reports. Among participants with multi-informant reports, slightly more mothers reported a history of hyperactivity (10.5% vs. 9.4%), girls were more represented (51.3% vs. 49.9%) and more children were living with both parents (86.7% vs. 84.9%) than participants without multi-informant reports. Children with missing teacher SDQ report (participants without multi-informant reports) were reported by the mother to have significantly more problems on all SDQ subscales than participants with multi-informant reports (Table 1).

Boys presented with higher scores on the hyperactivity/inattention and conduct scales while girls presented with more emotional problems when reported by all informants (Table 2). Teachers reported statistically significantly higher scores on the hyperactivity/inattention and conduct scales in both boys and girls than did mothers, while mothers reported significantly more emotional problems in both boys and girls than did teachers (Table 2). Girls reported more emotional problems than mothers, while no difference was found for boys between mothers and self-reports. In contrast, both boys and girls reported more hyperactivity/inattention and conduct problems than the mothers (Table 2).

As presented in Table 3 and 4, maternal depression, when reported during pregnancy or at child age 7 years, was associated with an increase in maternal reported hyperactivity/inattention problems in both boys and girls, while no association was found for the teacher report. Similar results were
found in relation to conduct problems when reported by the mother (adjusted results). For girls, teachers reported significantly fewer conduct problems when maternal depression was reported at both time-points. Both boys and girls reported significantly higher hyperactivity/inattention and conduct problems but only when maternal depression was reported at child age 7 years. For emotional problems agreement was present between the informants with higher emotional problems for both boys and girls when maternal depression was reported at child age 7 years (Tables 3 and 4).

The associations between maternal depression and SDQ predicted ADHD reported by each informant and in combination are presented in Table 5. We found different risk estimates (ORs) depending on informant. Maternal depression, only when reported at child age 7 years, statistically significantly increased the risk of SDQ predicted ADHD reported by each informant. When combining the reports from all informants almost twice the risk of SDQ predicted ADHD was observed among children with depressive mothers (ORadj 1.78 (1.29; 2.46)). The association between maternal depression and SDQ predicted ADHD was stronger when the mother reported compared to the teacher (ORadj 2.04 (1.54; 2.69) vs. ORadj 1.47 (1.09; 1.98)).

**Discussion**

Consistent with previous findings from clinical and population-based studies, we found discrepancies in the reporting of child behavioral problems when reported by different informants. Maternal depression was associated with child hyperactivity/inattention and conduct problems when reported by the mother and child (only when depression was reported at child age 7 years) but not when reported by the teacher. Thus, we cannot reject the depression-distortion hypothesis in relations to child externalizing behavior. However, De los Reyes et al. point out that given the lack of a “gold standard” by which to measure psychopathology in children, informant discrepancies
cannot be used to draw inferences to the validity of a particular informant’s ratings of child psychopathology. Lack of a standard by which to gauge the child’s true level of dysfunction precludes establishing which informant is providing correct or incorrect information of the child’s behavior [17]. Hence, an alternative explanation for our findings is the possibility that children of depressed mothers in fact show higher levels of behavior problems at home than at school. Cross-situational differences in the behavior of the child could be a plausible explanation, given that children may behave differently at home because of potential negative parenting resulting from the mother’s depressive symptoms [24, 28].

We used the SDQ ADHD prediction to assess the influence of maternal depression on clinically relevant ADHD behavior. We found that risk estimates of maternal depression as predictor of SDQ ADHD differed by informant, with the highest risk when reported by the mother. These results suggest that depression-related distortions might potentially result in an overestimation of the association between maternal psychopathology and offspring mental health problems. In epidemiological studies the methodological problem is that the reliance on different informants (and with different characteristics) leads to identifying different children in a given population as meeting criteria for disorder [42]. In the assessment of child ADHD multi-informant methods are preferred. However, the results suggest that when combined categories are generated, thus identifying ADHD problems if present according to either one of the informants, bias by maternal reports cannot be ruled out [16].

Prior research has found greater levels of correspondence for informant’s ratings of child externalizing problems than internalizing problems, which has been interpreted as suggesting that informant agreement is better for problems that are more observable (externalizing) than problems that are less observable (internalizing) to informants [17]. We found that maternal depression was associated with increased emotional problems reported by all informants suggesting a higher
agreement of internalizing problems. However, for boys the association was stronger when reported by the mother compared to teacher or self-report.

Our results point to different mechanisms in relation to the time-point of the mother’s depressive episodes. When reported by the mother, maternal depression was associated with increased ADHD behavior in both boys and girls when maternal depression was present either before pregnancy or during the first seven years of the child’s life. However, when self-reported by boys and girls the associations were only significant when maternal depression had been present during the child’s life. The presence of depression during the child life could be influenced by the child’s behavior problems. Parents of children with ADHD tend to suffer from high levels of psychiatric distress, which may antedate and interact with the child’s ADHD symptoms [43]. Meanwhile depression before pregnancy would only be related to the mother. We would speculate that the further apart the maternal depressive incident would be from the reporting at child age 11 years, the lesser influence it would have. However, our findings suggest that the mother may be biased in the report of the child even though depression occurred more than 11 years earlier than the reporting of child behavior. Only few mothers reported depression at both time-points and although this reporting would suggest a far more severe psychiatric condition it seemed only to have had an influence on the reports of child emotional problems.

Strengths and limitations

To the authors knowledge no studies have investigated the maternal depression-related distortions in the reports of child behavioral problems using the SDQ and in a large population-based sample. As the SDQ is frequently used both in the clinical practice and in research the results of this study is of great importance.

All informants were reporting about the same time period and with the same instrument. This would avoid spurious reporting effects that can occur from slightly different instruments to different
informants and when measured in different time periods.

The current study has some limitations mainly due to the validity of maternal reports of psychopathology. The questions assessing maternal depression and history of hyperactivity were not standardized and the data used for the study was not collected to specifically address our hypotheses. In addition, we did not have information on depression status at the time-point of the SDQ reports, hence, we do not know how current depressive symptoms would affect the associations.

In our analyses, we adjusted for maternal history of hyperactivity. The adjustment did not alter the estimates significantly, but this could be due to the validity of the assessment. However, a study by Faraone et al. did not find statistically significant support for parental ADHD-related distortions in a clinical sample of ADHD diagnosed. Faraone argues that the disturbance of mood and emotion that characterizes depression may be associated with reporting biases of offspring problems, whereas other psychiatric disorders without a primary mood component, although associated with cognitive deficits are not [39].

In the current study the number of loss to follow-up was high (about 85%). Loss to follow-up associated with both exposure and outcome could have caused selection bias resulting in an underestimation of children with behavior problems and in turn an underestimation of the association reported by the teacher. Teacher SDQ reports in the 11-year follow-up was missing for more than half of participants and among those, more mothers had a history of hyperactivity, fewer mothers had a high SES, fewer children were living with both parents and they had higher scores on all SDQ subscales reported by the mother. However, missing teacher response was not associated with maternal depression. In addition, the raw mean scores of the SDQ scales by informant and stratified by gender yielded similar results as has previously been reported in a study of Danish children [37].
Implications for research and clinical practice

In epidemiological studies of prevalence of child mental health problems or of associations between maternal mental health and offspring behavior problems, one must be aware that the choice of informant may impact the estimate of the analyses. Informant discrepancies may also play a significant role in the clinical practice by clouding the assessment, classification and treatment of child ADHD. Consequently, when there are hints to the existence of psychopathology in a parent, clinicians should focus on involving the ratings of other informants, e.g., the other parent, or the teacher. Furthermore, it would be reasonable to include an evaluation of the mother's emotional state in the clinical assessment of children [23].

In conclusion the recent findings suggest the need to consider influences on maternal perceptions of child behavior in research and in the clinical setting as this could potentially bias the reports on child ADHD and behavior problems. These findings emphasize the importance of considering each informants ratings when obtaining observations from multiple sources both in epidemiological studies as well as in clinical practice.

References

25. van der Toorn, S.L., et al., *Maternal depressive symptoms, and not anxiety symptoms, are associated with positive mother-child reporting discrepancies of internalizing problems in
42. Caye, A., et al., Attention-Deficit/Hyperactivity Disorder Trajectories From Childhood to Young Adulthood: Evidence From a Birth Cohort Supporting a Late-onset Syndrome. JAMA Psychiatry, 2016.
Figure 1. Flowchart of the attrition in the study

Population

The Danish National Birth Cohort

Interview 1: Pregnancies, N=92 696
Pregnant woman, N=84 171
Exposure: maternal depression before pregnancy

Attrition

Excluded
Siblings and multiple births
n= 8 720

Loss to follow-up n=33 449

7-year follow-up: Children N=51 527
Exposure: maternal depression from child age 0-7 years, maternal hyperactivity in childhood

Loss to follow-up n=16 049

11-year follow-up, N=35 479

Missing SDQ:
Parent, n = 2 779
Teacher, n = 2 679
Self, n = 3 639

Outcome: complete SDQ reported by all informants; parent, child and teacher reported SDQ; N=12 961
Table 1. Parent and child characteristics among participants without and with multi-informant reports in the 11-year population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Participants without multi-informant SDQ</th>
<th>Participants with multi-informant SDQ</th>
<th>Pearson chi-square</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>N=22 518</td>
<td>N=12 961</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal depression before pregnancy</td>
<td>Yes 506 (2.3)</td>
<td>296 (2.3)</td>
<td></td>
<td>0.819</td>
</tr>
<tr>
<td></td>
<td>No 21 988 (97.6)</td>
<td>12 647 (97.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>missing 24 (0.1)</td>
<td>18 (0.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal depression at child age 0-7</td>
<td>Yes 1 496 (6.6)</td>
<td>853 (6.6)</td>
<td></td>
<td>0.828</td>
</tr>
<tr>
<td></td>
<td>No 21 012 (93.4)</td>
<td>12 097 (93.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>missing 10 (&lt;0.1)</td>
<td>11 (0.1)</td>
<td></td>
<td></td>
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<td>Maternal depression at both time-points</td>
<td>Yes 209 (0.9)</td>
<td>124 (0.9)</td>
<td></td>
<td>0.784</td>
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<tr>
<td></td>
<td>No 22 275 (98.9)</td>
<td>12 809 (98.8)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>missing 34 (0.2)</td>
<td>28 (0.2)</td>
<td></td>
<td></td>
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<tr>
<td>Maternal history of hyperactivity</td>
<td>Yes 2 374 (10.5)</td>
<td>1 214 (9.4)</td>
<td></td>
<td>&lt;0.001</td>
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<tr>
<td></td>
<td>No 19 833 (88)</td>
<td>11 594 (89.4)</td>
<td></td>
<td></td>
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<td></td>
<td>missing 311 (1.5)</td>
<td>153 (1.2)</td>
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<td>Child gender</td>
<td>Boys 11 275 (50.1)</td>
<td>6 318 (48.7)</td>
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<td>Girls 11 239 (49.9)</td>
<td>6 643 (51.3)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>missing 4 (&lt;0.1)</td>
<td>0</td>
<td></td>
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<td>Socio-economic status of the mother</td>
<td>High 12 267 (54.5)</td>
<td>8 126 (62.7)</td>
<td></td>
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<td></td>
<td>Medium 8 200 (36.5)</td>
<td>3 909 (30.2)</td>
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<td></td>
<td>Low 1 726 (7.6)</td>
<td>710 (5.5)</td>
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<tr>
<td></td>
<td>missing 325 (1.4)</td>
<td>216 (1.6)</td>
<td></td>
<td></td>
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<tr>
<td>Family status, living with both parents</td>
<td>Yes 19 126 (84.9)</td>
<td>11 243 (86.7)</td>
<td></td>
<td>&lt;0.001</td>
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<td></td>
<td>No 3 350 (14.9)</td>
<td>1 702 (13.1)</td>
<td></td>
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<td></td>
<td>missing 42 (0.2)</td>
<td>16 (0.2)</td>
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<td>6 764 (52.2)</td>
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<td>6 197 (47.8)</td>
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<tr>
<td></td>
<td>missing 0</td>
<td>0</td>
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<td>Maternal SDQ report</td>
<td>Mean (SD)*</td>
<td>Mean (SD)</td>
<td>T-test P value</td>
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<td>Hyperactivity/inattention</td>
<td>2.31 (2.20)</td>
<td>1.98 (2.04)</td>
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<td>Conduct problems</td>
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<td>0.78 (1.09)</td>
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<td>Emotional problems</td>
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<td>1.62 (1.79)</td>
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<tr>
<td>Impact</td>
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<td>0.24 (0.91)</td>
<td>&gt;0.001</td>
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*Among participants without multi-informant SDQ 2 779 children with missing maternal SDQ report
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<th>Boys N=6 318</th>
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<th>Teacher</th>
<th>Child</th>
<th>Paired T-test</th>
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<table>
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<td>SDQ scale</td>
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<td>M</td>
<td>SD</td>
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<td>1.63</td>
<td>1.84</td>
<td>3.91</td>
<td>0.89</td>
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<td>0.18</td>
<td>0.65</td>
</tr>
</tbody>
</table>

M Mean, SD Standard deviation, PT parent-teacher comparison, PC parent-child comparison
Table 3. Associations between maternal depression and child problems measured with standardized SDQ subscale scores for **boys** N=6 318

<table>
<thead>
<tr>
<th></th>
<th>Mother</th>
<th></th>
<th>Teachers</th>
<th></th>
<th>Child</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>β_{adj}</td>
<td>95% CI</td>
<td>β</td>
<td>β_{adj}</td>
<td>95% CI</td>
</tr>
<tr>
<td><strong>Hyperactivity/inattention</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal depression before pregnancy</td>
<td>.38***</td>
<td>.32***</td>
<td>.14; .49</td>
<td>.08</td>
<td>-.09</td>
<td>-.29; .10</td>
</tr>
<tr>
<td>Maternal depression child age 0-7 years</td>
<td>.27***</td>
<td>.19***</td>
<td>.09; .30</td>
<td>.02</td>
<td>.01</td>
<td>-.11; .12</td>
</tr>
<tr>
<td>Maternal depression at both time-points</td>
<td>.25</td>
<td>.10</td>
<td>-.16; .36</td>
<td>-.18</td>
<td>-.22</td>
<td>-.51; .08</td>
</tr>
<tr>
<td><strong>Conduct problems</strong></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Maternal depression before pregnancy</td>
<td>.26*</td>
<td>.22*</td>
<td>.04; .39</td>
<td>.07</td>
<td>.05</td>
<td>-.14; .25</td>
</tr>
<tr>
<td>Maternal depression child age 0-7 years</td>
<td>.25***</td>
<td>.19***</td>
<td>.09; .29</td>
<td>.13*</td>
<td>.09</td>
<td>-.02; .21</td>
</tr>
<tr>
<td>Maternal depression at both time-points</td>
<td>.34*</td>
<td>.24</td>
<td>-.01; .49</td>
<td>-.03</td>
<td>-.03</td>
<td>-.32; .26</td>
</tr>
<tr>
<td><strong>Emotional problems</strong></td>
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</tr>
<tr>
<td>Maternal depression before pregnancy</td>
<td>.45***</td>
<td>.43***</td>
<td>.27; .59</td>
<td>.27*</td>
<td>.29*</td>
<td>.12; .46</td>
</tr>
<tr>
<td>Maternal depression child age 0-7 years</td>
<td>.49***</td>
<td>.45***</td>
<td>.36; .55</td>
<td>.31***</td>
<td>.27***</td>
<td>.17; .37</td>
</tr>
<tr>
<td>Maternal depression at both time-points</td>
<td>.56***</td>
<td>.52***</td>
<td>.28; .76</td>
<td>.22</td>
<td>.21</td>
<td>-.04; .46</td>
</tr>
</tbody>
</table>

A β estimate of .5 corresponds to an increase of half a standard deviation.

*P<0.05

**P<0.001

***P<0.0001

Table 4. Associations between maternal depression and child problems measured with standardized SDQ subscale scores for **girls** N=6 635

<table>
<thead>
<tr>
<th></th>
<th>Mother</th>
<th></th>
<th>Teachers</th>
<th></th>
<th>Child</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>β_{adj}</td>
<td>95% CI</td>
<td>β</td>
<td>β_{adj}</td>
<td>95% CI</td>
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<td><strong>Hyperactivity/inattention</strong></td>
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</tr>
<tr>
<td>Maternal depression before pregnancy</td>
<td>.19*</td>
<td>.15*</td>
<td>.02; .28</td>
<td>-.01</td>
<td>-.03</td>
<td>-.16; .09</td>
</tr>
<tr>
<td>Maternal depression child age 0-7 years</td>
<td>.24***</td>
<td>.15***</td>
<td>.07; .23</td>
<td>.01</td>
<td>.02</td>
<td>-.06; .09</td>
</tr>
<tr>
<td>Maternal depression at both time-points</td>
<td>.33*</td>
<td>.28*</td>
<td>.06; .49</td>
<td>-.01</td>
<td>-.02</td>
<td>-.23; .18</td>
</tr>
<tr>
<td><strong>Conduct problems</strong></td>
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</tr>
<tr>
<td>Maternal depression before pregnancy</td>
<td>.09</td>
<td>.06</td>
<td>-.08; .20</td>
<td>-.09</td>
<td>-.11</td>
<td>-.24; .02</td>
</tr>
<tr>
<td>Maternal depression child age 0-7 years</td>
<td>.24***</td>
<td>.17***</td>
<td>.08; .25</td>
<td>.05</td>
<td>.03</td>
<td>-.05; .11</td>
</tr>
<tr>
<td>Maternal depression at both time-points</td>
<td>.28*</td>
<td>.23</td>
<td>-.002; .46</td>
<td>-.17</td>
<td>-.24*</td>
<td>-.45; -.03</td>
</tr>
<tr>
<td><strong>Emotional problems</strong></td>
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<tr>
<td>Maternal depression before pregnancy</td>
<td>.37***</td>
<td>.33***</td>
<td>.18; .48</td>
<td>.13</td>
<td>.09</td>
<td>-.07; .25</td>
</tr>
<tr>
<td>Maternal depression child age 0-7 years</td>
<td>.38***</td>
<td>.32***</td>
<td>.23; .41</td>
<td>.33***</td>
<td>.26***</td>
<td>.17; .36</td>
</tr>
<tr>
<td>Maternal depression at both time-points</td>
<td>.43***</td>
<td>.39*</td>
<td>.15; .63</td>
<td>.22</td>
<td>.20</td>
<td>-.06; .46</td>
</tr>
</tbody>
</table>

A β estimate of .5 corresponds to an increase of half a standard deviation.

*P<0.05

**P<0.001

***P<0.0001
Table 5. Associations between maternal depression and maternal, teacher, child and combined SDQ ADHD predictions

<table>
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<th></th>
<th>Mother</th>
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<th></th>
<th>Teacher</th>
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<th></th>
<th>Child</th>
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<td>OR adj</td>
<td>95%CI</td>
<td>OR</td>
<td>OR adj</td>
<td>95%CI</td>
<td>OR</td>
<td>OR adj</td>
<td>95%CI</td>
<td>OR</td>
<td>OR adj</td>
</tr>
<tr>
<td>Maternal depression before</td>
<td>1.58</td>
<td>1.42</td>
<td>.84; 2.39</td>
<td>.94</td>
<td>0.79</td>
<td>.42; 1.51</td>
<td>1.45</td>
<td>1.35</td>
<td>.74; 2.45</td>
<td>1.35</td>
<td>1.21</td>
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<tr>
<td>pregnancy</td>
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<tr>
<td>Maternal depression child 0-7</td>
<td>2.50**</td>
<td>2.04**</td>
<td>1.54; 2.69</td>
<td>1.67*</td>
<td>1.47*</td>
<td>1.09; 1.98</td>
<td>2.13**</td>
<td>1.72*</td>
<td>1.24; 2.39</td>
<td>2.24**</td>
<td>1.78**</td>
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<td>years</td>
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</tr>
<tr>
<td>Maternal depression at both</td>
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<td>0.91</td>
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<td>.59</td>
<td>.53</td>
<td>.17; 1.67</td>
<td>.84</td>
<td>.68</td>
<td>.21; 2.19</td>
<td>1.47</td>
<td>1.16</td>
</tr>
<tr>
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</tbody>
</table>

*P<0.05  **P<0.0001