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Impact of asthma medication and familial factors on the association between childhood asthma and attention-deficit/hyperactivity disorder: a combined twin- and register-based study: Epidemiology of Allergic Disease.

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Impact of asthma medication and familial factors on the association between childhood asthma and ADHD

A combined twin- and register-based study

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Running head: The association between childhood asthma and ADHD

Abstract

Background

Asthma and attention-deficit/hyperactivity disorder (ADHD) are prevalent in childhood and may cause functional impairment and stress in families. Previous research supports an association between asthma and ADHD in children, but several aspects of this relationship are unclear.

Objective

Our aim was to study if the association between asthma and ADHD is restricted to either the inattentive or the hyperactive/impulsive symptoms of ADHD, to explore the impact of asthma severity and asthma medication and the contribution of shared genetic and environmental risk factors on the asthma-ADHD relationship.

Methods

Data on asthma, ADHD, zygosity, and possible confounders were collected from parental questionnaires at 9 or 12 years on 20 072 twins through the Swedish Twin Register, linked to the Swedish Medical Birth Register, the National Patient Register and the Prescribed Drug Register. The association between asthma and ADHD, the impact of asthma severity and medication, was assessed by generalized estimating equations. Cross-twin-cross-trait correlations (CTCT) were estimated to explore the relative importance of genes and environment for the association.

Results

Asthmatic children had a higher risk of also having ADHD (odds ratio [OR] 1.53, 95% confidence interval [CI]: 1.16–2.02). The association was not restricted to either of the two dimensions of ADHD. The magnitude of the association increased with asthma severity (OR 2.84, 95% CI: 1.86–4.35) for ≥ 4 asthma attacks in the last 12 months and was not affected by

asthma treatment. The CTCTs possibly indicate that the genetic component in overlap of the disorders is weak.

Conclusions and Clinical Relevance

Childhood asthma, especially severe asthma, is associated with ADHD. Asthma medication seems not to increase the risk of ADHD. Clinicians should be aware of the potential of ADHD in asthma. Optimal asthma care needs to be integrated with effective evaluation and treatment of ADHD in children with co-existing disorders.

Introduction

Asthma and attention-deficit/hyperactivity disorder (ADHD) [1] are prevalent chronic health conditions in childhood which may cause functional impairment and stress in families [2, 3]. There is evidence from some cross-sectional studies to suggest an association between asthma and ADHD [4-7], while other studies did not find a relationship [8, 9]. Several aspects of this relationship are still poorly understood [8, 10].

There are several potential explanations to the observed overlap between asthma and ADHD. Asthma may contribute to the subsequent development of ADHD, and a dose-response relationship between asthma severity and rates of behavioural problems has been suggested [11]. In a longitudinal study of 1480 Swedish twin pairs our group recently found that childhood asthma was associated with a linear increase in risk of hyperactivity–impulsivity behaviours later in adolescence [12]. Asthma severity and medication are however tightly linked, and it is possible that medication rather than asthma is the explanation for the association. Treatment with β_2 -agonists and inhaled corticosteroids (ICS) have been reported to cause behavioural side effects [13, 14]. However, we did not find any significant difference in hyperactivity–impulsivity between asthmatic children with or without asthma medication [12].

Alternatively, asthma and ADHD may be indirectly linked via shared genetic and/or environmental risk factors. Several environmental risk factors such as low parental socioeconomic status and parental smoking have been associated with both asthma and ADHD [15-18]. Although it has been proposed that there is a common environmental mechanism underlying the development of asthma and/or ADHD [19], the association seems to remain in other studies after adjustment for these potential confounders [11, 12].

Twin studies have demonstrated that both asthma and ADHD are highly heritable [20, 21]. However, the few previous family and twin studies have produced conflicting results regarding the genetic and shared environmental contribution to the overlap between asthma and ADHD. Two previous family studies did not find any genetic and/or shared environmental component underlying the association [8, 9], whereas our recent twin study reported that the overlap between asthma and hyperactivity–impulsivity was largely due to genetic influences [12]. Clearly, additional research in larger populations is needed to clarify the impact of environmental and genetic factors on the link between asthma–ADHD.

The aim of this study was to i) confirm the association of asthma and ADHD symptoms in childhood and to explore if the association was restricted to the inattentive or the hyperactive/impulsive symptoms of ADHD, ii) investigate the impact of asthma severity and asthma medication (inhaled β_2 -agonists and/or inhaled corticosteroids) on the asthma-ADHD relationship and iii) examine the contribution of shared genetic and environmental risk factors to the overlap between the two conditions. We used a large cross-sectional twin cohort based on the population-based Swedish Twin Register with data on asthma and ADHD-symptoms as well as asthma medication and specialist care diagnoses from the Swedish National Health Registers.

Methods

Study design and population

This population-based cross-sectional study used data from the Child and Adolescent Twin Study in Sweden (CATSS) [22] and three Swedish national registers held by the Swedish National Board of Health and Welfare. CATSS collects information on 9-year-old (born since July 1995) or 12-year-old (born July 1992–June 1995) twins through parental interviews [22]. The population used in this study included all children born between 1992 and 2002 whose parents were contacted for interviews between Aug 2003 and Aug 2011 (n=27 260). Twins were excluded if they were living abroad, had a parent not fluent in Swedish, or they or their parent were disabled (n=860). In total, 26 400 twins were eligible and 20 302 (75%) completed the interview. The final study population (n=20 072) was restricted to twins with complete answers to the main questions on asthma and ADHD.

Data from CATSS was linked to the Medical Birth Register (MBR), National Patient Register (NPR) and Prescribed Drug Register (PDR) using the Personal Identification Number (PIN), a unique identifier for each resident. Further details regarding data collection and linkage to these national registers are described elsewhere [17, 18, 23-25]. The MBR contains maternal and child characteristics data on more than 99% of all births in Sweden since 1973. The NPR covers all inpatient diagnoses since 1987 and about 80% of all outpatient diagnoses since 2001, recorded with *International Classification of Disease (ICD)-9* and ICD-10 codes. The PDR encompasses data on all prescribed drugs dispensed in Swedish pharmacies since July 1, 2005 [26], coded by the Anatomical Therapeutic Chemical (ATC) system. Register data was available for twins born 1992–2001 (94% of the study population). Data from NPR and PDR was collected until Dec 31, 2009.

Measures

Asthma

The main definition of asthma, “asthma reported by questionnaire”, and a secondary variable “doctor's asthma diagnosis reported by questionnaire”, were derived from the International Study of Asthma and Allergies in Childhood (ISAAC) questions in CATSS [18, 27]. Asthma cases were also identified from the NPR “asthma diagnosis based in register”, if a record in the NPR with asthma as the primary or a secondary diagnosis (ICD-9 code 493 or ICD-10 codes J45 and J46) was recorded at least once. The quality of doctor-diagnosed asthma in the NPR is considered high [24]. Finally, a fourth asthma variable “any asthma” was derived from “asthma reported by questionnaire” and “asthma diagnosis based in register”.

Asthma severity

Parents were also asked ISAAC questions about wheezing. If they reported either asthma or wheezing, they were asked follow-up questions on number of attacks in the last 12 months [27]. Answers were categorised into five levels: No; Yes, previous asthma only; Yes, current asthma but no attacks in the last 12 months; 1-3 attacks in the last 12 months, and ≥ 4 attacks in the last 12 months.

Asthma medication

Dispensed asthma medications β_2 -agonists (R03AC), inhaled corticosteroids (ICS) including those combined with long-acting β_2 -agonists (R03BA, R03AK) and leukotriene receptor antagonists (R03DC) were retrieved from the PDR up until the date of interview, for the subset of individuals with any asthma and at least 18 months between start of the PDR and the interview (i.e. individuals with interviews later than Dec 31, 2006). In our analyses, asthma

medication was categorised in three ways: (1) dispensed any asthma drugs or (2) dispensed inhaled β_2 -agonists and/or ICS at least once or (3) dispensed inhaled β_2 -agonists and/or ICS at least three times.

ADHD

The CATSS interviews included an ADHD scale as part of the Autism – Tics, ADHD, and other Comorbidities inventory (A-TAC). This screening instrument asks symptom questions based on the DSM-IV criteria including two modules: Attention and Hyperactivity. Response options for each question are coded as “0 – no”, “0.5 – yes, to some extent” and “1 – yes”. The A-TAC ADHD scale or subscales can be used to identify possibly impairing ADHD symptoms. A score of 6 or more is used as a “screening” ADHD diagnosis, and a score of 12.5 or more selects children with ADHD at a level of clinical concern (“research” ADHD diagnosis) [28].

In this study, the ADHD outcome variable was defined as parental report of either a screening or research-level ADHD diagnosis. The two modules Attention and Hyperactivity (with cut-off score > 6 on each scale) in A-TAC were also analysed separately. Finally, we defined “register-based ADHD diagnosis” as either an ADHD diagnosis in NPR (Hyperkinetic syndrome, ICD-9 code 314; or Hyperkinetic disorders, ICD-10 code: F900 registered, and/or dispensed ADHD-drugs in PDR: centralstimulants (N06BA01, N06BA04) or atomoxetine (N06BA09) registered at least once.

Covariates

Atopic eczema was denoted if parents reported “atopic eczema” or “flexural eczema” according to the ISAAC question in CATSS [29] . Information on a child's sex and zygosity

[30] as well as data on the mother's birth country and level of education (<9 years, 10–12 years or graduate education) and parental cohabitation at time of interview (yes/no) was collected in the CATSS interview. Data on birth weight and gestational age (GA) and maternal smoking habits at the first antenatal care visit (0, 1–9 or >10 cigarettes per day) and age at delivery were retrieved from MBR.

Statistical analysis

The associations between asthma and ADHD were analysed using the different ADHD diagnoses (screening, research, or register-based) as dichotomous outcome variables, and the different asthma measures as independent variables, one by one. We used generalized estimating equations with the logit link and exchangeable covariance structure to address the correlation caused by the clustering of observations within twin pairs [31]. Odds ratios and 95% confidence intervals (CI) were first adjusted for the child's sex and age. Secondly, models were adjusted for the child's sex, age, birth weight, GA; as well as the maternal characteristics age at delivery, smoking, birth country, education, and parental cohabitation. Thirdly, models were adjusted for all the previous covariates and additionally for atopic eczema. Furthermore we tested sex differences in the associations between asthma and ADHD by including an interaction term, and if statistically significant we estimated separate ORs for males and females. The classical twin design was used to explore the relative impact of genetic, shared environmental and non-shared environmental factors for asthma, ADHD and the overlap between the disorders. Briefly, tetrachoric twin correlations for asthma and ADHD were estimated separately for monozygotic (MZ) and dizygotic (DZ) twin pairs. The corresponding cross-twin cross-trait correlations (i.e. correlation between asthma status in one

twin and ADHD status in the co-twin) were estimated to assess the relative importance of genetic and environmental influences for the overlap between asthma and ADHD.

All statistical analyses were carried out using the SAS software package version 9.2 and the significance level was 0.05.

Permission for the study was obtained from the Regional Ethical Review board in Stockholm, Sweden.

Results

The proportion of study subjects with parent reported asthma and screening ADHD diagnosis by child and maternal characteristics is presented in Supplementary Table S1. The overall cumulative incidence of asthma was 14.0%, and 9.9% of the study population had a screening diagnosis of ADHD. Two percent had both disorders at 9 or 12 years of age. The cumulative incidence of research ADHD diagnosis in the study population was 1.9% (375/20,072) and 2.0% (383/18,931) had a register-based diagnosis of ADHD. About 76% of the children with a register-based ADHD diagnosis also had a parent-reported screening ADHD diagnosis in the A-TAC interviews.

Table 1 presents the associations between asthma and the ADHD outcomes. After adjusting for sex, children with asthma were more likely to have ADHD than children with no asthma. Children with parent-reported asthma in questionnaires had an increased odds of a screening diagnosis of ADHD (fully adjusted OR 1.32, 95% CI: 1.14–1.52), a research diagnosis of ADHD (OR 1.86, 95% CI: 1.39–2.49) and a register-based ADHD diagnosis (OR 1.55, 95% CI: 1.16–2.07). The table displays similar findings for the association between doctors' diagnosis of asthma reported by questionnaires and in registers, or with any asthma, and the various ADHD outcomes. There were no sex differences in the association between asthma and ADHD, except that a research diagnosis of ADHD was more strongly associated with a doctor's diagnosis of asthma in females (p for interaction=0.044; OR 2.88, 95% CI: 1.69–4.89 in females; OR 1.48, 95% CI: 1.02–2.13 in males).

Asthma was associated equally with Attention and Hyperactivity. Using the Attention and Hyperactivity subscales of ADHD separately as outcome variables, we obtained similar adjusted ORs for the association with asthma: parental report of at least six inattentive symptoms: OR 1.56, 95% CI: 1.24–1.97 and parental report of at least six hyperactivity–

impulsivity symptoms: OR 1.59, 95% CI: 1.21–2.10. The association between asthma and ADHD did not change with adjustment for eczema (data not shown).

Table 2 displays the relation between the parent-reported frequency of asthma attacks in the last 12 months and the odds of ADHD. After adjusting for all potential confounders, the OR for the association with the screening ADHD diagnosis consistently increased with an increasing number of asthma attacks compared to no asthma (1-3 attacks: OR 1.40, 95% CI: 1.08–1.83 and ≥ 4 attacks: OR 1.55, 95% CI: 1.17–2.04. The association was also statistically significant for the “yes, previous asthma only” category of asthma attacks (OR 1.29, CI 95%: 1.04–1.60). Similar results were obtained for the association between asthma attacks in the last 12 months and research diagnosis of ADHD, but were only significant for ≥ 4 attacks (OR 2.84, 95% CI: 1.86–4.35) and “yes, previous asthma only” (OR 1.87, 95% CI: 1.23–2.84). Furthermore, there was a similar significant association between a register-based ADHD diagnosis in all categories of asthma attacks in the last 12 months except the 1-3 attacks category (data not shown).

Table 3 illustrates the association between different classes of dispensed asthma medications and the risk of ADHD. Both asthma groups, that is with and without dispensed asthma drugs, had increased odds of a screening or research diagnosis of ADHD, but there was no significant difference between the groups (screening diagnosis of ADHD: OR 1.36, 95% CI: 1.03–1.80 for asthma, but no dispensed drugs; OR 1.56, 95% CI: 1.21–2.01 for asthma with any dispensed asthma medication in the fully adjusted model). A higher number of dispensed drugs did not increase the odds of a screening diagnosis of ADHD: OR 1.46, 95% CI: 1.16–1.84 for no dispensed drugs; OR 1.55, 95% CI: 1.08–2.22 for dispensed both inhaled β_2 -agonists and ICS ≥ 3 times in the fully adjusted model). For a research diagnosis of ADHD,

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the OR for having dispensed both inhaled β_2 -agonists and ICS ≥ 3 times (OR 2.69, 95% CI: 1.57–4.62) was slightly higher than for children with asthma but without dispensed drugs (OR 2.06, 95% CI: 1.39–3.07).

Table 4 shows the results of the twin analyses. These include intra-class and cross-trait cross-twin correlations (CTCT; the correlation between one twin's status on asthma and the co-twin's status on a screening or research ADHD diagnosis), correlations for parent-reported asthma and the two ADHD diagnoses, by zygosity. MZ intra-class correlations were consistently higher than the corresponding DZ correlations [parent-reported asthma: MZ (OR 0.87, 95% CI: 0.85–0.90) and DZ same sex (OR 0.43, 95% CI: 0.36–0.49); research ADHD diagnosis: MZ (OR 0.85, 95% CI: 0.77–0.93) and DZ same sex (OR 0.37, 95% CI: 0.20–0.54)]. These results support genetic influences on asthma and on ADHD in both sexes. However, the CTCT correlations for MZ twins and DZ twins were similar in strength, or even higher among DZ twins [asthma and research ADHD diagnosis: MZ 0.05 (-0.08, 0.17) vs DZ same sex 0.13 (0.03, 0.23)], possibly suggesting that any genetic component in the overlap in the liability of the phenotypes is weak.

Discussion

In this cohort analysis of 20,072 Swedish twins aged 9 or 12 we found that children with asthma had an almost twofold increased risk of ADHD compared with those without asthma. The association was not restricted to the inattentive or the hyperactive/impulsive symptoms of ADHD. The magnitude of the association increased with asthma severity defined as frequency of asthma attacks, but was not affected by asthma treatment. The results were robust after adjusting for potential confounders including atopic eczema [32] and independent of whether asthma or ADHD was defined as parent-reported symptoms on a questionnaire or as a register-based diagnosis. To our knowledge, the effect of asthma severity and asthma drug treatment on associated ADHD symptoms in childhood has not been studied previously. The study design is novel, and combines parent reported symptoms with national registers in a large population of twins. Furthermore, this is the largest population-based twin- and register-based study on childhood asthma and ADHD to date, and supports the hypothesis that asthma is associated with ADHD. However, due to the cross-sectional study design, we could not determine the causal direction in the association between asthma and ADHD.

Previous large epidemiological studies have shown a cross-sectional association between asthma and ADHD [4, 6, 33, 34] in contrast to studies with small sample sizes ($N \sim 1,000$) [8, 9]. Recent analyses from nationwide population-based studies with diagnosis based on parental report [6], register-based diagnoses [34] or prescription data [33] reported similar ORs for the association between asthma and ADHD as we found in our study. In a previous study we distinguished between the two DSM-IV ADHD symptom dimensions and reported that childhood asthma predicts hyperactivity–impulsivity, but not inattention, in adolescence [12]. In the present study, we found that the ORs for the association between asthma and ADHD were similar regardless of defining ADHD symptoms as hyperactivity–impulsivity or

inattention, or the combination of those. This divergent result may depend on the difference in study designs or age. In the present cross-sectional study information on asthma and ADHD were collected at the same age (9 or 12 years). In contrast, the previous study was longitudinal between 7 to 14 years of age. Although recent studies have shown a relationship between atopic eczema and ADHD [32], our results did not change when adjusting for eczema which is in line with our previous study [12].

The prevalence of research ADHD diagnosis was rather low and in line with the prevalence of register-diagnosed ADHD, indicating that this group consisted of children with severe ADHD in need of health care. Another explanation is that parents of children with high A-TAC scores might tend to underreport or not participate in the study.

Current asthma severity was linearly associated with ADHD which confirms results from previous studies [10-12]. ADHD causes psychological distress and may exacerbate the severity of asthma [11, 35]. On the other hand, childhood asthma, especially severe disease, may be associated with family distress and behavioural problems and interpreted as ADHD or worsen functional impairment caused by ADHD [2, 16, 35]. The stress of treating severe asthma may also have psychological impact on children and family relationships. In addition, we found an increased prevalence of ADHD in children who only had reported a history of previous asthma. The explanation may be that asthma at a young age influences the risk of developing ADHD symptoms by school-age. This result is in line with our longitudinal study of asthma and ADHD, indicating that the correct causal pathway is that asthma precedes ADHD [12]. Although the present study is cross-sectional, there may be other explanations for the overlap. Gene expression resulting in immune system dysfunction may be a common pathophysiological mechanism underlying both disorders [36].

We found no evidence to support the notion that the association between asthma and ADHD was modified by asthma medication. Even children who had dispensed both inhaled β_2 -agonists and ICS > 3 times had similar odds of screening ADHD diagnosis as those without dispensed medication. This may be due to severe asthma in spite of intensive medication or severe cases being undertreated. Possibly the ADHD symptoms are being ignored, or misinterpreted as asthma or as side-effects caused by asthma medication. Another possibility is that the restlessness caused by β_2 -agonist may be a transient effect [37]. Our findings of no significant effects by medication on the association based on information from the PDR replicate the result from our previous longitudinal study of Swedish twins where use of inhaled β_2 -agonists and/or ICS was assessed from parental questionnaires [12].

The association between asthma and ADHD was stable when controlled for child and maternal characteristics, including sex, birth weight, maternal level of education and smoking habits. Previous research has not adjusted for all these covariates [11, 34, 38]. Results from the twin analyses confirm previous research suggesting a strong genetic component for asthma and ADHD in both sexes [11, 20, 21]. However, the estimated cross-twin cross-trait correlations were similar in MZ and DZ twins, or even higher in DZ twins. This contradicts the notion of a genetic component in the co-occurrence of asthma and ADHD. Consequently, we could not fit a model for estimating the size of such a genetic component.

There are several strengths of our study. Firstly, we studied a large population. Secondly, we obtained robust results independent of whether validated questionnaire or register-based variables on asthma and ADHD were used [24, 28], and we investigated the two subscale measures of ADHD – Attention or Hyperactivity – separately. Thirdly, we adjusted for several socioeconomic confounders which have been limited in previous studies [10, 34].

Fourthly, we were able to evaluate the severity of both asthma and ADHD symptoms in contrast to a recent study which was register-based only [34].

This study should be interpreted in the context of its limitations. Firstly, the study is cross-sectional, which constrains possibilities to study the direction of effect between asthma and ADHD. Secondly, we have no external validation of parent-reported hyperactivity or inattention, such as teacher reports. Teachers tend to report more ADHD symptoms both in children with or without asthma than parents do [2, 39]. However, there were no substantial differences between the results in the parent-reported ADHD groups of screening- or research-based diagnoses of ADHD and the group with the register-based clinical diagnosis of ADHD, which usually includes assessment of impairment in school [1]. Thirdly, asthma severity was based on number of asthma attacks in the last 12 months. We did not have additional ways to assess severity such as children's lung function or other clinical data. Fourthly, we have no access to detailed clinical information on treatment with asthma drugs, doses or duration, or treatment compliance. Finally, we did not control for comorbid psychiatric disorders, [38] or sleeping problems which have been reported to increase the risk of ADHD symptoms [40]. Generalizability of our findings in twins to the general population may be a concern, although previous studies indicate that twins do not differ from singletons concerning their risk of asthma [41] or ADHD [42]. Moreover, our estimated ORs for the association between asthma and ADHD are of similar magnitude as those found in studies in non-twin populations [6, 33, 34], suggesting a similar etiology in twins and singletons.

In conclusion, this large population-based cross-sectional study indicates that asthma and asthma severity but not asthma medication is associated with ADHD symptoms in childhood. These findings highlight the need for optimal clinical care of children with asthma to be

integrated with effective management strategies for ADHD symptoms [34]. Clinicians need to be aware of the potential for ADHD especially in children with severe asthma and optimize drug treatment also for children with both conditions. Our results indicate that it would be valuable to further elucidate the relationship between parental perception of child's behaviour and illness to establish services for early identification and intervention for behavioural difficulties in children with asthma – or asthma intervention for children with ADHD – to minimize the impact of physical illness and psychological disturbance [2, 10].

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Conflict of Interest: The authors have no potential conflicts of interest to disclose.

Authors' contributions

Dr Holmberg conceptualized and designed the study, had full access to all of the data in the study, conducted the initial analysis and interpretation, drafted the manuscript and revised it critically. Dr Holmberg had final responsibility for the decision to submit for publication.

MSc Lundholm assisted in acquisition of data, took active part in the analysis and interpretation, drafting and critical revision of the manuscript for important intellectual content.

Dr Larsson participated in the conceptualization and design of the study, contributed to the analysis and interpretation of data and revision of the manuscript.

Professor Anckarsäter assisted in acquisition of data and critically reviewed the manuscript.

Professor Almqvist obtained funding for the study and participated in study design, analysis and interpretation, drafting and critical revision of the manuscript. Together with Dr Holmberg, Professor Almqvist had final responsibility for the decision to submit for publication. All authors approved the final manuscript as submitted.

Supplementary Material

Table S1. Study population characteristics, parent-reported asthma in questionnaire and screening ADHD diagnosis in a cohort of 20,072 Swedish twins born 1992 – 2002 with completed questionnaires at 9 or 12 years of age.

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