ADHD and atopic diseases

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Chapter 5

ASSOCIATION BETWEEN MEDICATION PRESCRIPTION FOR ATOPIC DISEASES AND ATTENTION-DEFICIT/ HYPERACTIVITY DISORDER

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ABSTRACT

Background Data on the association between atopic diseases and attention-deficit/hyperactivity disorder (ADHD) have been inconclusive.

Objective We assessed whether children with drug treated ADHD are more likely to receive treatment for asthma, allergic rhinitis, or eczema prior to the start of the ADHD medication compared to controls. Secondly, we assessed the effect of parents receiving medication for ADHD and atopic diseases on receiving ADHD medication in their offspring.

Methods We conducted a retrospective nested case-control study among children (6-12 years of age) using the Groningen University prescription database (IADB.nl). Cases were defined as children with at least two prescriptions of methylphenidate within 12 months. For each case, four controls were matched on age, gender, and regional area code. Parental prescription data were linked to cases and controls to assess the influence of parents receiving medication for ADHD and atopic diseases on receiving ADHD medication in their offspring.

Results We identified 4257 cases and 17,028 matched controls. Drug treatment for asthma, allergic rhinitis, and eczema was more common in cases than controls (adjusted odds ratios [aOR] 1.4, 95%CI: 1.3-1.6; 1.4, 95%CI: 1.1-1.8; and 1.3, 95%CI: 1.1-1.5, respectively). Medication for allergic rhinitis and asthma among parents was associated with ADHD treatment in their children (aOR=1.3, 95%CI: 1.1-1.5; 1.2, 95%CI: 1.1-1.3, respectively).

Conclusion This study provides further evidence to support the hypothesis that atopic diseases are associated with ADHD. The parental-offspring association suggests a possible genetic and/or environmental component.

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a common behavioural disorder with onset in late childhood.[1] On the basis of several studies, the estimated worldwide prevalence rate of ADHD varies between 4% and 12%, with a 3- to 4-fold higher rate among boys than girls.[2] Besides behavioural treatment, pharmacotherapy has an important part in the treatment strategy among children and adolescents with ADHD. ADHD is characterized by inattention, impulsivity and hyperactivity, and is a risk factor for the development of antisocial behaviour, substance abuse, social disabilities, and a variety of problems related to academic performance.[3]

The increased prevalence of ADHD during the past decades is also paralleled by a worldwide increase in atopic diseases.[4-8] This and other arguments may point to a link between atopic diseases and ADHD. Both ADHD and atopic disorders are complex disorders in which not only environmental factors but also genetics play a major role.[9-11] Currently, the etiological pathways of the possible association between atopic diseases and ADHD are still not well understood.[4,7,12] It has been hypothesized that ADHD might be a distinct form of an allergic disease based on the possible role of hypersensitivity to foods and inhalants in the etiology of ADHD. This hypothesis might have significant implications for prevention, diagnosis, and treatment.[12] Epidemiologic data supporting this hypothesis are scarce and inconclusive.[13-19] A systematic review by Schmitt et al. concluded that among the atopic diseases only eczema was independently associated with ADHD. After the publication of this landmark review, both Chen et al.[20] and Tsai et al.[21] who conducted large cohort studies using administrative databases observed an independent association between asthma and ADHD and among rhinitis, eczema and ADHD. We recently used the widely researched United Kingdom General Practitioner Research Database and found a clear association between drug treated ADHD and presence of clinically diagnosed asthma and use of medications for different atopic diseases in boys.[22] Although most studies reported a positive association between asthma, rhinitis or eczema and ADHD, outcomes are still conflicting possibly caused by methodological flaws. We extend these findings by conducting research using the representative University Groningen prescription database IADB.nl covering more than 1 million persons in the Northern part of the Netherlands and performing a case-control study to assess the associations between drug treatments for atopic disorders including asthma, allergic rhinitis, and eczema and childhood ADHD.[23] We further explored the association between parents having received medication for atopic diseases and prescriptions of ADHD medication in their offspring to provide more evidence on the potential etiologic pathway of the association.

METHODS

Design, Setting and Participants

This nested case-control study was conducted using data from the IADB.nl containing pharmacy-dispensing data from community pharmacies in the Northern part of the Netherlands. Founded in 1994, the database covers a population of approximately 600,000 individuals annually, and 1.2 million persons in total. Dutch patients usually register at a single community pharmacy in their neighbourhood and therefore this pharmacy can provide an almost complete listing of the patient's dispensed drugs. [23,24] A validation study found that both the distribution of age and the prevalence of the drugs used are similar between the IADB.nl and the general Dutch population.[24] The IADB.nl contains information about the name of the drug dispensed, the Anatomical Therapeutic Chemical (ATC) classification, and date of prescription. Patient anonymity is guaranteed by the use of a unique anonymous identifier, hence the ethical approval for observational studies with data from the IADB has been waived; other data available on the patient are date of birth and sex. The database does not cover over-the-counter drugs and in-hospital prescriptions. Data between 1994 and 2013 were used for our study.

Definition of Cases and Controls

Cases were defined as children born from January 1 1985 through December 31 2007 who had at least 2 prescriptions of methylphenidate (ATC code, N06BA04) within 12 months in the period between 6 and 12 years of age. We used the date of the first prescription of methylphenidate as the index date.

Before this index date the cases also had to be in the IADB.nl database for at least 3 years. For the nested case-control study, each case was matched to 4 controls on sex, date of birth (±12 months), and urbanization of the living area (1-5 based on the number of addresses on each square kilometer as supplied by the National Bureau of Statistics; 1:>2,500 addresses per km^2, 2:1,500-2,500 addresses per km^2, 3:1,000-1,500 addresses per km^2, 4:500-1,000 addresses per km^2, 5:< 500 addresses per km^2). Controls were selected from the source population of children born from January 1, 1985 through December 31, 2007 who had no prescription for methylphenidate, atomoxetine (ATC code, N06BA09), or dexamphetamine (ATC code, N06BA02) during their lifetime medication history. The controls also had to be in the IADB.nl database for 3 years before the index date of their matching case. Both cases and controls were excluded from this study when they had received drug treatment (≥2 prescriptions within 12 months) for diabetes mellitus type 1 (ATC code, A10A), epilepsy (ATC code, N03A), or depression (ATC code, N06A), in the years before the index date, because of the possible association between these diseases and ADHD.[25-27]

Definition of Atopic Diseases

For each case and control, we recorded the presence of drug prescriptions for asthma, allergic rhinitis, and eczema in the medical histories in the 3 years before the index date (first prescription of methylphenidate). We used the Dutch College of General Practitioners guidelines and the guidelines of the Dutch Paediatric Foundation to define the drugs advised to be prescribed for asthma, allergic rhinitis, and eczema in children. Drug therapy for asthma was defined as having at least 3 prescriptions of an inhaled corticosteroid (ATC code, R03BA) or a short-acting β-mimetic (ATC code, R03AC02/03) within 12 months. Allergic rhinitis treatment was defined as having at least 3 prescriptions of a corticosteroid for nasal use (ATC code, R01AD) within 12 months. Eczema treatment was defined as having at least three prescriptions of ointments containing steroids (ATC code, D07) within 12 months or at least three prescriptions of calcineurin inhibitors (ATC code, D11AH01/02) also within 12 months. Asthma, allergic rhinitis, and eczema are disease entities that may often occur in parallel; for this reason, we also examined the prevalence of combinations of drug therapies among cases and controls. A validation of the medication proxies was performed using the International Classification for Primary Care (ICPC) codes in a general practitioner-based questionnaire ("Is the patient diagnosed with asthma [ICPC1 code, R96], atopic eczema [ICPC1 code, S87] or allergic rhinitis [ICPC1 code, R97]?") as a gold standard compared with the medication proxies used in this study. Test characteristics as sensitivity and positive predictive value (PPV) were calculated.

Parental Exposure

We assessed whether prescription medication for ADHD and atopic diseases in parents was associated with the prescription of ADHD medication in their offspring. In the IADB.nl database it is possible to match children to their parents if prescription data are available. A woman, between the ages of 15 and 50 years or a man between the ages of 18 and 50 years, with the same address code as the child in the first year after birth was identified as the mother or father, respectively. In general, approximately 65% of the mothers and 69% of the fathers can be linked to their children in the IADB.nl database, with an accuracy of 99%.[28]

Prescription of ADHD medication in parents was defined as having at least 2 prescriptions of methylphenidate (ATC code, N06BA04) within a 12-month period in the person's lifetime medication history. Prescription of parental atopic disease medication was defined similarly as in children except the lifetime medication history of parents was used. Parents of whom we only had a medication history less than 3 years available in the database were excluded to avoid wrongfully missing a history of having received ADHD or atopic medication because of the short period of available medication history. For each case and each control, parental presence of ADHD and/or an atopic disease medication was defined as having at least 1 parent with prescription medication for ADHD or for an atopic disease. For these explorative analyses, the subgroup of cases and controls was used whenever parental prescription data were available for 1 or 2 parents. In the parental analyses the matching was maintained, but the matching ratio (1:4 case:controls) could differ because of incomplete data of the parental controls.

Statistical Analysis

We first calculated prevalences of childhood exposure to drug treatment for asthma, allergic rhinitis, and eczema or combinations across both cases and controls. If parental data were available we calculated the prevalences of parental drug treatment for the atopic diseases and ADHD in both cases and controls. Conditional logistic regression was used to obtain matched odds ratios (ORs) with their corresponding 95% confidence intervals (CI). A multivariable conditional logistic regression model was developed to assess the unique association between ADHD medication and drug treatment of different atopic diseases. For the parental analysis a multivariable conditional logistic regression model was developed taking into account the effect of both ADHD and atopy medication used in parents, and childhood atopic medication on the association with the prescription of childhood ADHD medication. The statistical analyses were performed using SPSS statistical software (SPSS Inc, Chicago, Illinois).

RESULTS

We identified 4,257 children as cases between 6 and 12 years of age who were drug treated for ADHD and 17,028 matched controls. Among the 4,257 children with ADHD medication, 3,265 (76.7%) were boys and 992 were (23.3%) girls; there were 13,060 (76.7%) boys and 3,968 (23.3%) girls without ADHD drug treatment. The mean age of cases was 8.3 years; the controls had a mean age of 8.6 years.

Among cases and controls, 503 (11.8%) and 1408 (8.7%), respectively, were exposed to medication for asthma in the 3 years before index date, yielding a matched OR of 1.4 (95% CI 1.3-1.6) (Table 1). Similarly, increased odds were observed for drug treatment for allergic rhinitis (OR, 1.4; 95% CI, 1.1-1.8) and eczema (OR, 1.3; 95% CI, 1.1-1.5). The occurrence of drug treatment of any atopic disease was associated with an increased odds of 40% compared to controls (OR, 1.4; 95% CI, 1.2-1.5). The combination of treatment for asthma and allergic rhinitis was associated with an OR of 1.7 (95% CI, 1.2-2.3), combined treatment for asthma and eczema with an OR of 1.5 (95% CI, 1.0-2.1), and combined treatment for rhinitis and eczema with a statistically nonsignificant OR of 1.8 (95% CI, 0.9-3.5).

Table 1. Matched conditional logistic regression analyses on the independent effect of selected characteristics of children aged 6 to 12 years on the risk of developing drug-treated ADHD[a] (total n=21,285).

Medication	Cases n (%) (N=4257)	Controls n (%) (N=17028)	Odds ratio (95% CI)[b]	P value
Asthma	503 (11.8)	1408 (8.7)	1.4 (1.3-1.6)	<0.001***
Allergic rhinitis	94 (2.2)	269 (1.6)	1.4 (1.1-1.8)	0.005**
Eczema	170 (4.0)	541 (3.2)	1.3 (1.1-1.5)	0.008**
Asthma & Allergic rhinitis	53 (1.2)	127 (0.7)	1.7 (1.2-2.3)	0.002**
Asthma & Eczema	45 (1.1)	123 (0.7)	1.5 (1.0-2.1)	0.028*
Allergic rhinitis & Eczema	12 (0.3)	27 (0.2)	1.8 (0.9-3.5)	0.097
Allergic rhinitis, Eczema & Asthma	6 (0.1)	15 (0.1)	1.6 (0.6-4.1)	0.331
Allergic rhinitis or Eczema or Asthma	663 (15.6)	2028 (11.9)	1.4 (1.2-1.5)	<0.001***

* p<0.05, ** p<0.01, *** p<0.001

[a] Attention-Deficit/Hyperactivity Disorder

[b] 95% CI = 95% confidence interval

The multivariate conditional logistic regression (Table 2) revealed similar results for asthma medication (OR, 1.4; 95% CI, 1.2-1.5) and eczema medication (OR, 1.2; 95% CI, 1.0-1.4), but did not indicate a statistically significant OR for rhinitis medication (OR, 1.2; 95% CI, 0.9-1.5).

We further examined subgroups according to sex. The results for the boys and girls were similar as the overall results, but some associations appeared more pronounced in either boys or girls. The association between ADHD medication was the strongest in girls with asthma and allergic rhinitis medication (OR, 4.0; 95% CI, 1.7-9.2) and in boys with allergic rhinitis and eczema medication (OR, 2.2; 95% CI, 1.1-4.6).

Table 2. Multivariate matched conditional logistic regression analyses of the characteristics of children aged 6 to 12 years with drug-treated ADHD[a] compared with controls (total n=21,285).

Medication	Odds ratio (95% CI)[b]	P value
Asthma[§]	1.4 (1.2-1.5)	<0.001***
Allergic rhinitis[§]	1.2 (0.9-1.5)	0.127
Eczema[§]	1.2 (1.0-1.4)	0.043*

* p<0.05, ** p<0.01, *** p<0.001

§ Adjusted for asthma, allergic rhinitis and/or eczema

[a] Attention-Deficit/Hyperactivity Disorder

[b] 95% CI = 95% confidence interval

Of all original 4,257 children with ADHD medication, we had prescription data of at least 1 of their parents in 2,075 cases (48.7%). Of these 2,075 children, 24.0% were female, and the mean age of the total group was 8.0 years. In 7,972 of the 17,028 original control children (46.8%) there were also prescription data available. Of these 7,972 controls 29.9% were female, and the mean age of the total group was 8.5 years. The difference between cases and controls with and without parental prescription was significant in both age (P < .001) and sex (P <0.001). The mean level of urbanization in cases (2.64) also differed from the level of urbanization level in controls (2.73) (P = 0.001).

Within the group of cases, 228 children (11.0%) had 1 or more parents with ADHD medication compared with 89 (1.1%) in the control group (OR, 3.8; 95% CI, 3.3-4.3) (Table 3). Presence of treatment of parents with eczema medication did not result in an increased risk of receiving ADHD medication in the child later in life (OR, 1.1; 95% CI, 1.0-1.2). Treatment of parents with allergic rhinitis and asthma medication, however, was associated with an increased risk of 30% and 20% respectively compared with controls (allergic rhinitis: OR, 1.3; 95% CI, 1.1-1.5; asthma: OR=1.2; 95% CI 1.1-1.3).

Table 3. Conditional logistic regression analyses of the effect of parental characteristics on offspring aged 6 to 12 years with drug-treated ADHD[a] compared with controls (total n=10002).

Medication	Cases n (%) (N=2075)	Controls n (%) (N=7927)	Odds ratio (95% CI)[b]	P value
Parental ADHD	228 (11.0)	89 (1.1)	3.8 (3.3-4.3)	<0.001***
Parental asthma	336 (16.2)	1058 (13.3)	1.2 (1.1-1.3)	0.003**
Parental allergic rhinitis	140 (6.7)	398 (5.0)	1.3 (1.1-1.5)	0.006**
Parental eczema	540 (26.0)	1923 (24.3)	1.1 (1.0-1.2)	0.139
Parental Allergic rhinitis or Eczema or Asthma	827 (39.9)	2851 (36.0)	1.1 (1.0-1.2)	0.004**
Parental ADHD & an atopic disease	99 (4.8)	35 (0.4)	3.7 (3.0-4.5)	<0.001***

* p<0.05, ** p<0.01, *** p<0.001
[a] Attention-Deficit/Hyperactivity Disorder
[b] 95% CI = 95% confidence interval

The multivariate conditional logistic regression (Table 4) revealed similar results for parental ADHD medication (OR, 3.7; 95% CI, 3.2-4.3), parental atopic disease (asthma, eczema and/or allergic rhinitis medication) (OR, 1.1; 95% CI, 1.0-1.2), and atopic disease in children (asthma, eczema and/or allergic rhinitis medication) (OR, 1.2; 95% CI, 1.1-1.4) in general as an independent predictor for childhood ADHD.

Table 4. Multivariate conditional logistic regression analyses of the effect of parental characteristics on offspring aged 6 to 12 years with drug-treated ADHD[a] compared with controls (total n=10002).

Medication	Odds ratio (95% CI)[b]	P value
Parental ADHD[§]	3.7 (3.2-4.3)	<0.001***
Parental Atopic disease[§]	1.1 (1.0-1.2)	0.035*
Atopic disease child[§]	1.2 (1.1-1.4)	<0.001**

* p<0.05, ** p<0.01, *** p<0.001
§ Adjusted for ADHD parent, atopic disease parent and/or atopic disease child
[a] Attention-Deficit/Hyperactivity Disorder
[b] 95% CI = 95% confidence interval

The information from which parental exposure to ADHD and/or an atopic diseases medication was defined differed between cases and controls. In 30.2% of the cases the parental exposure was based on maternal prescription data only, whereas in the controls this was 27.2% (P = .007). In 57.2% of the cases and 62.1% of the controls was parental exposure based on both maternal

and paternal data ($p < 0.001$). Availability of only paternal data differed also between cases (12.7%) and controls (10.8%) ($P = .01$).

Test Characteristics of Medication Proxies

PPV was highest in the allergic rhinitis (n = 286) medication proxy (0.73; 95% CI, 0.68-0.79) with a sensitivity of 0.52 (95% CI, 0.47-0.58). For asthma (n = 289) and atopic eczema (n = 288) the PPV of our medication proxies was somewhat lower (asthma: 0.60; 95%CI, 0.55-0.66; atopic eczema: 0.52; 95%CI, 0.47-0.58) with higher sensitivity (asthma: 0.93; 95%CI, 0.90-0.96; atopic eczema: 0.73; 95%CI, 0.68-0.79)

DISCUSSION

Our findings suggest an increased risk of ADHD drug treatment in children with a history of drug treatment for atopic diseases. The associations were adjusted for potential differences in age, sex, and urbanization and not modified by sex or the presence of other child diseases such as diabetes mellitus type 1, epilepsy, or depression. Children whose parents were exposed to asthma and allergic rhinitis drug treatment were also at increased risk of using ADHD medication. This finding suggests a possible genetic or shared environmental component in the association between the diseases. Multivariate conditional logistic regression revealed that these associations were independent of predisposition of parental drug treatment of ADHD, parental drug treatment of atopy, and childhood atopic drug treatment.

These results support the hypothesis of Pelsser et al.[12] that ADHD might have an allergic component. Pelsser et al. [29] found that a strictly supervised restricted elimination diet improved the symptoms of ADHD in 64% of all children and relapse occurred in 63% of them after ending the specific diet. Another possible underlying mechanism behind the association could be the effect of chronic allergic inflammation as proposed by Buske-Kirschbaum et al [30]. Both the release of inflammatory cytokines and increased levels of psychological stress caused by atopy could affect the young developing brain and neurotransmitter systems which can lead to an increased risk for the development of ADHD. By passing the blood brain barrier, cytokines can have their effect on the neuroimmune system involved in the behavioural and emotional development. In addition, the codevelopment of both atopy and ADHD under the influence of shared risk factors, such as genetics or prenatal stress, could be part of the development of this association.[30]

The association between atopy and ADHD might also be explained by a link between allergy and emotional problems. Recent studies have found increased rates of depression and anxiety in children with allergy compared with nonallergic children.[31,32] This more general association is in line with our findings and emphasizes the complexity of the underlying mechanism between allergy and emotional or behavioral problems.

Perhaps those who are prescribed medications for 1 diagnosis are more likely to have additional diagnoses or are more likely to see physicians or seek treatment. Future research should take into account this possible explanation for the association between prescription of medications for atopy and ADHD. Although it cannot be ruled out that the association between prescription of medication for atopic diseases and for ADHD may partially be explained by generally increased health seeking behaviour or access to care, our findings of a potential link between atopic disease and ADHD agree with observations of a higher frequency of hyperactivity-impulsivity and inattention symptoms in children with asthma[33] and untreated allergic rhinitis[34].

The independent OR for asthma medication was higher than for rhinitis and eczema medication. This finding could be explained by the difference in sensitivity of the atopic diseases, where in the case of rhinitis and eczema a substantial part of these atopic diseases are missed in our medication proxies.

The results of our study regarding allergic rhinitis are consistent with some previous studies. Shyu et al.[18], for example, reported a slightly higher risk than we observed between the presence of allergic rhinitis and development of ADHD in their population-based prospective study using the National Health Insurance database of Taiwan. They compared the prevalence of ADHD in the general population with the prevalence of ADHD in patients with allergic rhinitis and found a significantly increased prevalence of ADHD (OR, 1.7) in patients with allergic rhinitis. Shyu et al. found a significantly increased prevalence of ADHD in persons with asthma, but not in those with eczema. Schieve et al.[17] also observed a significantly increased risk of ADHD presence in those with asthma, allergic rhinitis, and eczema, although the estimated risks were somewhat higher than ours. This finding might be attributable to recall bias, because they used interview surveys to collect data. Mogensen et al.[33] also found a positive independent association between asthma and hyperactivity-impulsivity in their prospective cohort study (OR, 1.9). However, they did not find an association between asthma and inattention which could explain the lower OR in our study because we did not separate these 2 dimensions of ADHD.

A systematic review of the association between atopic diseases and ADHD included several studies that mentioned an overall positive association between allergic diseases and ADHD, however, some studies did not find an association. These conflicting results might be attributable to differences in study design, such as adjusting for confounding factors and data collection, such as the identification of both ADHD and the atopic diseases.[19] In addition, sample size, age range of the patients, and looking into medical history instead of current diagnoses of ADHD and atopy could explain the differences. A meta-analysis is needed to give an overview of the current knowledge concerning the association between ADHD and atopic diseases. Our study is the first retrospective case-control study, to our knowledge, with identification of ADHD and atopy in a large prescription database.

Strengths of our study include the use of a large and representative database, which contains accurate and almost complete data on prescriptions. Because ADHD is more common

in boys than in girls, the age of children affects the likelihood of using medicine, and the living area can determine the exposure to environmental factors, we matched our cases on sex, age, and living area. We also corrected for possible confounding by performing the analyses among boys and girls together but also separately.[34]

Despite these strengths, potential limitations must be considered in the interpretation of the results. A limitation of our study was that we did not have data on the actual clinical diagnosis; the presence of asthma, allergic rhinitis, eczema, and ADHD were all based on prescription data. Although the identification of patients can be a valuable tool [35], misclassification may have occurred because we included only children with these diseases at the more severe disease spectrum. Treatment with methylphenidate, atomoxetine, or dexamphetamine is advised only in severe cases in which behavioural interventions such as psychological-education, parent training, and child-directed behavioural interventions have not been sufficient. This possible misclassification could have underestimated the association between the atopic diseases and ADHD because of nonmedically treated ADHD in the control group. In some rare cases methylphenidate is used as a treatment for other diseases [36], such as narcolepsy, which could have weakened the association between atopic diseases and ADHD in this study. The same is true for topical ointments used in the treatment of eczema, but not restricted to atopic eczema, which may have weakened the association between the atopic disease and ADHD. However, the association between treatment of both diseases remained present.

There was no information available on factors such as socioeconomic status, diets and parental smoking that could have led to confounding. However, there should have been a large difference between cases and controls in the prevalence of these factors to explain our results.

The use of corticosteroids has been associated with behavioural problems in several studies [13,37,38], which have suggested that corticosteroid use may induce behavioural problems in such a way that it could have led to an overestimation of the association between atopic disease and ADHD drug treatment. However, the study of Holmberg et al. [39] found an association between asthma and ADHD independent of asthma medication. It has also been mentioned that having a chronic disease and associated difficulties might lead to behavioural problems, which is seen in corticosteroid use and specialist care.[40] This finding might have led to an overestimation of the association between atopic disease and ADHD drug treatment.[41] Even if it is possible that these factors have had some confounding effect on our results, it is unlikely that they explain the association between parental atopy medication and childhood ADHD drug treatment.

Regarding the parental analysis it is not likely that the older age and higher percentage of females of children in the control group may have explained the association between parental diseases and childhood ADHD drug treatment. However, the urbanization of the cases also differed from the controls. In the cases a higher level of addresses per square kilometer was observed, which may be associated with the development of allergic diseases of the parents,

assuming a similar exposure in childhood.[42] This could explain part of the association between parents having received medication for atopic diseases and prescription of ADHD medication in their offspring.

Although the identification accuracy of true parents based on address code in the first year after birth is as high as 99%, there is still a possibility that the identified parent was not the biological parent. However, the possible overestimation of the (biological) parent is likely to be random and cannot explain the results found in the parental analysis of our study.

In addition, the higher percentage of prescription data available in both parents in the controls compared with the cases, might have led to biased results toward a higher chance of having parental exposure to medication for ADHD or medication for an atopic disease in controls compared with the cases. This would give an underestimation of our results.

Our study provides additional evidence to support the hypothesis that atopic disorders such as asthma increase the risk of developing ADHD. This evidence could indicate that there is a link between atopy and ADHD or that certain patients are more prone to health care-seeking behavior and therefore more likely to receive atopy and ADHD medication. Future studies should focus on genetic and/or environmental components of the association to clarify the possible underlying mechanism. The association between atopy and ADHD could lead to new views on pathogenesis and treatment of both diseases. A prospective longitudinal study is needed to assess the effect of atopy on the development of ADHD. In addition, investigating the dose-response relation of atopy and ADHD treatment could give more insight into the association of both diseases.

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