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### ADHD and atopic diseases

van der Schans, Jurjen

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*Document Version*  
Publisher's PDF, also known as Version of record

*Publication date:*  
2017

[Link to publication in University of Groningen/UMCG research database](#)

*Citation for published version (APA):*  
van der Schans, J. (2017). *ADHD and atopic diseases: Pharmacoepidemiological studies*. Rijksuniversiteit Groningen.

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# Chapter 9

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# ASSOCIATION BETWEEN ATTENTION-DEFICIT/ HYPERACTIVITY DISORDER AND ASTHMA AMONG ADULTS: A CASE-CONTROL STUDY

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Jurjen van der Schans, Brech Aikman, Tjalling W. de Vries, Pieter J. Hoekstra, Eelko Hak.

**Published as:** Association Between Attention-Deficit/Hyperactivity Disorder and Asthma Among Adults: A Case-Control Study. van der Schans J, Aikman B, de Vries TW, Hoekstra PJ, Hak E. *Chest*. 2017 Jun;151(6):1406-1407.

## ABSTRACT

**Background** Recently, we showed in a meta-analysis that in children there is an association between attention-deficit/hyperactivity disorder (ADHD) and atopic diseases, especially asthma. Not much is known about this association among adults. The aim of the present study was to assess the association between ADHD and asthma (severity) in an adult population. As secondary aim we investigated the association between the presence of ADHD and the presence of eczema and allergic rhinitis.

**Methods** We conducted a case-control study using a prescription database. Cases were defined as adults aged between 18 and 50 years with at least two prescriptions of ADHD medication within 12 months. Controls were defined as adults without any history of ADHD medication prescriptions and were matched (4:1) on age and sex for each case. The presence of asthma, eczema, allergic rhinitis, and asthma severity was based on the type and frequency of the prescription of drugs used to treat the specific atopic allergy. Multivariable logistic regression analyses were applied to control for urbanization and presence of allergic rhinitis and eczema.

**Results** We identified a total of 3,987 individuals being treated with ADHD medication who were matched to 15,948 controls. Among ADHD patients, 387 (9.7%) were prescribed drugs to treat asthma, versus 499 (3.1%) among controls. The adjusted odds ratio for asthma medication in patients with ADHD was 2.9 (95% Confidence Interval 2.5-3.4;  $p < 0.001$ ), 1.5 (95% CI 1.3-1.7) for rhinitis, and 1.4 (95% CI 1.2-1.7) for eczema compared to controls. No significant association was seen between asthma severity and the presence of ADHD.

**Conclusion** This study supports the hypothesis that also in adults asthma is more common among ADHD patients than the general population.

## INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a common childhood-onset disorder which affects between 3 and 7% of school-aged children.<sup>1,2</sup> Approximately 65% of individuals with ADHD continue to have symptoms as adults.<sup>3,4</sup> Over recent years, there has been a steep increased prevalence of ADHD treatments<sup>5</sup>, paralleled by an increased prevalence of atopic diseases<sup>6</sup> which fueled the interest in research into the association between both disorders.<sup>7</sup> While early studies on the relationship between ADHD and atopic diseases in children presented conflicting results concerning a possible association<sup>7</sup>, a recent meta-analysis from our group showed the existence of a clear association between ADHD and the prevalence of atopic diseases, particularly asthma, in children.<sup>8</sup> The nature of this relationship is still unknown, although findings suggest links with environmental and/or genetic risk factors contributing to inflammatory mechanisms.<sup>9</sup> Asthma medication is also mentioned as a possible explanation for the association; however, results are conflicting.<sup>10,11</sup>

In adults, much less is known about a possible association between ADHD and asthma. A better understanding of the association between ADHD and atopic diseases adults could contribute to a better understanding of both disorders. The aim of this study was to investigate associations between the presence of ADHD and the presence and severity of asthma in adults. As secondary aim we investigated the association between the presence of ADHD and the presence of eczema and allergic rhinitis.

## METHODS

### Study population

We performed a matched case-control study following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.<sup>12</sup> Information on drug prescription data was obtained from the University Groningen IADB.nl database containing pharmacy-dispensing data from 60 community pharmacies in the Netherlands, covering a population of approximately 600,000 people since 1994. The medication data were used as proxies for the diagnoses of ADHD and asthma. Dutch patients usually register at a single community pharmacy and therefore one pharmacy can provide an almost complete listing of a subject's prescribed drugs.<sup>13</sup> Pharmacy data contain, among other data, information on the name of the drug dispensed, Anatomical Therapeutic Chemical (ATC) classification, date of prescription, number of days the drug was prescribed, and dosage. The database is representative for drug use in the Netherlands as a whole.

### Definition of cases and controls

Cases were defined as adults between the age of 18 and 50 years who had at least two prescriptions of ADHD medication, i.e., of methylphenidate (ATC: N06BA04), atomoxetine (ATC:

N06BA09), or dexamphetamine (ATC: N06BA02) within a period of 12 months. The requirement of at least two prescriptions within a 12 month period was to prevent the inclusion of sporadic, non-chronic, medication use. The date of the first prescription of ADHD medication was set as the index date. Controls were defined as adults who were matched on age and sex to the case (4:1) on the index date ( $\pm 1$  year), but had no history of ADHD medication anywhere in the database. To ensure both cases and controls had a similar at risk time in the database, it was necessary for both cases and controls to have prescription data of at least three years prior to the index date.

### Definition of asthma

In both cases and controls we identified whether individuals had received treatment for asthma before the index date. Treatment for asthma was defined as at least two prescriptions of anti-asthma medication (Drugs for obstructive airway diseases, ATC: R03) within a period of 12 months. When studying asthma in adults based on prescriptions, it is possible that other airway related diseases treated with anti-asthma drugs could be a confounding factor. Especially chronic obstructive pulmonary disease (COPD) must be considered as both diseases are prescribed similar medication.<sup>14</sup> To avoid misclassification, only adults below the age of 50 were included in the study and combinations of medication specifically for COPD treatment were excluded (long-acting inhaled anticholinergics)<sup>14</sup>, therefore, making misclassification in this study unlikely.

As part of our sensitivity analyses, we also defined asthma treatment based on alternative medication proxies as defined by Mulder et al.<sup>15</sup> and described in table 3, to assess the possible association between asthma severity and ADHD.

The assessment of asthma severity categories (intermittent, persistent mild, persistent moderate - severe) was estimated using different medication proxies based on the evidence-based guidelines on adult asthma from the Dutch College of General Practitioners and the local pharmaceutical formulary, 10<sup>th</sup> edition (Appendix I).

### Covariates

We also recorded whether individuals had received treatment for rhinitis and eczema, because of the observed association of these atopic diseases with childhood ADHD.<sup>8,16</sup> Having received treatment for rhinitis and eczema that are both strongly linked to asthma, was defined as  $\geq 2$  prescriptions within a period of 12 month of specific anti-allergic agents and corticosteroid nasal preparations for topical use, and specific dermatological preparations with corticosteroids (ATC: R01AC/R01AD/R06AE/R06AX and D07, respectively).

Urbanization of the living area was measured to correct for the association between high urbanization levels and a higher prevalence of asthma.<sup>17,18</sup> Based on the address code of each individual the urbanization level was determined (1-5 based on the numbers of addresses on each km<sup>2</sup> as supplied by the National Bureau of Statistics; 1=2500 or more addresses per km<sup>2</sup>, 2=1500-2500 addresses per km<sup>2</sup>, 3=1000-1500 addresses per km<sup>2</sup>, 4=500-1000 addresses per km<sup>2</sup>, and 5=less than 500 addresses per km<sup>2</sup>).

**Statistical analysis**

We first assessed the frequency of the occurrence of asthma medication prescription in both cases and controls. In addition, the co-variables age, sex, urbanization, eczema, and rhinitis were compared between cases and controls. Pearson chi-square test was used to compare the frequencies of categorical variables and Student's t-test for the continuous variables. To estimate the associations between ADHD and asthma prescriptions, the association between ADHD and eczema/rhinitis prescriptions, and the association between ADHD and the different severity categories of asthma, odds ratios (OR) with 95% Confidence Interval (CI) were calculated using conditional logistic regression analysis. The adjusted ORs were calculated by matching the cases and controls on age and gender, and adjusting for urbanization level and two of the other atopic diseases (asthma, eczema and rhinitis). We also stratified the analysis of the association between asthma and ADHD by sex. A p-value <0.05 was considered statistically significant. All analyses were conducted using Statistical Package for Social Sciences, version 22.

## RESULTS

A total of 3,987 individuals were identified as cases that were matched to 15,948 adult controls that met all study criteria. Table 1 shows the characteristics of the study population. Among cases, methylphenidate (95.7%) was the most prescribed ADHD drug.

**Table 1:** Cohort characteristics of patients with ADHD and the matched comparator group

		<b>Cases with ADHD medication (3,987), N(%)</b>	<b>Controls without ADHD medication (15,948), N(%)</b>	<b>P value</b>
Gender (Female)		1,652 (41.4%)	6,608(41.4%)	
Age in years (mean)		32.4 (SD 8.2)	32.8 (SD 8.3)	.147 <sup>a</sup>
Urbanization level <sup>1</sup>	1	1248 (31.3%)	4610 (28.9%)	<.001 <sup>b</sup>
	2	1123 (28.2%)	3823 (24.0%)	
	3	811 (20.3%)	3260 (20.4%)	
	4	437 (11.0%)	1868 (11.7%)	
	5	323 (8.1%)	2124 (13.3%)	
	Missing	45 (1.1%)	263 (1.6%)	
Rhinitis		310 (7.8%)	651 (4.1%)	<.001 <sup>b</sup>
Eczema		222 (5.6%)	534 (3.3%)	<.001 <sup>b</sup>
Asthma		387 (9.7%)	499 (3.1%)	<.001 <sup>b</sup>

Abbreviations: SD, standard deviation.

<sup>1</sup>1=2500 or more addresses per km<sup>2</sup>, 2=1500-2500 addresses per km<sup>2</sup>, 3=1000-1500 addresses per km<sup>2</sup>, 4=500-1000 addresses per km<sup>2</sup>, and 5=less than 500 addresses per km<sup>2</sup>

<sup>a</sup> Pearson chi-square test

<sup>b</sup> Student's t-test

The multivariable analysis revealed that asthma, rhinitis, and eczema were significantly more common in cases than controls (see table 2). After matching the cases and controls on age and gender, and adjusting for urbanization level and for the other two atopic diseases the association with ADHD medication still existed and was the strongest for asthma with an adjusted odds ratio of 2.9 (95% CI 2.5-3.4), odds ratios of 1.5 (95% CI 1.3-1.7) for rhinitis, and 1.4 (95% CI 1.2-1.7) for eczema.

**Table 2:** Multivariable conditional logistic regression model of association of atopic diseases and ADHD in adults

	<b>Cases (n=3987)</b>	<b>Controls (n=15948)</b>	<b>Crude OR</b>	<b>95% CI Lower Upper</b>		<b>p value</b>	<b>Adjusted OR<sup>1</sup></b>	<b>95% CI<sup>1</sup> Lower Upper</b>		<b>p value<sup>1</sup></b>
Asthma	387 (9.7%)	499 (3.1%)	3.3	2.9	3.9	<0.001	2.9	2.5	3.4	<.001
Rhinitis	310 (7.8%)	651 (4.1%)	2.0	1.7	2.3	<0.001	1.5	1.3	1.7	<.001
Eczema	222 (5.6%)	534 (3.3%)	1.7	1.5	2.0	<0.001	1.4	1.2	1.7	<.001

Abbreviations: OR, Odds Ratio; CI, Confidence Interval

<sup>1</sup> Adjusted for urbanization level and the other two atopic diseases.

In a sub-analysis the data was stratified per sex. In both groups asthma had the highest adjusted odds ratio with 2.4 (95% CI 2.0-3.0;  $p < .001$ ) in males and 3.5 (95% CI 2.8-4.3;  $p < .001$ ) in females, although the difference was not significant ( $p = 0.147$ ). Table 3 describes the odds ratios using two alternative definitions of asthma, based on an earlier study by Mulder B et al., and the severity categories of asthma with ADHD. Using our first alternative definition (i.e., more than three prescriptions for asthma medications within 12 months), we identified 643 patients with asthma. With our second alternative definition of the presence of asthma (i.e., at least one prescription of an inhaled corticosteroid and one other anti-asthma drug) a total of 408 (2.2%) adults were considered patients with asthma. The adjusted ORs for these two alternative definitions of asthma were similar as the OR when using the original proxy of  $\geq 2$  prescriptions per year.

There was no significant difference between the different severity categories of asthma and the odds of receiving ADHD medication. In addition, no significant difference between cases and controls was detected in the asthma persistent severe category probably due to a low number of patients in this category.

**Table 3:** Multivariable conditional logistic regression model of association of ADHD in adults and asthma defined by different proxies<sup>2</sup> and severity<sup>3</sup>

		Cases (n= 3987)	Controls (n= 15948)	Crude OR	95% CI		p value	Adjusted OR <sup>1</sup>	95% CI <sup>1</sup>		P value <sup>1</sup>
					Lower	Upper			Lower	Upper	
<b>Asthma definition<sup>2</sup></b>	Asthma medication ≥2 prescriptions*	387 (9.7%)	499 (3.1%)	3.3	2.9	3.9	<0.001	2.9	2.5	3.4	<.001
	Asthma medication ≥3 prescriptions*	272 (6.8%)	371 (2.3%)	3.1	2.6	3.6	<0.001	2.6	2.2	3.1	<.001
	Asthma ≥1 ICS + ≥1 other asthma medication*	171 (4.3%)	237 (1.5%)	3.0	2.5	3.7	<0.001	2.5	2.1	3.1	<.001
<b>Asthma severity<sup>3</sup></b>	Asthma Intermittent	45 (1,1%)	64(0,4%)	2.9	1.9	4.2	<.001	2.4	1.5	3.5	<.001
	Asthma Persistent Mild	129 (3,2%)	193 (1,2%)	2.7	2.2	3.4	<.001	2.3	1.8	2.9	<.001
	Asthma Persistent Moderate - Severe	137 (3,4)	168 (1,1%)	3.4	2.7	4.2	<.001	2.8	2.2	3.5	<.001

Abbreviations: OR, Odds Ratio; CI, Confidence Interval; ICS, Inhaled corticosteroid

\* Within a period of 12 months.

<sup>1</sup> Adjusted for urbanization level and, eczema and rhinitis.

<sup>2</sup> Asthma medication: drugs for obstructive airway diseases, ATC: R03.

<sup>3</sup> Asthma severity was estimated using different medication proxies (Appendix I).

## DISCUSSION

The results of our study suggest that there is an even stronger association between ADHD and asthma in adults than what has been reported among children.<sup>8</sup> Having ADHD significantly increases the odds of a history of asthma. Even after adjustment for eczema and rhinitis the odds ratio remained significant. The association found in our study is in accordance with another study, in which the presence of prescriptions for anti-asthma drugs were significantly higher in adult patients with ADHD compared to controls.<sup>9</sup> Similar studies also found a higher co-occurrence of both diseases than would be expected by chance.<sup>19</sup> However, in our study we determined an association of a history of asthma before the first prescription of ADHD medication.

In children, the magnitude of the association between asthma and ADHD was found to increase with asthma severity.<sup>10</sup> In this study, the association between asthma and ADHD did not increase as the severity of asthma increased making a severity-response relation between asthma and ADHD less likely.

Besides an increased co-occurrence of asthma in children with ADHD compared to children without ADHD, longitudinal studies in children have indicated that there is also a higher chance of ADHD developing in the presence of asthma.<sup>16,20,21</sup> This is similar to the results of our study in adults which indicate an association between ADHD and a history of asthma independent of medication definition of asthma or asthma severity and corrected for age, sex, urbanization, and the presence of eczema and rhinitis. In addition to environmental and/or genetic risk factors as underlying mechanism for the association between ADHD and asthma in both children and adults, the association could also be explained by a higher health care seeking behavior of asthma patients making it more likely to receive a diagnosis and treatment for ADHD and vice versa. This is a form of selection bias which is unavoidable in a prescription database. However, all persons in the database have received at least one drug to become registered.

### **Strengths and limitations**

A major strength of our study is the use of a large and representative prescription database and statistical power of the study. In addition, we corrected for the possible confounding of age, sex, urbanization and other atopic diseases, important strong risk factors that could have influenced the association between ADHD and asthma. However, our results must be considered in the context of possible limitations. Confounding must be considered when interpreting results from an observational study, as it can lead to an over- or underestimation of the association between ADHD and asthma. Since the cases and controls were matched not only on age but also on sex, the possible confounding influence of these factors was controlled in the analysis. Sex could be an effect modifier, however, as boys are more prone to develop asthma and ADHD compared to girls.<sup>22</sup> This sex-based difference was expected to also exist in adults. In this study, ADHD was indeed more common in males than females, but unexpectedly the asthma occurrence was similar as in females. Though non-significant, the stratified analysis showed some higher odds ratio among females than males. This is in accordance with the result from a previous study where the association between ADHD and asthma was stronger for women than men.<sup>9</sup> It is often thought that ADHD in women is probably underrecognized.<sup>23</sup> We can only speculate that a potential explanation might be found in differences in health care seeking behavior of asthmatic women in combination with under-recognition of their ADHD in childhood.

Since there was no diagnostic information provided with the prescriptions, the diagnostic status remains uncertain. This may have led to misclassification bias, in both the case and control groups. However, previous studies have indicated that asthma medication proxies in the IADB database correspond with the diagnosis of asthma.<sup>13,15</sup> As shown in our sensitivity

analysis the alternative definitions of presence of asthma yielded similar results. Therefore, we assume that our results indicate an association of ADHD with asthma rather than just asthma medication.

To what extent prescription data is a valid proxy for a diagnosis of ADHD in adults remains uncertain. In this study population, at least two prescriptions of either methylphenidate, atomoxetine, or dexamphetamine were used as a proxy for presence of ADHD, as these drugs are specific for ADHD and usually not prescribed for other diseases. Methylphenidate is also prescribed for narcolepsy, but only for a very small group, making confounding negligible. Since treatment of ADHD in adults in the Netherlands also is done through behavioral therapy, only a limited number of the actual patients with ADHD can be determined through a prescription database.<sup>24</sup> This could have led to an underestimation of the strength of the associations in our study.

As the information was purely based on prescription data, it is not possible to take environmental or genetic factors into account. Particularly in the case of asthma, environmental risk factors such as exposure to pets or air quality in urban areas could play a role in the development or expression of the disease. Especially smoking may be a relevant factor, as the prevalence of smoking is higher in adults with ADHD. Although arguably not causal, smoking could worsen symptoms in adults with pre-onset asthma leading to aggravate the need for medication.<sup>25</sup> This could lead to an overestimation of our results.

## CONCLUSIONS



This study shows that adult asthma is associated with ADHD. ADHD and asthma both have an early onset and it is therefore difficult to determine the effect of asthma on ADHD in adults or vice versa. Future studies should determine the underlying mechanism and the possible clinical implications of the association between ADHD and asthma.

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## APPENDIX I

### **Medication proxies for the definition of atopic diseases and asthma severity\*.**

**Rhinitis;** Rhinitis was defined as at least two prescriptions of anti-rhinitis medication (Specific anti-allergic agents and corticosteroid nasal preparations for topical use, ATC: R01AC/R01AD/R06AE/R06AX) within a period of 12 months.

**Eczema;** Eczema was defined as at least two prescriptions of anti-eczema medication (specific dermatological preparations with corticosteroids, ATC: D07) within a period of 12 months.

**Asthma;** Asthma was defined as at least two prescriptions of anti-asthma medication (Drugs for obstructive airway diseases, ATC: R03) within a period of 12 months.

**Asthma intermittent;** Asthma intermittent was defined as  $\geq 2$  prescriptions of a short acting beta-2-agonist (ATC: R03AC) within a period of 12 months.

**Asthma persistent mild;** Asthma persistent mild was defined as  $\geq 1$  prescriptions of a short acting beta-2-agonist (ATC: R03AC0) and  $\geq 1$  prescriptions of a glucocorticoid (ATC: R03BA) within 12 months or  $\geq 2$  prescriptions of a glucocorticoid within a period of 12 months.

**Asthma persistent Moderate-Severe;** Asthma persistent moderate was defined as  $\geq 1$  prescriptions of a short acting beta-2-agonist (ATC: R03AC0) and  $\geq 1$  prescriptions of a glucocorticoid (ATC:R03BA) and  $\geq 1$  prescriptions of a long acting beta-2-agonist (ATC:R03AC1) within 12 months or  $\geq 1$  prescriptions of a combination preparation of a glucocorticoid and a long acting beta-2-agonist and  $\geq 1$  prescriptions of a short acting beta-2-agonist (ATC: R03AC0) within 12 months or  $\geq 2$  prescriptions of a combination preparation of a glucocorticoid and a long acting beta-2-agonist.

\* Different medication proxies were based on the evidence-based guidelines on adult asthma from the Dutch College of General Practitioners and the local pharmaceutical formulary, 10th edition.

