

Comorbidity of Asthma With ADHD

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Journal of Attention Disorders
XX(X) 1–8
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DOI: 10.1177/1087054710372493
http://jad.sagepub.com



Abstract

Objective: To assess how frequently drugs used to treat asthma and ADHD are prescribed to the same patients. **Method:** The authors used data from the Norwegian Prescription Database for 2006, including the total Norwegian population ($n = 4,640,219$). **Results:** Anti-asthma drugs were prescribed to 350,894 persons (7.56 % of the population), anti-ADHD drugs to 18,481 persons (0.40 %), and both to 1,730 persons. There was a 65% increased overall risk ($OR = 1.65$) of being prescribed one of the drugs given a prescription of the other. Women had a markedly higher risk than men. When data for each age group (10 years interval) and each gender were analyzed separately, the strongest associations were found for women between 20 and 49 years of age and men between 30 and 49 years of age. **Conclusion:** These prescription patterns suggested a marked comorbidity between asthma and ADHD. (*J. of Att. Dis.* 2010; XX(X) 1–XX)

Keywords

asthma, ADHD, comorbidity

ADHD is a common disorder in childhood, with significant morbidity for those afflicted (Barkley, 2006; Barkley, Fischer, Smallish, & Fletcher, 2002; Faraone, Sergeant, Gillberg, & Biederman, 2003). During the last 10 to 15 years, there has been increasing interest in ADHD in adults (Adler & Chua, 2002; Barkley, 2006). It is now widely accepted that many ADHD patients retains symptoms as adults, with significant impairments both socially and at work (Halmøy et al., 2009; Kessler et al., 2005). ADHD is associated with many other psychiatric disorders, in particular anxiety and mood disorders, and drug abuse (Kessler et al., 2006). Investigations into the pathophysiology and genetics of ADHD have focused on dopaminergic mechanisms (Johansson et al., 2008). However, a comprehensive understanding of this disorder is still lacking. Recently, Pelsser, Buitelaar, and Savelkoul (2009) advanced the hypothesis that ADHD may be a nonallergic hypersensitivity disorder, with pathophysiological links to asthma.

Children with asthma have a higher prevalence of behavioral difficulties than children without asthma (McQuaid, Kopel, & Nassau, 2001). Among adult asthmatics, there is a higher prevalence of depression and anxiety disorders than in the general population (Goodwin, Jacobi & Thefeld, 2003, Katon et al., 2007). The few studies that have examined the potential relationship between ADHD and asthma have not presented consistent results. Both a study of 140 boys with ADHD (Biederman, Milberger, Faraone, Guite, & Warburton, 1994) and a study of 140 girls with ADHD

(Hammerness et al., 2005) failed to find a positive association between ADHD and asthma. However, in a large study from the National Survey of Children's Health in the United States, children with asthma were more likely to have comorbid ADHD compared with children without asthma (Blackman & Gurka, 2007). In the single previous study on adults, using data from a large claims database, a diagnosis of ADHD was significantly associated with a diagnosis of asthma (Secnik, Swensen, & Lage, 2005).

The Norwegian Prescription Database contains information on all prescription drugs dispensed in Norway since 2001 and offers a unique opportunity to address the issue of whether the diagnoses of ADHD and asthma are associated with each other, over a wide age range.

Our hypothesis was that there is a comorbidity of asthma and ADHD and that the prescription rates of anti-asthma and anti-ADHD drugs would reflect this.

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Table 1. Number of Patients Being Prescribed Anti-Asthma and Anti-ADHD Drugs (With ATC Codes) in the Norwegian Prescription Database.

	ATC		N	Percent
Asthma				
Salbutamol	R03A C	02	161,600	46.1
Terbutaline		03	46,582	13.3
Salmeterol		12	9,630	2.7
Formoterol		13	18,468	5.3
Salmeterol + fluticasone	R03A K	06	92,468	26.4
Formoterol + budesonide		07	68,289	19.5
Beclomethasone	R03B A	01	5,090	1.5
Budesonide		02	35,120	10.0
Fluticasone		05	49,821	14.2
Ipratropium bromide	B	01	39,147	11.2
Tiotropium bromide		04	11,795	3.4
Sodium cromoglycate	C	01	769	0.2
Salbutamol	C	02	6,242	1.8
Terbutaline		03	12,399	3.5
Bambuterol		12	215	<0.1
Theophylline	R03D A	04	7,096	2.0
Theophyllinetylendiamin		05	44	<0.1
Montelukast	C	03	29,667	8.5
Omalizumab	X	05	24	<0.1
ADHD				
Amphetamine	N06B A	01	156	0.8
Methylphenidate		04	16,273	88.1
Atomoxetine		09	3,207	17.4

Note: Percent refers to percentage of patients within each disease group having received the listed drug. ATC = anatomical therapeutic chemical.

a. The sum of the percentages exceeds 100% because many patients, particularly within the asthma group, were prescribed more than one drug.

Method

The study population consisted of the complete Norwegian population as of January 1, 2006 ($n = 4,640,219$; men, $n = 2,301,981$; and women, $n = 2,338,238$). All individuals having received prescription for drugs to treat asthma and ADHD during 2006 were registered through the Norwegian Prescription Database, which contains information from all pharmacies on all prescription drugs dispensed in Norway since 2001. For hospital pharmacies information is available only for outpatients. In the present study, we registered all individual patients who at least once during 2006 were prescribed drugs used to treat asthma, ADHD, or both (Table 1). Each individual was counted only once even if this individual received more than one prescription during the observation year. We did not include drugs that are used against ADHD and also have other common indications (such as modafinil, tricyclic antidepressants, and clonidine). We have omitted ephedrine from the list of anti-asthma drugs because this drug is mainly prescribed for children below the age of 5 years and primarily for other indications

than asthma (acute subglottic laryngitis). The drugs were grouped according to the anatomical therapeutic chemical (ATC) classification. Some drugs are listed twice, due to different formulations or combination with other drugs. Age was categorized in 10-year groups.

An overall odds ratio (OR) estimating the association between the asthma and ADHD prescriptions was calculated using logistic regression analysis, with presence of asthma prescription as a dependent variable, and ADHD prescription, age group, and gender as categorical independent variables. Overall ORs were also calculated for each gender using logistic regression and adjusting for age-groups. Furthermore, OR was calculated for each age group within each gender. A deviation from unity of these OR's was tested using a simple chi-square test. All analyses were performed using the Statistical Package for Social Sciences (SPSS) version 15.0.

Results

Anti-asthma drugs were prescribed to 350,894 persons (7.56 % of the whole population) and anti-ADHD drugs to 18,481 persons (0.40 %). Table 1 presents the number of persons prescribed each drug and the percentage within each disease category. About 11% of those who were prescribed anti-ADHD drugs had received only one prescription during 2006. The mean number of prescriptions of any anti-ADHD drug was 5.4, with a median of 4. A total of 66% of those who were prescribed anti-asthma drugs had received more than one prescription during 2006. The mean number of prescriptions of any anti-asthma drug was 4.4 with a median of 2.

Prescription profiles of men according to age (10-year intervals) are shown in Figure 1, and Figure 2 illustrates these profiles for women (in percentage of the population in each age group). For anti-ADHD drugs, 74.9% of all prescriptions are issued to men aged less than 20 years, and the corresponding figure for women in the same age group is 53.2%. Concerning anti-asthma drugs, 30.3% of prescriptions are issued to men aged less than 20 years, which was 19.9% for women in the corresponding age category.

When analyzed according to gender, the number of prescriptions of anti-asthma drugs were higher for men than for women in the 0-9 and 10-19 years age group (men: women = 1.49:1, and 1.15:1), but in all other age groups, up to 69 years, the number of prescriptions were higher for women (Table 2). For anti-ADHD drugs (Table 2), the number of prescriptions were higher for men than for women in all age groups below 60 years, but the difference was particularly strong in the age group of 0 to 9 years (men:women = 4.05) and 10 to 19 years (men:women = 3.00).

A total of 1,730 persons were prescribed both types of drugs, 1,121 men and 609 women. These 1730 persons

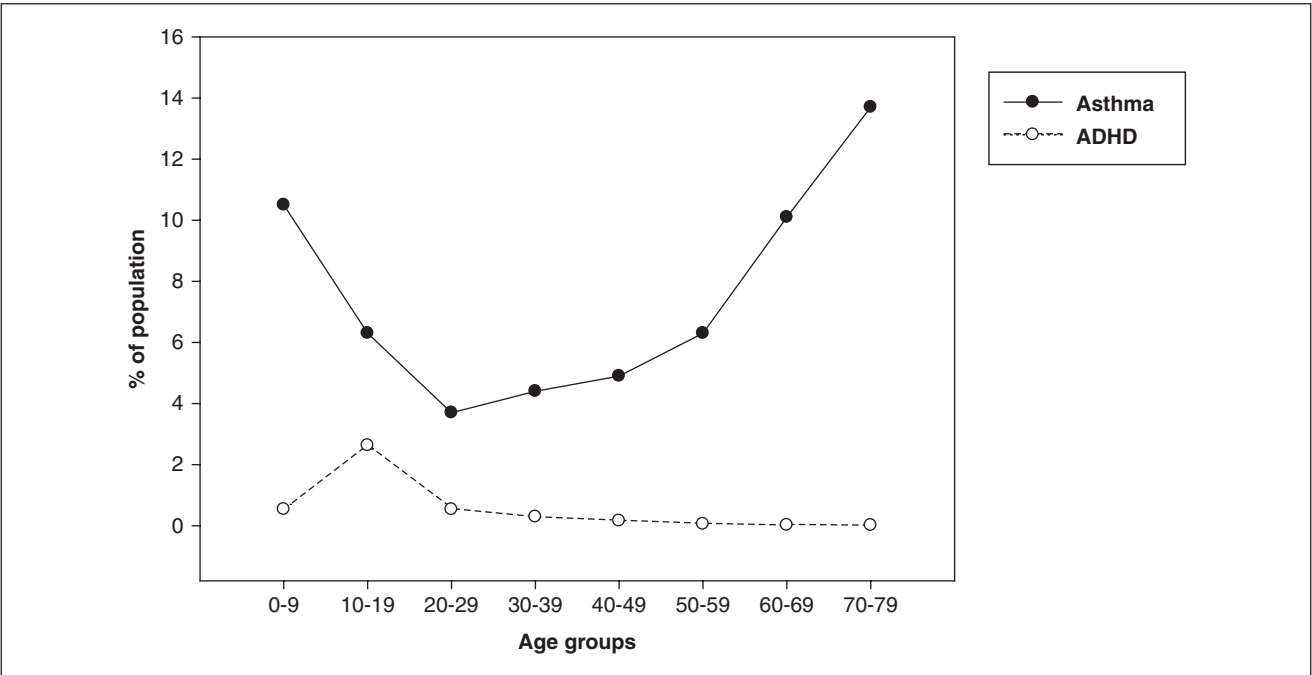


Figure 1. Prescriptions of anti-asthma and anti-ADHD drugs to men

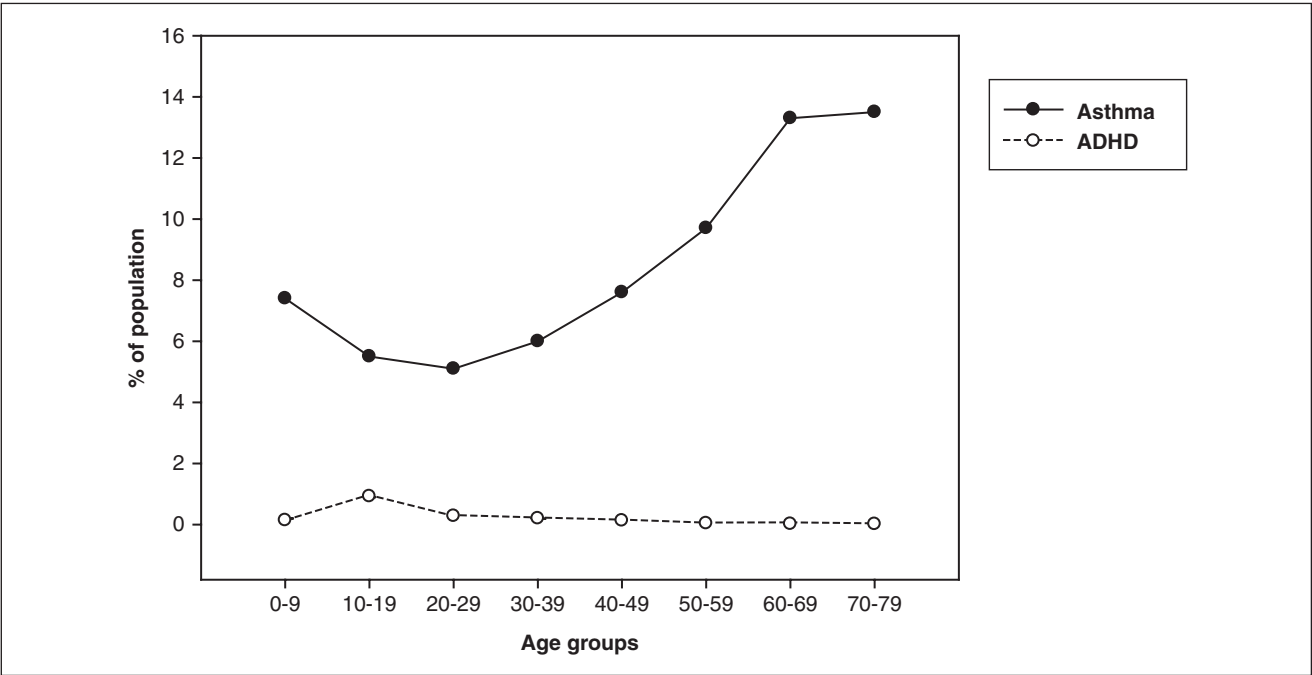


Figure 2. Prescriptions of anti-asthma and anti-ADHD drugs to women

comprise 0.49 % of those prescribed anti-asthma drugs and 9.4 % of those prescribed anti-ADHD drugs. The overall OR being prescribed one of these drugs given a prescription of the other was 1.65 (CI: 1.57-1.74), [Carries page 3, both columns], adjusting for age and gender in a logistic regression model. There was a striking difference in the overall

Table 2. Prescription of Anti-Asthma and Anti-ADHD Drugs in Relation to Gender (Men: Women)

	Asthma	N	ADHD	N
0-9	1.49	53,138	4.05	2,050
10-19	1.21	36,125	3.00	11,021
20-29	0.74	24,937	1.94	2,292
30-39	0.75	35,817	1.50	1,709
40-49	0.68	40,875	1.26	962
50-59	0.66	48,023	1.32	295
60-69	0.73	48,784	0.93	87
70-79	0.82	39,396	0.83	42

N = number of patients, both genders, prescribed anti-asthma or anti-ADHD drugs.

age-adjusted risk between men (OR = 1.38, CI: 1.30-1.47) and women (OR = 2.06, CI: 1.89-2.24). Furthermore, there was also marked variation of the codistribution of the two types of drugs for each age group within each gender (Table 3). For the age groups from 10 to 19 and up to 50 to 59 years, and for both genders, increased OR's were found, with values in the range of 1.25 to 3.05. For all age groups the OR's for women were higher than for men, particularly so in 20- to 29-year age group (2.92 vs. 1.54). For men the OR's were highest in the 30- to 39-year and 40- to 49-year age group (2.72-2.75), whereas for women the OR's were highest in the four age groups, between 20 and 59 years (3.05-2.28). For the age range of 10 to 59 years, 5.1 % of the men (81,406 of 1,589,855) and 6.8% of the women (104,371 of 1,535,482) were prescribed anti-asthma drugs, and 0.7% of the men (11,509) and 0.3% of the women (4,770) were prescribed anti-ADHD drugs. Omitting ipratropium, tiotropium, and the theophyllins from the analyses produced only small alterations in the ORs (data not shown).

For anti-ADHD drugs most prescriptions were for methylphenidate, so a table showing coprescription of methylphenidate with anti-asthma drugs is very similar to the data in Table 3. Only 3,207 persons were prescribed atomoxetine, and of these 269 (8.4 %) were also prescribed anti-asthma drugs. For men, ORs for the coprescription of atomoxetine with anti-asthma drugs are significantly increased in the age groups of 30 to 39 and 40 to 49 years (1.97, $p = .004$ and 2.00, $p = .033$), whereas for women the ORs are significantly increased for all age groups, between 10 and 59 years (1.61-3.72, p value between .017 and .000).

Discussion

Analyzing the complete Norwegian population in 2006, we have shown that there is a significantly increased prescription of anti-asthma drugs to individuals who were prescribed anti-ADHD drugs and vice versa. This was found for all age

Table 3. Concurrent Prescription of Anti-Asthma and Anti-ADHD Drugs

Age group	Men		Women	
	OR (CI)	N	OR (CI)	N
0-9	1.10 (0.94-1.28)	187	1.34 (0.96-1.86)	39
10-19	1.25 (1.15-1.36)***	637	1.62 (1.42-1.86)***	236
20-29	1.54 (1.24-1.92)***	85	2.92 (2.38-3.58)***	106
30-39	2.72 (2.24-3.31)***	113	3.02 (2.46-3.71)***	110
40-49	2.75 (2.13-3.55)***	67	3.05 (2.40-3.87)***	85
50-59	1.80 (1.10-2.94)*	18	2.28 (1.47-3.53)***	25
60-69	1.49 (0.63-3.54)	6	0.81 (0.32-2.06)	5

OR = Odds ratios with 95 % confidence intervals (CI).

N = number of patients with concurrent prescription of anti-asthma and anti-ADHD drugs.

* $p < .05$. *** $p < .001$.

groups, and for both genders, but the association was particularly strong for women aged between 20 and 49 years and men aged between 30 and 49 years. Furthermore, the OR was stronger for women than for men (2.06 vs. 1.38). These findings, therefore, suggest that there is a comorbidity between ADHD and asthma.

The prescription profile of anti-asthma drugs according to age and gender corresponds to the prevalence of asthma found in epidemiological studies (Nystad, Meyer, Nafstad, Tverdal, & Engeland, 2004; Rees, 2005; Von Behren, Kreutzer, & Hernandez, 2002). It is probable that in a country such as Norway, with a strongly subsidized health service, including prescription drugs, most patients with asthma are treated with drugs; thus, present figures represent the prevalence of active asthma. In an epidemiological study from Norway, which was conducted between 1998 and 1999, the prevalence of asthma in adults was 9.3% (Brogger et al., 2003); in another study of adolescents in Norway (1995-1997), findings showed that among participants in the age group of 13 to 16 years, the prevalence of asthma was 8.5% among girls and 7.1% among boys (Tollefsen, Bjermer, Langhammer, Johnsen, & Holmen, 2006).

However, prescription of anti-asthma drugs to patients with bronchospasm for other causes than asthma may represent a confounding factor. The most common other cause is chronic obstructive pulmonary disease (COPD); however, also for bronchospasm during acute respiratory infections, broncholytic medications like salbutamol, terbutaline, and formoterol are sometimes prescribed. Particularly in the case of persons aged more than 40 and presenting with COPD, prescription of anti-asthma drugs could represent a confounding factor (Halbert et al., 2006). The increased prescription of anti-asthma drugs in the older age groups in our study probably reflects increasing numbers of COPD patients. On the other hand, the clear results we find in the age groups below 40 years indicate that there is an

association between asthma and ADHD. We also find very similar ORs, across genders and age groups, when we exclude ipratropium, tiotropium, and the theophyllins from the analyses, the drugs that are primarily used to treat COPD (Cyr et al., 2008; Seemungal, Hurst, & Wedzicha, 2009).

For ADHD the situation is different. ADHD is a disorder starting in childhood, and although symptoms decline with increasing age (Biederman, Mick, & Faraone, 2000), a substantial number of patients maintain considerable symptoms and high level of dysfunction as adults (Barkley et al., 2002; Rasmussen & Gillberg, 2000). In a large epidemiological study of children in Bergen, Norway, the prevalence *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., Text Revision; *DSM-IV-TR*) of ADHD was 1.7 % (Heiervang et al., 2007). The present prescription data thus indicate that a significant proportion of Norwegian children with ADHD are treated with drugs. There are some data from epidemiological studies of adults (Kessler et al., 2006; Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007), but no studies in Norway, so it is difficult to tell how representative the numbers in the present study are in relation to the total number of adult patients with ADHD in Norway. There are strong regulations on the prescription of anti-ADHD drugs in Norway. The diagnosis has to be verified by a specialist in psychiatry, child psychiatry, or neurology, and the doctor writing such prescriptions has to obtain a special permit from the health authorities. This should reduce the likelihood of using these drugs to treat conditions other than ADHD.

Though some of the anti-asthma drugs are also prescribed for COPD, the situation is different for the anti-ADHD drugs. Atomoxetine has ADHD as its sole indication for use (Simpson & Plosker, 2004). Methylphenidate is sometimes prescribed for patients with narcolepsy; however, patients in this group are fewer compared to those with ADHD. This is, therefore, an unlikely confounding factor. In addition, we find a very similar codistribution of anti-asthma and anti-ADHD drugs, when we restrict anti-ADHD drugs to only atomoxetine.

We think that negative findings in previous clinical studies on the relationship between asthma and ADHD (Biederman et al., 1994; Hammerness et al., 2005) can be reconciled with the results from the present study. The comparatively low ORs we found in the younger age groups obviously require a large number of patients to give significant results, whereas in the older age groups the results are more clear-cut. In the study of Biederman et al. (1994), the mean age of the 140 boys was 11 years, whereas in the study of Hammerness et al. (2005), the mean age at the time of the study was not given; however, the patients ($n = 140$) were all children. The findings from the current study, together with the results from the study on children by Blackman

and Gurka (2007) and on adults by Secnik et al. (2005), offer strong support for the notion that there is a comorbidity between ADHD and asthma.

Obviously, it is not possible to answer on the basis of a cross-sectional study of prescription patterns the question of why a comorbidity exists. At least part of the reason is the risk behavior associated with ADHD, most notably smoking. Teenage and adult patients with ADHD have a higher prevalence of smoking compared with the general population (McClernon & Kollins, 2008). Whether active smoking is a cause of asthma is still a matter of controversy, but it is certain to aggravate symptoms among participants who were prone to asthma before they started smoking (Thomson, Chaudhuri, & Livingston, 2004). In the current study, we did not have information on individual smoking habits. However, the strong association between ADHD and asthma among the older participants in the current study is an indication that smoking played a part. It is worth noting that regardless of whether older participants using anti-asthma drugs actually had asthma or COPD, the increased comorbidity with ADHD was very significant. This suggests that providing health and behavioral advice to patients with ADHD could have positive health benefits, which in turn would help reduce the later comorbidity of obstructive lung disease. Another possible etiological factor in relation to tobacco may be passive smoking in childhood (Stoddard & Gray, 1997) or prenatal exposure, because children with ADHD presumably have been exposed to this to a larger extent than do children without ADHD (Braun, Kahn, Froehlich, Auinger, & Lanphear, 2006). Both passive smoking in childhood and prenatal exposure are associated with an increased risk for asthma, both in childhood (Cook & Strachan, 1999) and adulthood (Skorge, Eagan, Eide, Gulsvik, & Bakke, 2005).

However, it is unlikely that passive smoking accounts for more than a part of the association between asthma and ADHD. Thus, it is tempting to speculate that the apparent comorbidity must reflect its underlying pathophysiological patterns, which are common to both disorders. Both ADHD and asthma have similar comorbid patterns with regard to anxiety and mood disorders. ADHD exhibits substantial comorbidity with generalized anxiety disorder, panic disorder, depressive disorders, and bipolar disorder in adults (Kessler et al., 2006). Asthma is to a similar degree associated with the same anxiety disorders and with bipolar disorder (Goodwin et al., 2003; Hasler et al., 2005; Katon et al., 2007). It is, therefore, possible that the association between prescription of anti-asthma and anti-ADHD drugs is mediated by these other comorbid disorders. This is supported by the finding that the association is stronger in women than in men, as both mood and anxiety disorders are more prevalent in women (Fan et al., 2009).

Another conjecture is that inflammatory mechanisms may be one common factor for these disorders. Such mechanisms are of central importance in the pathophysiology of asthma (Barrios, Kheradmand, Batts, & Corry, 2006; Bousquet, Jeffery, Busse, Johnson, & Vignola, 2000), are involved in mood disorders (Bremner et al., 2008; Dickerson, Stallings, Origoni, Boronow, & Yolken, 2007), and are also postulated to be involved in ADHD (Bazar, Yun, Lee, Daniel, & Doux, 2006).

Both ADHD and asthma are associated with obesity. A number of studies indicate a higher-than-expected prevalence of obesity in ADHD patients (Cortese et al., 2008), and obesity is a risk factor for the development of asthma (Delgado, Barranco, & Quirce, 2008). In this connection, it is also interesting to note that obesity leads to a proinflammatory state (Delgado et al., 2008). However, we do not know to what extent this may be a contributing factor in the present study.

Strengths and Limitations

The strengths of this study are the large number of patients covered and the data that are inclusive of the whole population over the entire age range. It is, of course, a limitation that we have only indirect data on the diagnoses we focus on, even though they are based on a doctor's decision to prescribe a drug. However, in a large epidemiological study like this, it is not possible to obtain a diagnostic accuracy comparable to that in a smaller clinical study.

In spite of the large number of prescriptions covered, only a limited number of individuals with concurrent prescriptions were found, underscoring the importance of studying a whole population to look for such a relation between asthma and ADHD. The lack of inclusion of data from hospital pharmacies probably represents a small error, as most inpatients probably also have received prescriptions as outpatients and have thus been included in the study groups.

Though the prescription patterns for anti-asthma drugs to children and adults and anti-ADHD drugs to children reflect, to a large extent, the prevalence of these disorders, the situation is different for anti-ADHD drugs prescribed to the adult population. Probably only a minor part of adult ADHD patients are treated with such drugs, and it is reasonable to suppose that these patients are the ones who are more seriously affected. Therefore, we cannot conclude that the postulated comorbidity extends to adult ADHD patients who are not prescribed drug treatment. Furthermore, it is conceivable that when patients are prescribed multiple medications, this is related to the severity of the disorders, introducing a form of Berkson's bias (Conn, Snyder, & Atterbury, 1979). Nevertheless, we think it is unlikely that this alone could explain the threefold increased risk found for some of our study groups.

In conclusion, the present study has shown that both children and adult patients who are prescribed drugs for ADHD are also prescribed anti-asthma drugs significantly more often than the rest of the population. This strongly supports a comorbidity between these two disorders. Even if such a comorbidity may have no immediate clinical relevance, it may provide clues to common pathophysiological mechanisms. Longitudinal studies focusing on the temporal relationship between ADHD and asthma are needed to further examine this relationship.

Declaration of Conflicting Interests

The authors declared that they had no conflicts of interests with respect to their authorship or the publication of this article.

Funding

This study was supported financially by the Western Norway Regional Health Authority.

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