

## Research Article

# Comorbidity of Asthma and Attention Deficit Hyperactivity Disorder: A Population-Based Cohort Study

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## ABSTRACT

**Objective:** To assess the comorbidity of asthma and Attention Deficit Hyperactive Disorder (ADHD) based on how frequently drugs used to treat asthma and ADHD are prescribed to the same patients. This study is stimulated by the work of Fasmer, et al. in Norway.

**Method:** A cohort study of 1,890,990 patients selected based on anti-ADHD or anti-asthma medication. The authors used data from the University of California Davis Medical Center, Cohort Discovery System between 2006-2012.

**Results:** Patients who had been prescribed anti-ADHD drugs had an abnormally high risk (odds ratio (OR) = 4.19) of also being prescribed asthma medication. Female patients with

ADHD had an overall higher probability to be prescribed anti-asthma medication than did males (OR=1.28). For both males and females, the association was stronger for older age groups (the OR exceeded 6.0 for men 35-84 years and for women 45-84 years of age).

**Conclusion:** These prescription patterns suggested a marked comorbidity between asthma and ADHD for both genders and across all age groups, but which is lower in the younger age groups.

**MeSh Headings/ Keywords:** Anti-ADHD medication; Asthma medication; Comorbidity

## Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is a common childhood-onset neuro-developmental disorder with a lifetime prevalence of 5.9% to 8.7% [1,2]. Although ADHD was originally described as limited to childhood, prospective follow-up studies of clinic-referred children with ADHD indicate that approximately 15% will continue to meet full diagnostic criteria and an additional 50% will continue to have impairing ADHD symptoms as young adults [3,4]. ADHD is associated with many psychiatric disorders including anxiety disorders, mood disorders and drug misuse disorders [5-7].

Like ADHD, asthma is also perceived as a disease of childhood; however, it is currently noted to have a significant adult prevalence and incidence [8]. Asthma has a well established co-morbid connection with psychiatric disorders. Children with asthma have a higher prevalence of behavioral difficulties than children without asthma [9]. Among adult asthmatics, there is a higher prevalence of depression and anxiety disorders than in the general population [10]. Although the etiology of ADHD is not clear yet, immunologic factors have been proposed to play roles

in the etiology, as is the case with many other neuropsychiatric disorders [11].

It is thought that both the nature of asthma and the medications used to treat it can increase the frequency of ADHD symptoms [12-14]; however, studies that have examined the potential relationship between ADHD and asthma have not given consistent results. A study of 140 boys with ADHD [15] and a study of 140 girls with ADHD [16] both failed to find a positive association between ADHD and asthma; however, a nationwide population-based prospective case-control cohort study hypothesized that asthma in infancy or early childhood would increase the risk of ADHD in later life [17].

In a previous study on adults using data from a large claims database, a diagnosis of ADHD was significantly associated with a diagnosis of asthma [18]. Each subject was counted only once even if this individual received more than one prescription during the observation year. In this work, we examine via the Cohort Discovery System at University of California, Davis (UCD), association between two disorders, asthma and ADHD, using their treatments as a proxy for diagnosis, respectively.

These odds assessments are performed over age blocks (0-9, 10-17, 18-34, 35-44, 45-54, 55-64, 65-74, 75-84) and for both sexes in the broader Sacramento area. So, we get a broader range of age blocks as well as a different population.

## Methods and Materials

### Data Source

Our study population consisted of complete UCD Medical Center patients from January 2006 to September 2012 (total,  $n = 1,890,990$ ; men,  $n = 916,313$ ; and women,  $n = 974,677$ ), collected through Cohort Discovery System. The Cohort Discovery System is a repository of de-identified patient information gathered from multiple sources, including electronic medical records, laboratory results and demographic data on all patients seen through UCD Medical Center since 2006. In the present study, we registered all individual patients who at least once were prescribed drugs used to treat asthma, ADHD, or both during January 2006-September 2012. Each subject was counted only once even if this individual received more than one prescription during the observation year. Table 1 presents the list of medications used to treat ADHD and asthma in our study.

### Statistical Analysis

An overall odds ratio (OR) and 95% Confidence Interval (CI) 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. Our model also included terms for all two-way interactions, as well as a term for the three-way interaction of gender, anti-ADHD prescription, and age group. This model allowed us to estimate gender and age-specific ORs for the association between prescriptions of anti-ADHD and anti-asthma medication. All tests were two-sided, with  $\alpha = 0.05$ . Analyses were implemented using PROC LOGISTIC in SAS Version 9.4 (SAS Institute, Cary NC).

## Results

Anti-asthma medications were prescribed to 125,006

patients (6.61% of the total patients in the system), and anti-ADHD medications were prescribed to 12,442 patients (0.66%). Total of 2,983 (0.16%) patients were prescribed both type of medications. Table 2 shows the percentage of patients taking each medication by age group. The highest percentage of anti-asthma medications was in the youngest age group (13.32%), followed by 10-17 age group (8.43%). For anti-ADHD medications, the highest percentage of people with prescriptions was in the 10-17 age group (2.42%), followed by 18-34 (0.83%).

Table 3 presents the percentage of males and females taking anti-asthma and anti-ADHD medications by age group. The percentage of males being prescribed anti-asthma medication was higher than women in the two youngest age groups (0-9 and 10-17). In all the other age groups, the percentage of women being prescribed anti-asthma medication was higher. Similarly, for anti-ADHD medications, the percentages of women and men being prescribed medication were similar, with the exception of the three younger age groups, for which more men were prescribed anti-ADHD medications than women.

Among patients receiving anti-ADHD drugs, 48.20% are males aged less than 34 years, and the corresponding percentage for females in the same age groupings is 22.47%. Among patients receiving anti-asthma drugs, 17.42% are males aged less than 34 years, and the corresponding percentage for females in the same age groupings is 20.86%. Analyzed according to gender, more males in the 0-9 and 10-17 years age group were prescribed anti-asthma drugs than females (males: females = 1.51:1 and 1.32:1) but in all other age groups up to 84 years, the number of prescriptions was higher for females than males (Table 2).

Prescriptions of anti-ADHD drugs (Table 2) were more frequent for males than for females in the age groups 0-9, 10-17, 18-34, 65-74, 75-84, but the difference was particularly strong in the age group 0-9 (males: females = 3.22:1), 10-17 (2.62:1) and 18-34 (1.69:1).

Table 4 presents the pattern of anti-ADHD medications stratified by age group, gender and by being prescribed anti-asthma medications. A total of 2,990 patients (1,719 males and 1,271 females) were prescribed both anti-ADHD and anti-asthma medications. Out of all the males being prescribed

**Table 1:** Class of drugs queried in Cohort Discovery System.

Anti-asthma class of drug	Anti-ADHD class of drugs
Beta adrenergic agents	Selective alpha 2 receptor agonist
Beta adrenergic and anticholinergic combinations	Stimulants
Beta adrenergic and glucocorticoid combinations	Noradrenergic Reuptake I's- Type
Glucocorticoids	
5 Lipoxygenase inhibitors	
Adrenergic agents, catecholamines	
Leukotriene receptor antagonist	
Mast cell stabilizers	
Phosphodiesterase-4 inhibitors	
Xanthines	

**Table 2:** Number (percentage) of patients being prescribed anti-asthma medication, anti-ADHD medication or both in the UCD Cohort Discovery System.

Age group	N	Prescribed Medication		
		Asthma Only	ADHD Only	ADHD and Asthma
0-9	92,652	12,344 (13.32%)	541 (0.58%)	183 (0.20%)
10-17	1,21,716	10,189 (8.37%)	2,947 (2.42%)	836 (0.69%)
18-34	3,85,843	25,386 (6.58%)	3,198 (0.83%)	870 (0.23%)
35-44	2,71,293	15,532 (5.73%)	738 (0.27%)	251 (0.09%)
45-54	3,32,437	17,511 (5.27%)	880 (0.26%)	342 (0.10%)
55-64	3,39,446	19,150 (5.64%)	751 (0.22%)	309 (0.09%)
65-74	2,13,168	13,447 (6.31%)	323 (0.15%)	142 (0.07%)
75-84	1,34,435	8,464 (6.30%)	81 (0.06%)	50 (0.04%)

Note: Percentage refers to percentage of patients within each age group having been prescribed each medication.

**Table 3:** Frequency (percent) of anti-asthma and anti-ADHD drug prescriptions for females and males stratified by age group.

Age group	Females			Males		
	N	Asthma	ADHD	N	Asthma	ADHD
0-9	41,785	4,950 (11.85)	176 (0.42)	50,867	7,577 (14.90)	548 (1.08)
10-17	56,464	4,574 (8.10)	1,007 (1.78)	65,252	6,451 (9.89)	2,776 (4.25)
18-34	1,98,991	17,221 (8.65)	1,578 (0.79)	1,86,852	9,035 (4.84)	2,490 (1.33)
35-44	1,45,019	10,380 (7.16)	561 (0.39)	1,26,274	5,403 (4.28)	428 (0.34)
45-54	1,73,173	10,425 (6.02)	680 (0.39)	1,59,264	7,428 (4.66)	542 (0.34)
55-64	1,80,480	11,054 (6.12)	653 (0.36)	1,58,966	8,405 (5.29)	407 (0.26)
65-74	1,10,549	7,443 (6.73)	219 (0.20)	1,02,619	6,146 (5.99)	246 (0.24)
75-84	68,216	4,524 (6.63)	64 (0.09)	66,219	3,990 (6.03)	67 (0.10)
Total	9,74,677	70,571 (7.24)	4,938 (0.51)	9,16,313	54,435 (5.94)	7,504 (0.82)

**Table 4:** Prevalence of anti-ADHD medication among patients with and without anti-asthma medication across age groups and gender.

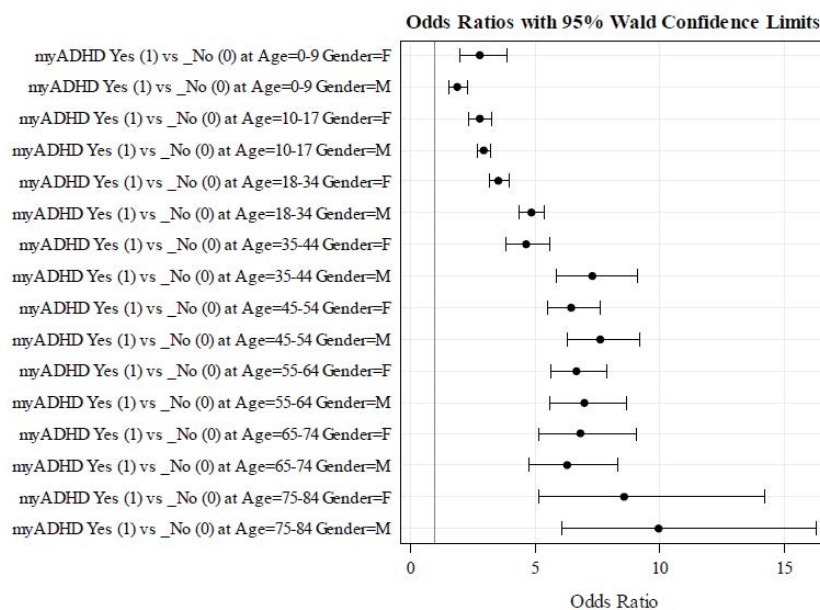
Age group	Anti-Asthma Medication Prescribed		Anti-Asthma Medication Not Prescribed	
	Female with Anti-ADHD Medication Prescribed	Male with Anti-ADHD Medication Prescribed	Female without Anti-ADHD Medication Prescribed	Male without Anti-ADHD Medication Prescribed
0-9	48/4,950 (1%)	135/7,577 (2%)	128/36,835 (0.4%)	413/43,290 (1%)
10-17	195/4,574 (4%)	641/6,451 (10%)	812/51,890 (2%)	2,135/58,801 (4%)
18-34	392/17,221 (2%)	478/9,035 (5%)	1,186/181,770 (0.7%)	2,012/177,817 (1%)
35-44	147/10,380 (1%)	104/5,403 (2%)	414/134,639 (0.3%)	324/120,871 (0.3%)
45-54	197/10,425 (2%)	145/7,428 (2%)	483/162,748 (0.3%)	397/151,836 (0.3%)
55-64	196/11,054 (2%)	113/8,405 (1%)	457/169,426 (0.3%)	294/150,561 (0.2%)
65-74	72/7,443 (1%)	70/6,146 (1%)	147/103,106 (0.1%)	176/96,473 (0.2%)
75-84	24/4,524 (0.5%)	26/3,990 (0.7%)	40/63,692 (0.1%)	41/62,229 (0.1%)

both drugs, 37.28% (641 of 1719) were in the age group 10-17 and 27.80% (478 of 1719) were in the age group of 18-34. Out of all the females being prescribed both drugs, 30.84% (392 of 1271) were in the age group of 18-34. For the three age groups between 0 and 34 years, and for the age group 75-84, the number of males being prescribed both drugs were higher than the number of females: 0-9 (males vs. females: 135 vs. 48); 10-17 (641 vs. 195); 18-34 (478 vs. 392); 75-84 (26 vs. 24). In the four age groups between 35 and 74 years, the number

of females being prescribed both drugs were higher than for males: 35-44 (females vs. males: 147 vs. 104); 45-54 (197 vs. 145); 55-64 (196 vs. 113) and 65-74 (72 vs. 70). For both sexes, the relationship between prescription of ADHD and asthma medications was strongest in older age groups and gradually increased with age. Table 5 and Figure 1 show the results of the multivariate logistic models. The overall OR of being prescribed one of the drugs, given a prescription of the others, was 4.53 (CI: 4.35-4.73), (Table 3), adjusting age and gender

**Table 5:** Concurrent prescription of anti-asthma and anti-ADHD drugs: frequency (percent) and odds ratios (OR) with 95% confidence intervals (CI).

Age group	Female		Male	
	N (%)	OR (95% CI)	N (%)	OR (95% CI)
0-9	48 (0.11)	2.81 (2.01 - 3.92)	135 (0.27)	1.88 (1.55 - 2.29)
10-17	195 (0.35)	2.80 (2.39 - 3.28)	641 (0.98)	2.93 (2.67 - 3.21)
18-34	392 (0.20)	3.55 (3.16 - 3.98)	478 (0.26)	4.88 (4.41 - 5.41)
35-44	147 (0.10)	4.66 (3.85 - 5.63)	104 (0.08)	7.30 (5.84 - 9.12)
45-54	197 (0.11)	6.47 (5.48 - 7.65)	145 (0.09)	7.59 (6.27 - 9.20)
55-64	196 (0.11)	6.67 (5.64 - 7.90)	113 (0.07)	6.97 (5.60 - 8.66)
65-74	72 (0.07)	6.84 (5.16 - 9.08)	70 (0.07)	6.30 (4.77 - 8.33)
75-84	24 (0.04)	8.49 (5.11 - 14.09)	26 (0.04)	9.95 (6.08 - 16.28)

**Figure1:** Odds Ratios for prescription of both anti-asthma and anti-ADHD medications to males and females, by age group.

in a logistic regression model. There was a variation of the co-distribution of the two types of drugs for each age group within each gender (Table 3). In all age groups, and for both genders, increased OR's was found, with values in the range of 1.88 to 9.95. The OR's for males was higher than for females in the age groups 10-17 (2.93 vs. 2.80), 18-34 (4.88 vs. 3.55), 35-44 (7.30 vs. 4.66), 45-54 (7.59 vs. 6.47), 55-64 (6.97 vs. 6.67), and 75-84 (9.95 vs. 8.49). The OR was particularly striking in the 35 to 44 years age group (7.30 vs. 4.66). For males, the highest OR's was found in the age groups from 18 to 84 (4.88-9.95), and for females the highest OR's was found in the age groups from 35 to 84 years (4.66-8.49). There was not a striking difference in the overall age-adjusted risk between males (OR = 4.79, CI: 4.54-5.06) and females (OR = 4.50, CI: 4.22-4.80).

## Discussion

This study was initiated to test the comorbidity between ADHD and asthma utilizing the ap-proach of Fasmer with the proxy of examining the respective treatments of ADHD and asthma in a different population with different treatment practices [14]. We analyzed data for all patients in the UCD

Cohort Discovery System between 2005-2012. We found that anti-asthma medications were prescribed to 125,157 patients (6.62% of the total patients), anti-ADHD medications were prescribed to 9,459 patients (0.50% of the total patients), and both medications were prescribed to 2990 patients. There was an increase in the overall risk (OR = 4.19) of being prescribed asthma medication given a prescription for anti-ADHD drugs. After controlling for presence of ADHD prescription and age, females had higher odds ratio of being prescribed anti-asthma medications than males (OR = 1.28), although the overall OR was strong for both genders (men: 4.79; women: 4.50).

From a logistic regression model including gender, ADHD medication, age group and all interac-tions, we estimated age group and gender specific OR for the association between anti-ADHD medication and asthma medication. For both females and males, the association was stronger for older age groups (the OR exceeded 6 for men age range of 35-84 years and for women age range of 45-84 years).

We have shown that there is a significantly increased prescription of anti-asthma drugs in pa-tients who were

prescribed anti-ADHD drugs; the converse also follows. These findings, therefore, suggest that there is comorbidity between ADHD and asthma in patients treated over 6 years and 8-month period at the UC Davis Medical Facilities. These results are generally consistent with findings of Fasmer study [14], apart from some gender pattern differences. Fasmer and colleagues addressed some negative findings in previous clinical studies concerning co-morbidity between asthma and ADHD [15,16]. They noted that in Biederman study [15], the mean age of the 140 boys was 11 years, whereas in Hammerness study [16], the mean age at the time of the study was not given although the patients were all described as children. Thus, in some studies primarily limited to children, co-morbidity was not evidenced. Our data indicated that in males, the ages zero to nine, the comorbidity as evidenced by OR was only moderately elevated, but the comorbidity increased over the subsequent decades until the subjects were aged 45 to 54, then it remained stable. For females, comorbidity also started out moderately but did not substantially increase until subjects were aged 18 to 34. This age-related pattern might be the reason why some previous studies that confined to younger aged groups, did not capture the comorbidity. Subtle differences with the Norwegian study might be related to various factors, including different social-geographic conditions, and different health systems/policies, access, and health seeking behaviors.

There have been some other interesting studies since 2011. The Mogensen study [19] showed evidence consistent with the pattern of greater comorbidity with higher age. They found that children with asthma aged eight to nine exhibited a nearly two-fold increased risk of having one or more symptoms of hyperactivity-impulsivity by age 13-14 independent of asthma medication. For the inattentive dimension, no such significant relationship was noted.

A relatively recent prospective study by Chen [7] utilizing an insurance medical databank from the entire nation of Taiwan examined 2,294 children with asthma and 9,176 controls aged between zero-three in 2000. Cases of ADHD that occurred by the end of follow-up (December 31, 2010) were identified. Children with asthma had a higher incidence of developing ADHD than control subjects during the follow-up period (7% vs. 4.6%,  $p < 0.001$ ). The investigators concluded that their study supported a temporal relationship between asthma and ADHD. Asthma in very early life might increase the risk of developing ADHD by the early teens.

Our study and other previous cross-sectional studies suggest an association between asthma and ADHD. A potential temporal relationship between asthma and ADHD as noted by Chen [17] is currently being investigated. Mogensen [19] felt that genetics may play a role in this temporal linkage. The comorbidity between the two conditions appears to increase with increasing age. This could be related to epigenetic phenomena due to one disorder increasing the likelihood of developing the other, or the opposite, as Chen [20] suggests, potentially due to an allergic immunity or inflammatory process that increase the likelihood of both disorders. Immunological dysregulation, such as hyper secretion of Ig-E, increased eosinophilic activity,

and a predominantly T helper type 2 (Th2) cytokine over-secretion, accounted for the hypothesized pathophysiology of the co-morbid association between ADHD and allergic diseases including asthma [21-23].

Inflammatory mechanisms are the central importance in the pathophysiology of asthma [24]; moreover, disturbances in the immuno-inflammatory system have been implicated in the etiology, pathophysiology, phenomenology and comorbidity of several psychiatric disorders such as schizophrenia, bipolar disorder, major mood disorders [25,26], suicidal behavior, post-traumatic disorder and autism [27-31]. Furthermore, many psychiatric disorders are also often accompanied by chronic medical conditions related to immune dysfunction such as autoimmune disorders [32], diabetes and atherosclerosis [33-35]; moreover, in recent years there has been an interest in the potential role of atopy and allergic immune pathology in ADHD [36].

ADHD has a high comorbidity with both Th1- and Th 2-mediated disorders. As compared to control, ADHD patients have a higher incidence of stomach aches and ear infections, which are Th1-mediated conditions [37], as well as hypersensitivity and atopic diseases such as eczema, asthma and rhinitis, which are Th 2-mediated conditions [38,39]. In a recent study Chen, et al. [17] showed that there is an association between ADHD and various allergic/autoimmune diseases (allergic rhinitis OR = 1.59, atopic dermatitis OR = 1.53, urticaria OR = 1.39, ulcerative colitis 2.31, autoimmune thyroid disease OR = 2.53, ankylosing spondylitis OR = 2.7) and believe their findings provide evidence that immune or inflammatory systems may play a role in the temporal linkage.

Mounting evidence in the last decade pointed to a possible significant association between ADHD and certain somatic conditions, including obesity [40]. ADHD and overweight/obesity share familial risk factors, which are not limited to those causing overweight/obesity through the mediation used for ADHD treatment [41].

Obesity is a risk factor for asthma [42] and obese asthmatics have lower disease control and increased symptom severity. Several putative links have been proposed, including genetics, mechanical restriction of the chest and the intake of corticosteroids. The most consistent evidence, however, comes from studies of cytokines produced by the adipose tissue called adipokines. Adipokine imbalance is associated with both proinflammatory status and asthma. Although reverse causation has been proposed, it is now acknowledged that obesity precedes asthma symptoms [43]. Studies suggest that obesity often leads to a proinflammatory state [44], and may also play a role in the temporal linkage with ADHD [45].

## Strengths and Limitations

Our study used prescription data to indirectly assess comorbidity of ADHD and asthma. There is an inherent limitation in predicting medical disorders based upon treatments. There may be some liberality in whom would receive anti-ADHD medications, as in the United States physicians other than psychiatrists could prescribe anti-ADHD medications for

patients with hyperactive symptoms. This practice might have some impact on the computed odds ratio.

Another limitation of our study is that our results are based on the prescription of a class of medications rather than a specific diagnostic work up. Searching a database for medications designated for treatment of a specific clinical condition is likely to be problematic for other indications of these medications. Though the prescription patterns of anti-asthma drugs to children and adults and of anti-ADHD drugs to children probably reflect, to a large extent, the prevalence of these disorders, prescription patterns of anti-ADHD drugs prescribed to the adult patients may not. It is likely that only a subset of adult patients diagnosed with ADHD is treated with such medications, and it is reasonable to assume that these patients are those most seriously affected. Therefore, we cannot conclude that the postulated comorbidity extends to adult ADHD patients who are not prescribed medication treatment. A useful follow up to our results would consist of a long term, prospective and diagnosis-based study for both asthma and ADHD conditions. Meanwhile the percentage of ADHD for our group was recorded as 0.5% of the population, based on the prescribed medications. This might mean a significant underrepresentation of both total number of ADHD and treated ADHD cases [46].

The strength of this study is the large sample size, the lengthy six years and eight-months data collection period, and the inclusion of data from all age blocks ranging from zero to 84 years. However, we have only indirect data on the diagnoses we focus on. It is unknown how frequently the patients received the listed drugs.

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 frequently than those not receiving anti-ADHD drugs in the UCDMC Cohort System. This supports comorbidity between asthma and ADHD based on co-prescription behaviors, which increases with age block. Although such comorbidity may have no immediate clinical relevance, it could provide clues to pathophysiological mechanisms that might be common in both disorders. Longitudinal studies focusing on the temporal relationship between ADHD and asthma are needed to further examine this possibility.

### Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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