



The Temporal Hyper-Morbidity of Asthma and Attention Deficit Disorder: Implications for Interpretation Based on Comparison of Prospective and Cross-Sectional Population Samples

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Objective The purpose of this study was to test the hypothesis that a significant temporal relationship exists between asthma and attention deficit hyperactivity disorder (ADHD).

Methods The population dataset consisted of 95,846,511 physician diagnoses for 768,460 (46% male) individuals spanning 1993–2010. Four groups were labeled as having neither Asthma nor ADHD, Asthma only, ADHD only, or both Asthma and ADHD and formed the basis of calculating the odds ratios for each sex describing the association of Asthma and ADHD by age, and, in addition, a prospective sample age (<5 years) between 1993 and 1996 was utilized to evaluate the temporal association between Asthma and ADHD.

Results There was a significant relationship between ADHD and Asthma within the age strata of the sample, one from the cohort and two from the whole sample. When both ADHD and Asthma were diagnosed in the same patients, the age was younger in both cross-sectional and prospective cohort samples. ADHD arose significantly more often after Asthma in the cross-sectional samples stratified on age and in the prospective cohort sample.

Conclusion The results are consistent with previous literature where ADHD has been linked to allergic diseases, such as asthma.

Psychiatry Investig 2021;18(2):166-171

Key Words Asthma, Attention deficit hyperactivity disorder, ADHD, Population, Epidemiology, Temporal hyper-morbidity.

INTRODUCTION

Previous research has indicated that there was no statistical relationship between attention deficit hyperactivity disorder (ADHD) and asthma, arguing against a substantial etiological or pathophysiological relationship between the two conditions.¹⁻⁴ However, other findings have suggested that behavioral disorders, including ADHD, are recurrent in children being treated for asthma.^{5,6}

ADHD has been linked to other behavioral disorders and

allergic disorders, such as mood disorders and asthma.^{7,8} For example, two-thirds of children with ADHD experience co-morbidities.⁹ Furthermore, ADHD symptoms should not be dismissed as part of asthma symptomatology or as a consequence of its treatment.¹⁰ Additionally, ADHD is associated positively with asthma⁹ and pediatric asthmatic patients have a higher chance to develop ADHD and other behavioral disorders and the severity of asthma symptoms is strongly correlated with the severity of ADHD symptoms.^{11,12} An important common denominator between ADHD and allergic disorders is the probable effect of prenatal stress on both; findings suggest that ADHD children born preterm and/or with mothers who have experienced moderate to acute stress during pregnancy, have a significantly higher chance of acquiring asthma as compared to children born in term and whose mothers were exposed to little stress or no stress at all.¹³ Finally, lifetime prevalence rates of asthma in ADHD patients was 36.6%, compared to a prevalence of 24.3% in control subjects. In this study, we

Received: September 14, 2020 **Revised:** November 18, 2020

Accepted: December 9, 2020

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examined the relationship between Asthma and ADHD in a population, with a focus on the temporal association between these two disorders in children similar to other studies,¹⁴ however, without any focus on the influence of other family factors.¹⁵⁻¹⁷ The hypothesis tested in this report employing two sampling methods for comparison was that there is a significant temporal relationship between Asthma and ADHD.

METHODS

Data source was Alberta health physician visit and diagnosis data for the Calgary Health Zone in Alberta Canada (Ethics ID: REB15-1057). The data constituted a sixteen-year population dataset consisting of 95,846,511 (36% male) physician International Classification of Disease (ICD-9) diagnoses and visit dates for 768,460 (46% male) individuals spanning 1993–2010. These data served as the basis for constructing the dataset employed in this analysis. All individuals in this dataset (whole sample) were labelled as having neither Asthma nor ADHD (a), Asthma only (b), ADHD only (c) or both Asthma and ADHD (d). These four groups, represented the two by two cell counts (a, b, c, d) of unique individuals, formed the basis of calculating the odds ratios $\{OR=[(ad)/(bc)]\}$ for each sex describing the association of Asthma and ADHD within each of the sample frames described below.

From this population dataset, a subset of those under the age of 5 years between 1993 and 1996 was extracted, and these individuals' Asthma and ADHD diagnoses were labelled as being from the prospective cohort within the whole sample from first to last visits up to 2010, with the oldest in December 1995 begin less than 18 years of age in 2010 (<18 years cohort) and the oldest in 1993 begin less than 22 years in 2010 (<22 years cohort). Similarly, other cross-sectional age strata (<22 years from the whole sample, and the whole sample) were labelled to examine the effects of sampling frame and age on the relationship between ADHD and asthma in comparison with the prospective cohorts employing odds ratio calculations respective to each sample frame. A separate label was created for the unique individuals in each of the four groups. All diagnoses for these individuals within the large dataset were then labelled in order to link and examine the specific associations between Asthma and ADHD within each group of over time.

Based on the age (<5 years) and time (1993–1996) constraints, it was possible to evaluate the data for a temporal association between Asthma and ADHD in the group with both Asthma and ADHD employing a comparison of proportions where Asthma preceded or followed ADHD, in addition to an overall association employing the odds ratios. For each sample, in the group with both ADHD and Asthma, the data

was compared further on the basis of the temporal co-occurrence of the index diagnoses of either Asthma or ADHD, based on the index (first) diagnosis date among those with Asthma and ADHD, two groups were identified with respect to whether or not Asthma arose before or after ADHD. Proportions and 95% confidence intervals formulated the basis for comparison of the temporal co-occurrence of Asthma and ADHD. Significant statistical differences between proportions in were estimated by comparison of the 95% confidence intervals using the standard formula, wherein non-overlapping 95% confidence intervals represent significant differences ($p < 0.05$, with z set to 1.96).

Therefore, the null hypothesis was constructed on the assumption that, based on chance alone, the respective proportion occurring before or after either disorder would not be significantly different from one another (e.g., non-overlapping 95% confidence intervals).

RESULTS

Whole sample

The sample consisted of 768,460 (46% male) individuals with a total of 95,846,511 (36% male) physician-assigned ICD-9 diagnoses between April 1993 and April 2010. Males had an average of 97 (SD 130) diagnoses and a range from 1 to 4,343 diagnoses. Females had an average of 148 (SD 155) diagnoses and a range from 1 to 3,558.

Table 1. Mean minimum age and standard deviation (SD) of index ADHD and Asthma diagnoses by sex

Sample	Group	Mean age (SD)	
		Males	Females
Whole sample	ADHD only	13 (10)	18 (15)
	Asthma only	26 (22)	32 (22)
	Both Asthma and ADHD	6 (8)	11 (13)
Whole sample <22 years	ADHD only	9 (6)	11 (4)
	Asthma only	8 (6)	11 (6)
	Both Asthma and ADHD	4 (5)	6 (5)
Cohort <5 years (1993–1996)	ADHD only	3 (1)	3 (1)
	Asthma only	2 (1)	2 (1)
	Both ADHD and Asthma*	1.7 (1)	2 (1)
Cohort <22 years	ADHD only	8 (3)	9 (4)
	Asthma only	5 (4)	7 (5)
	Both ADHD and Asthma*	1.7 (1)	2 (1)

*same result for Cohort <5 years and Cohort <22 years. ADHD: attention deficit hyperactivity disorder

ADHD

The 28,729 patients with ADHD had a total of 269,936 ADHD diagnoses. Of the ADHD-diagnosed patients there was a per-patient average of 9 (SD=16) ADHD diagnoses and a range from 1 to 464. These ADHD-diagnosed patients had 3,769,393 linked diagnosed disorders/diseases.

Asthma

Of the 158,064 Asthma-diagnosed patients, there were a total of 971,770 Asthma diagnoses with a per-patient average of 6 (SD=11) Asthma diagnoses and a range from 1 to 474. These Asthma-diagnosed patients had 28,350,854 linked diagnosed disorders/diseases.

Age distributions within samples

Table 1 indicates that when both ADHD and Asthma are diagnosed in the same patients the age is consistently young-

Table 2. Total frequency of ADHD and Asthma diagnoses by sex by groups

Total# diagnoses by sample	ADHD		Asthma	
	Females	Males	Females	Males
Cohort <5 years	81	495	67	241
Cohort <22 years	12,586	46,399	406	2,712
Total <22 years	171,698	213,186	57,195	184,259
Whole sample	548,132	423,638	70,405	199,531

ADHD: attention deficit hyperactivity disorder

Table 3. Description of unique individuals within groups of whole sample

Group		Cell*	Female (row %)	Male (row %)	Total
No Asthma	No ADHD	a	320,535 (54.1)	272,120 (45.9)	592,655
Asthma	No ADHD	b	86,740 (59)	60,336 (41)	147,076
No Asthma	ADHD	c	5,492 (31)	12,249 (69)	17,741
Asthma	ADHD	d	3,559 (32.4)	7,429 (67.6)	10,988
Total			416,326 (54.2)	352,134 (45.8)	768,460

*a, b, c, d, represent cell values for calculating overall sample odds ratio (OR)=(ad)/(bc). ADHD: attention deficit hyperactivity disorder

Table 4. Description of unique individuals within categories within the prospective dataset

Group condition* (all<18 years)	Sex	N	Mean diagnoses and standard deviation (SD)	Min.	Max.
ADHD-/Asthma-	Female	110,336	46.96 (49.61)	1	1973
ADHD-/Asthma+	Female	2,780	104.28 (75.39)	1	920
ADHD+/Asthma-	Female	116	111.23 (68.72)	5	381
ADHD+/Asthma+	Female	23	171.52 (79.73)	60	374
ADHD-/Asthma-	Male	113,655	45.4 (47.73)	1	1567
ADHD-/Asthma+	Male	4,426	103.81 (70.43)	1	850
ADHD+/Asthma-	Male	254	123.74 (93.34)	3	707
ADHD+/Asthma+	Male	83	174.18 (116.09)	17	588

*prospective cohort inclusion criteria was <5 years between 1993 and 1996 up to 17 years of age by October 2010. ADHD: attention deficit hyperactivity disorder

er in both cross-sectional (Whole Sample and Whole Sample <22 years) and prospective (Cohort) samples. Asthma alone is more often diagnosed in the cross-sectional (Whole Sample) on average at an age than ADHD, whereas in the younger cross-sectional (Whole Samples<22 years) and prospective (Cohort<5 years and Cohort<22 years) samples, the diagnosis of Asthma is at a younger age than ADHD.

Frequencies of ADHD and asthma diagnoses within the samples

Table 2 summarizes the total frequency of diagnoses for each age grouping for cross-sectional and prospective samples for males and females. The frequency of diagnosis increases with age for both cross-sectional and prospective samples for males and females.

Counts of individuals for odds ratios

Table 3 describes the counts of unique individuals for the whole dataset in each cell employed to calculate the overall odds ratio that includes the other sample groups.

Table 4 presents the sample size (N), mean frequency, standard deviation (SD), minimum (Min.), and maximum (Max.) diagnoses for each category of the under 5 year old cohort.

Table 5 presents the unique individual counts for each age grouping employed in the calculation of odds ratios. Note in Table 5 that the same values arise for both prospective cohort categories as age was constrained to under five years of age

cohort was designed as <5 years of age before 1997 (up to the end of 1996), then measured prospectively until 2010. This redundancy serves as an algorithm reliability and validity check.

Table 6 presents for each sample a summary of odds ratios (OR) and their 95% confidence intervals illustrating the association of ADHD and Asthma. Table 6 shows that there is a significant relationship between ADHD and Asthma in three of the four age groupings, two from the cohort and one from

Table 5. Counts of unique individuals for calculating the odds ratios representing cross-sectional and prospective cohort samples for males and females

Groups	Cell*	Males	Females	Total
Whole sample				
Neither	a	272,120	320,535	592,655
Asthma	b	60,336	86,740	147,076
ADHD	c	12,249	5,492	17,741
Both	d	7,429	3,559	10,988
	Total	352,134	416,326	768,460
Whole sample <22 years				
Neither	a	88,956	98,900	187,856
Asthma	b	31,440	35,865	67,305
ADHD	c	10,981	4,229	15,210
Both	d	7,058	2,948	10,006
	Total	138,435	141,942	280,377
Cohort <5 years				
Neither	a	133,672	139,023	272,695
Asthma	b	4,426	2,780	7,206
ADHD	c	254	116	370
Both	d	83	23	106
	Total	138,435	141,942	280,377
Cohort <22 years				
Neither	a	133,672	139,023	272,695
Asthma	b	4,426	2,780	7,206
ADHD	c	254	116	370
Both	d	83	23	106
	Total	138,435	141,942	280,377

*a, b, c, d, represent cell values for calculating cohort sample odds ratio (OR)=(ad)/(bc). ADHD: attention deficit hyperactivity disorder

Table 7. Counts of unique individuals by sex where index ADHD was diagnosed in time either before or after the index Asthma diagnosis used to calculate the temporal proportions and their 95% confidence intervals

Sample	Males			Females		
	ADHD>Asthma	ADHD<Asthma	Total	ADHD>Asthma	ADHD<Asthma	Total
Cohort <5 years	60	22	82	16	7	23
Whole sample <22 years	4,637	2,410	7,047	1,763	1,178	2,941
Whole sample	4,870	2,544	7,414	2,163	1,138	3,301

ADHD: attention deficit hyperactivity disorder

the Whole Sample. Significance is indicated when the lower 95% confidence intervals are greater than the value one or when the upper 95% confidence intervals are less than the value one. When 95% confidence intervals include the value one, the association is not significant at $p<0.05$. This was the case for the Whole Sample <22 years odds ratio.

Table 6 also illustrates the results stemming from the different sampling techniques and outlines the limitations of the method. In terms of drawing inferences about causality, prospective designs are optimal. Note the magnitude of the associations in the two prospective samples are considerably larger than in the cross-sectional samples. In the cross-sectional samples patients can both enter and leave the dataset over time. Whereas, in the prospective sample, individuals can only leave cells, influencing cells 'a' and 'd' in the opposite direction. Of course, as entering and leaving is not likely random (e.g., economic migration), both would have an effect proportional to the net count. Leaving cells 'b' and 'c' would logically increase the ORs. Similarly, entering cells 'b' and 'c' would decrease the ORs.

Taken together, the ORs are mostly significantly greater than the value 1, and the range of the 95% CIs in the Whole Sample under 22 years also have their magnitude mostly >1 lending veritas to the association between ADHD and Asthma, as measured from different sample frames.

Temporal hyper-morbidity of ADHD and asthma

Table 7 shows the counts of unique individuals with ADHD diagnosed before or after Asthma employed to calculate the

Table 6. Summary of odds ratios (OR) and 95% confidence intervals (CI) illustrating the association of ADHD and Asthma within samples

Sample	OR males (95% CI)	OR females (95% CI)
Whole sample	2.74 (1.71, 3.77)	2.39 (1.35, 3.43)
Whole sample <22 years	1.82 (0.79, 2.85)	1.92 (0.87, 2.97)
Cohort <5 years	9.87 (8.59, 11.15)	9.92 (8.35, 11.49)
Cohort <22 years	9.87 (8.59, 11.15)	9.92 (8.35, 11.49)

*OR=(ad)/(bc) from corresponding cells a, b, c, and d in Table 5. ADHD: attention deficit hyperactivity disorder

Table 8. Proportions of ADHD within cell 'd' counts that occurred before or after Asthma

Sex	Sample	Proportion ADHD after Asthma (95% CI)	Proportion ADHD before Asthma (95% CI)
Males	Cohort <5 years	0.73 (0.72, 0.74)	0.27 (0.26, 0.28)
	Whole sample <22 years	0.66 (0.65, 0.67)	0.34 (0.33, 0.35)
	Whole sample	0.66 (0.65, 0.67)	0.34 (0.33, 0.35)
Females	Cohort <5 years	0.7 (0.66, 0.73)	0.3 (0.27, 0.34)
	Whole sample <22 years	0.6 (0.58, 0.62)	0.4 (0.38, 0.42)
	Whole sample	0.66 (0.64, 0.67)	0.34 (0.33, 0.36)

ADHD: attention deficit hyperactivity disorder

proportions and 95% confidence intervals for each sample.

The results shown in Table 8 provide an index of the temporal hyper-morbidity of ADHD and Asthma when these two diagnoses arise in the same individual at different times. ADHD arises significantly more often after Asthma in each cross-sectional and prospective sample. The significance of this relationship is given by the non-overlapping 95% CIs, with the larger proportions indicating the temporal order. Analysis indicated significant difference associated with group membership by gender and age. Males and females with both ADHD and Asthma are significantly different than the other two groups with ADHD or Asthma alone. This result is supported by the analysis of the age strata represented within and between the aged-based samples (Table 1).

DISCUSSION

There has been a resurgence of interest in the relationship between Asthma and ADHD in recent years^{4,18} and has identified a need for further investigation.¹⁹ While small clinical samples have also provided evidence of an association²⁰ the study of populations, similar as the present report, has advanced an understanding of the association between Asthma and ADHD.²¹ A range of identified factors appear to contribute to the identified association.¹⁶ As with the range of associated mental and physical disorders, the interaction amongst measured variables and factors in ADHD/Asthma study is complex,²² with relatively clear evidence of a genetic association.²³ Genome-wide cross-trait analysis that identifies shared genetics hold the potential to study causal links between asthma and ADHD, among other mental disorders.

As mentioned in the results section, more individuals were diagnosed with ADHD as compared to asthma. In addition, ADHD was more prevalent in males and asthma was more prevalent in females. Results also showed that boys and girls with both ADHD and Asthma are significantly different than boys and girls with ADHD or Asthma alone. These results are consistent with previous literature where ADHD has been

linked to allergic diseases such as asthma.^{7,8}

Asthma also occurred significantly more frequently after ADHD for both males and females, with a higher male occurrence as compared to females. These results are novel, as previous literature has suggested that ADHD symptoms could be a part of asthma symptomatology or as a consequence of its treatment¹⁰ and asthmatic children may have a higher chance to develop ADHD and other behavioral disorders.¹¹

In conclusion, more research is needed to further understand the etiological relationship in relationship to the combined risk of ADHD and asthma. More recent research has investigated the effect of the effect of prenatal stress and suggesting that ADHD children born preterm and/or with mothers who have experienced moderate to acute stress during pregnancy have a significantly higher chance of acquiring asthma.¹³ Research focusing on maternal stress, gestation, and risk for ADHD and asthma in children¹⁵ brings forward a novel model and evidence illustrating the importance of examining early childhood comorbidities. To some extent the more sophisticated population studies²³ provide support of such epigenetic models. The present study establishes the relevance of temporal-hyper-morbidity in any understanding of Asthma and ADHD.

Acknowledgments

None.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Pang Hua Chai. Data curation: David Cawthorpe. Formal analysis: Pang Hua Chai, David Cawthorpe. Methodology: David Cawthorpe. Supervision: Sam Chang, David Cawthorpe. Validation: Sam Chang, David Cawthorpe. Project administration: David Cawthorpe. Writing—original draft: Pang Hua Chai. Writing—review & editing: all authors.

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