**The association between Attention-Deficit/Hyperactivity Disorder (ADHD) and asthma:**

**systematic review with meta-analysis and new data from a Swedish population-based study**

Samuele Cortese, M.D. 1,2,3,4,5\*, Shihua Sun, Ph.D. 6\*, Junhua Zhang, Ph.D. 7, Esha Sharma, M.D.8, Zheng Chang, Ph.D. 6, Ralf Kuja-Halkola, Ph.D. 6, Catarina Almqvist, M.D. 6,9, Henrik Larsson, Ph.D. 6,10\*\*, Stephen V. Faraone, Ph.D. 11\*\*

1 Center for Innovation in Mental Health, Academic Unit of Psychology, University of Southampton, UK, SO17 1BJ

2 Clinical and Experimental Sciences (CNS and Psychiatry), Faculty of Medicine, University of Southampton, UK, SO17 1BJ

3 Solent NHS Trust, Southampton, UK, SO19 8BR

4 New York University Child Study Center, New York, NY, USA, 10016

5 Division of Psychiatry and Applied Psychology, School of Medicine, University of Nottingham, Nottingham, UK, NG72UH

6 Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, SE-171 77 Stockholm, Sweden

7 School of Education, Jiangsu Key Laboratory for Big Data of Psychology and Cognitive Science, Yancheng Teachers University, 224002,Yancheng, China

8 Psychiatric Epidemiology, Department of Public Health, Brown School, Washington University in St. Louis, St. Louis, MO, 63130, USA

9 Pediatric Allergy and Pulmonology Unit at Astrid Lindgren Children’s Hospital, Karolinska University Hospital, SE-171 76, Stockholm, Sweden

10 School of Medical Sciences, Örebro University, 702 81, Sweden

11 SUNY Upstate Medical University, Syracuse, NY, 13210, USA

\*Joint first authors

\*\*Joint last authors

**Address correspondence to:**

Dr. Samuele Cortese

Academic Unit of Psychology and Clinical and Experimental Sciences (CNS and Psychiatry) University of Southampton, Highfield Campus, Building 44, Southampton, SO17 1BJ, UK

Phone: +44 (0) 2380599645

E-mail: samuele.cortese@soton.ac.uk

**RESEARCH IN CONTEXT**

**Evidence before this study**

Recently, there has been an increasing interest in the association between somatic diseases and mental health problems. This line of research has important implications for the clinical management of patients with both conditions and may potentially yield insights into the pathophysiology of psychiatric disorders. With regards, more specifically, to Attention-Deficit/Hyperactivity Disorder (ADHD), a number of studies have been published on its possible association with asthma, the most common respiratory disorder.

Before designing this study, we searched Pubmed (Medline), Ovid databases (PsycInfo, Embase+Embase classic, Ovid Medline), and Web of Knowledge databases (Web of science (Science Citation Index Expanded), Biological abstracts, Biosis, Food science and technology abstracts) for systematic reviews with meta-analysis on the association between ADHD and asthma. We used the following search terms/syntax in Pubmed (and adapted them for the other databases): (ADHD OR attention deficit OR attention-deficit OR attention deficit hyperactivity disorder OR attention-deficit hyperactivity disorder OR hyperkinetic syndrome OR hyperkinetic disorder OR hyperactivity disorder OR hyperactive child syndrome) AND (Asthma OR Asthmatic OR Reactive Airway Disease) AND (meta-analy\* or metaanaly\*). No language, date, or type of document restrictions were applied. We updated the search on October 31st, 2017. We found two systematic reviews with meta-analysis exploring the link between ADHD and asthma. However, evidence from these meta-analyses is inconclusive as to whether the association between asthma and ADHD holds after controlling for a series of possible confounders. The finding of a significant association between asthma and ADHD, even after taking possible confounders into account, would be highly relevant from a public health standpoint, given that it would concern a large number of individuals in need of care.

To fill this gap, we conducted an updated systematic review with meta-analysis and a population-based study, the latter aimed to complement the results of the meta-analysis and address its limitations. Confounding factors controlled for in the population-based study were identified via our systematic review.

**Added value of this study**

Our meta-analysis, based on published and unpublished data from 49 datasets (210,363 participants with ADHD and 3,115,168 without ADHD) showed a significant association between asthma and ADHD considering not only pooled unadjusted odds ratio (OR, 1.66, 95% CI: 1.22 to 2.26) but also adjusted OR (1.53, 95% CI: 1.41 to 1.65). Inevitably, the variables adjusted for varied across the individual studies included in our meta-analysis. The population based study, based on 1, 575, 377 individuals (259, 253 with asthma and 57, 957 with ADHD), showed a significant association even when all the confounders identified via the systematic review were simultaneously adjusted for, with an OR (1.60, 95% CI: 1.57 to 1.63) very similar to the one found in the meta-analysis. Thus, by combining a comprehensive systematic-review and meta-analysis with a large population based study, we were able to rigorously confirm the hypothesis of a significant association between ADHD and asthma.

**Implications of all the available evidence**

Awareness of the association between ADHD and asthma may lead ADHD specialists to promptly refer patients with early forms of asthma and, vice-versa, asthma specialists to promptly refer children with problems of inattention, hyperactivity, or impulsivity for appropriate assessment, reducing the diagnostic delay which is a concerning clinical and public health issue for both ADHD and asthma. This is especially noteworthy given that current guidelines for asthma do not mention ADHD and available guidance on ADHD does not mention asthma. Additionally, study findings lend support to a possible role of allergic mechanisms in ADHD.

**ABSTRACT**

**BACKGROUND**

There is an increasing interest in the links between somatic and mental health conditions. In this context, a number of studies have assessed the possible association between Attention-Deficit/Hyperactivity Disorder (ADHD) and asthma. However, current evidence is inconclusive as to whether this association holds after controlling for possible important confounders. To fill this gap, we conducted a systematic review with meta-analysis and population-based study, the latter aimed to complement the results of the meta-analysis and address its limitations.

**METHODS**

*Systematic review/meta-analysis*

We searched Pubmed (Medline), PsycInfo, Embase+Embase classic, Ovid Medline, and Web of Knowledge databases for observational studies allowing the estimation of the association between asthma and ADHD. No date, language, or type of document restrictions were applied. The last search was conducted on October 31st, 2017. Unpublished data were also gathered from study authors.We considered unadjusted odds ratio (OR) expressing the association between asthma and ADHD as the primary outcome. Secondary outcome was the OR adjusted for confounders that, inevitably, varied across studies, thus representing a limitation of our meta-analysis. Two reviewers extracted data and assessed study quality using the Newcastle Ottawa Scale (NOS). Random effects model was used to calculate pooled OR, and heterogeneity was assessed using I2 statistics. The systematic review is registered with PROSPERO, number CRD 42017073368.

*Population-based study*

We linkedmultiple national registers in Sweden. We calculated the unadjusted OR and the OR simultaneously adjusted for all the confounders identified in a directed acyclic graph (DAG) based on previous studies on asthma and ADHD identified in our systematic review.

**FINDINGS**

*Systematic review/meta-analysis*

From 2,649 potentially eligible de-duplicated citations, 49 datasets, including a total of 210,363 participants with ADHD and 3,115,168 without ADHD, were retained for the meta-analysis. Pooled unadjusted OR (1·66, 95% CI: 1·22 to 2·26; I2 = 99·47) and adjusted OR (1·53, 95% CI: 1·41 to 1·65; I2 = 50·76) indicated a significant association between asthma and ADHD. Possible lack of appropriate representativeness of cases was detected with the NOS in 42 out of 49 datasets.

*Population-based study*

From a cohort of 1, 575, 377 individuals (51·6% male) born between January 01, 1992 and December 31, 2006, 259, 253 (16·5%) individuals with asthma, and 57, 957 (3·7%) individuals with ADHD were included.The crude model adjusting for sex and year of birth showed that asthma was significantly associated with ADHD (OR = 1·60, 95% CI: 1·57 to 1·63). The association remained statistically significant after simultaneous adjustment for all covariates (adjusted OR = 1·45, 95% CI: 1·41 to 1·48).

**INTERPRETATION**

The results of the meta-analysis and the population-based study concur in supporting a significant association between asthma and ADHD, which held even after simultaneously controlling for a number of possible confounders in the population-based study. Awareness of this association may contribute to reduce the concerning diagnostic delay for both ADHD and asthma.

Additionally, study findings lend support to a possible role of allergic mechanisms in ADHD.

**FUNDING**

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**Keywords:** ADHD; asthma; meta-analysis; population-based study

**INTRODUCTION**

Asthma is the most prevalent respiratory chronic disease, estimated to affect around 358 million people worldwide.1 Its prevalence ranges from 3-5% in developing countries to >20% in developed countries.2 Asthma is associated with a high burden of disability and its mean costs per patient per year have been calculated at $USD 1,900 in Europe and at $USD 3,100 in the USA.3 Attention-Deficit/Hyperactivity Disorder (ADHD), characterised by age-inappropriate and impairing levels of inattention and/or hyperactivity/impulsivity, is another major public health issue. It affects around 5% of school-age children4, 5 and 2·5 % of adults6 worldwide. Its annual incremental costs are estimated at $143-$266 billion in the USA7 and are substantial in other countries as well.8, 9

Recently, it has become clear that many conditions classically thought to be nervous system disorders also include alterations in other physiological systems.10 This has prompted a line of research on the possible association between neuropsychiatric and somatic conditions. Within this framework, there has been an increasing body of research on somatic disorders related to ADHD.11 A potential association between ADHD and asthma has been of special interest due to its important clinical, public health, and research implications. From a clinical/public health perspective, awareness of a significant association between these two conditions would prompt ADHD specialists to refer patients with early forms of asthma, and, vice-versa, asthma specialists to refer patients with problems of inattention, hyperactivity, and impulsivity for appropriate assessment, contributing to reduce the diagnostic delay which is currently a concerning issue for both ADHD (e.g.,12, 13 ) and asthma (e.g.,14, 15 ). Given the high prevalence of both disorders, this would benefit a large number of individuals in need of care. From a research standpoint, a significant link between asthma and ADHD would yield insights into the pathophysiology of ADHD, including, in particular, the possible role of allergic mechanisms. Furthermore, a causal role of asthma in ADHD development would strengthen the rationale for compounds acting on immune mechanisms as a possible pathophysiological-based treatment for ADHD, in contrast to the symptomatic drugs currently available.

Evidence from individual studies as well as from two currently available systematic reviews/meta-analyses16, 17 is inconclusive as to whether there is a significant association between asthma and ADHD after controlling for a series of possible confounders. In the first meta-analysis, Miyzaki et al. pooled five cross-sectional studies, and found a significant association between asthma and ADHD.17 However, the authors could not address the effects of possible confounders since unadjusted ORs were pooled. In the second meta-analysis, Van derSchans et al.16 examined longitudinal studies only, to assess to which extent childhood asthma (and other atopic disorders) predicted later ADHD. After pooling six studies (two on overlapping samples) they concluded that early asthma significantly predicts later onset of ADHD. Similarly to the Miyzaki et al.’s meta-analysis, since adjusted and unadjusted ORs were pooled, it is not clear if their findings would hold significant after taking confounders into account. It is also unclear if the available studies are based on representative samples.

Therefore, the hypothesis of a significant association between asthma and ADHD awaits rigorous testing. To fill this gap, we: 1) conducted a comprehensive, systematic review with meta-analysis of the association between asthma and ADHD using available published and unpublished data; 2) draw on data from a Swedish population-based cohort study to address the issues around the possible association between asthma and ADHD that could not be fully addressed with our meta-analysis.

**METHODS**

**Systematic review/meta-analysis**

We followed the recommendations of the Meta-Analysis of Observational Studies in Epidemiology group (MOOSE)18 and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement19 (see appendix 1). The protocol of this systematic review was registered in PROSPERO (CDR42017073368). Data were extracted from the published reports of the studies, or obtained by study authors.

Search strategy

The following electronic databases were searched until October 31st, 2017, with no language/date/type of document restrictions: Pubmed (Medline), Ovid databases (PsycInfo, Embase+Embase classic, Ovid Medline), and Web of Knowledge databases (Web of science (Science Citation Index Expanded), Biological abstracts, Biosis, Food science and technology abstracts). Additional details on the search strategy/syntax, including search terms for each database, are reported in the appendix 2. References of included studies were hand-searched to find any potential pertinent study not detected with the electronic search. Additionally, we systematically contacted study authors when the retrieved paper did not report usable data, but, based on the study design, we deemed they could be available from the authors (e.g., a study collecting information on asthma and ADHD prevalence but not reporting data to calculate the odds ratio, or conference proceedings with pertinent design but not reporting all the data of interest for the present meta-analysis).

Selection criteria

*Type of studies*

Observational studies allowing the estimation of the association between asthma and ADHD, except studies with fewer than ten subjects per arm (because of low statistical power), were included. For longitudinal studies, we extracted data at baseline or at the earliest time point (in the latter case, we included the study in a sensitivity analysis only). When several reports were available from the same cohort, to avoid duplication of data, we included the publication reporting the largest number of subjects.

*Types of participants*

In studies assessing the prevalence of asthma in individuals with ADHD, the population of interest included children and/or adults with either: 1) a categorical diagnosis of ADHD according to the DSM (III, III-R, IV, IV-TR or 5) or Hyperkinetic Disorder (HD) as per the ICD-10 or previous ICD versions; or 2) a definition of ADHD using a symptoms threshold on a validated ADHD rating scale (see appendix 3); or 3) for adults, a positive answer to the question: “Did your doctor ever tell you that you have ADHD?”); or 4) a diagnosis of ADHD recorded in medical files/registries. We excluded studies assessing only symptoms of ADHD, without a diagnosis. We also excluded studies including participants with a diagnosis of Minimal Brain Dysfunction (MBD), which would not be comparable with DSM definitions of ADHD. Studies were included regardless of the past or current treatment of the participants with ADHD drugs (since their potential link with asthma is not established). However, we planned a sensitivity analysis including only studies with ADHD medication-naïve participants. Studies were retained regardless of the setting (clinical or population base) and a subgroup analysis was planned splitting these two types of studies.

In studies assessing the prevalence of ADHD in individuals with asthma, the population of interest included children and/or adults with diagnosis of asthma as follows: 1) based on history and clinical course; 2) based on performing spirometry in patients five years of age and older, as recommended by National Asthma Education and Prevention Program (NAEPP);20 3) Symptom frequency and rescue medication use, as suggested by Childhood Asthma Management Program (CAMP);21 4) Based on questionnaires completed by the parents or caretakers; 5) In children younger than five years of age, since spirometry often cannot be performed in this age group, based on trial(s) of asthma medications.

*Outcomes*

The primary outcome was the unadjusted odds ratio (OR) expressing the crude association between asthma and ADHD. The secondary outcome was the adjusted OR, when available from the publication. Of note, the confounders adjusted for inevitably varied across studies.

Study selection and data extraction

Retrieved references were independently screened and blindly double-coded for eligibility by two study authors (ES, JH). Any disagreement was resolved by two senior authors (SC, SF). If needed, study authors were contacted to gather missing/additional information. Additional details are reported in the appendix 4.

Assessment of study quality/bias

As suggested by the Cochrane collaboration,22 we used the Newcastle-Ottawa Scale (NOS).23 Details on the NOS are reported in the appendix 5.

Statistical analysis

ORs were extracted when reported or calculated from available data in the paper. Meta-analyses used random-effects models because they allow the true population effect size to differ among studies. The primary analysis pooled unadjusted ORs from cross-sectional studies (or data from longitudinal studies at baseline) with *lifetime* or *current* rates (as available) of ADHD and asthma (when data on both *lifetime* and *current* asthma and/or ADHD prevalence were available in the same study, data related to the *lifetime* prevalence were considered for the primary analysis). The secondary analysis pooled adjusted ORs from cross-sectional studies.

We planned the following sensitivity analyses: 1) including only studies with *lifetime* (as opposed to *current*) prevalence of ADHD and asthma 2) including only studies with *current* (as opposed to *lifetime*) prevalence of ADHD and asthma; 3) including only studies with *current* or *past 12 months* (as opposed to *lifetime*) prevalence of ADHD and asthma; 4) including only clinical cross-sectional studies (or baseline data from longitudinal studies); 5) including only population based cross-sectional studies (or baseline data from longitudinal studies); 6) including only cross-sectional studies (or baseline data from longitudinal studies) where the diagnosis of ADHD was made via (semi-)structured interviews according to standardised criteria; 7) adding data from longitudinal (first post-baseline wave) studies to the primary analysis; 8) including only studies with ADHD medication-naïve participants only; 9) adding studies assessing the prevalence of ADHD in individuals with asthma seen in specialised asthma clinics; 10) removing studies based on Swedish samples (to avoid any concern about possible overlap with the empirical study presented in this paper). We also conducted a post-hoc analysis including the Swedish population-based study presented in the next section (excluding from the meta-analysis other Swedish studies retrieved in our systematic review, to avoid population overlap).

Additionally, we planned a meta-regression analysis including unadjusted ORs as outcome and year of study publication, age group (children/adolescents, adults), gender, study setting (clinical, population-based), study continent, and the rating on the NOS as regressors.

The meta-analyses and meta-analytic regressions were weighted by the reciprocal of the variance of the effect size, which gives greater weight to larger studies. We used the I-squared index to assess the heterogeneity of effect sizes. The I-squared index estimates the percentage of variation among effect sizes that can be attributed to heterogeneity.24 A significant I-squared indicates that the degree of heterogeneity is greater than would be expected by chance. We used Egger’s test25 and funnel plots to estimate publication biases. Analyses were performed using Comprehensive Meta-Analysis (http:// [www.meta-analysis.com/index.php)](http://www.meta-analysis.com/index.php%29). Changes/clarifications and post hoc analyses to the pre-registered protocol are reported in the appendix 6.

**Swedish population-based cohort study**

To further investigate the association between asthma and ADHD and rigorously address the role of confounding for the association between asthma and ADHD, we performed a population-based cohort study using data from the Swedish national registers. The study was approved by the Regional Ethics Committee in Stockholm (2013/862-31/5).

A birth cohort of individuals born between January 01, 1992 and December 31, 2006 was extracted from the Swedish Medical Birth Register (MBR). Linkage with other registers was done via unique personal identification numbers for all the cohort members. ADHD was defined as any clinical diagnosis (ICD 9: 314; ICD-10: F90) from the National Patient Register (NPR)26 before December 31, 2013. In line with previous research, asthma was identified using a validated algorithm by either a clinical diagnosis (ICD-9: 493; ICD-10: J45-J46) from the NPR or by filling two prescriptions for asthma medication (Anatomic Therapeutic Codes: R03AC, A03AK, R03BA, and R03DC) from the Prescribed Drug Register.27 ORs with 95% confidence interval (95% CI) were estimated by logistic regression to investigate the association between asthma and ADHD on population level.

We created a list of all covariates used in the individual studies of our systematic review. We then used a directed acyclic graph (DAG)28, 29 to visually describe the causal relationships of the covariates with Asthma and ADHD and to classify the covariates as confounder (common causes of asthma and ADHD), mediators (covariates lying on the causal pathway from asthma to ADHD), and colliders (common results of asthma and ADHD). Further details regarding our DAG are reported in the appendix 7. To estimate the adjusted OR in the population-based study, we only adjusted for covariates that were classified as potential confounders in the DAG, because adjustment for mediators and colliders may introduce bias.30 Two groups of covariates were classified as confounders and consequently adjusted for in the population-based cohort analysis: 1) parental/family level factors, with information obtained from MBR including maternal age at birth, mother’s country of birth (Sweden or other), mother’s cohabitation status at childbirth (cohabiting with father of the child, cohabiting with other people, or living alone), and information from the national health insurance and labour market database (LISA) including highest parental education status (primary and lower-secondary, upper-secondary, post-secondary, or postgraduate) and family disposable income; 2) individual level factors, including sex, year of birth, birth weight and gestational age from MBR, and a diagnosis of eczema in the child from NPR, since it has been suggested that eczema might confound the association between asthma and ADHD.31 Clinical diagnosis of eczema was defined using ICD-codes (ICD-9: 691·8; ICD-10: L20). Sex and year of birth were adjusted in the crude model, and all the above covariates were included in the adjusted model. Birth weight, gestational age in days, maternal age at birth, and family disposable income were treated as continuous variables, whereas year of birth was treated as a categorical variable. We also conducted a sensitivity analysis for the same cohort where asthma was identified only by clinical diagnosis in NPR. Data management and statistical analyses were performed using SAS, version 9·3 (SAS Institute, Cary, NC, USA).

**Role of the funding sources**

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**RESULTS**

**Systematic review/meta-analysis**

The study selection process is shown in appendix figure 1 and reported in detail in the appendix table 1 (list of excluded studies, with reasons for exclusion and list of retained studies). From 2,649 potentially eligible, de-duplicated citations, 49 datasets (reported in 84 references) were retained for the meta-analysis (appendix table 2). Study characteristics are reported in the appendix table 3. Studies retained for the meta-analysis included a total of 210,363 participants with ADHD and 3,115,168 without ADHD. Overall, 57·2% of studies recruited participants from America, 24·5% from Europe, 12·2% from Asia, and 6·1% from Australia. Variables adjusted for in each individual study are reported in the appendix table 4.

Results of the primary and secondary analysis, as well as of sensitivity analyses, are summarised in Table 1 and detailed in the appendix 8. Due to insufficient data, the two following sensitivity analyses could not be performed: 1) including only studies with ADHD medication-naive participants and 2) adding studies assessing the prevalence of ADHD in individuals with asthma seen in specialised asthma clinics.

The primary analysis (unadjusted ORs) indicated a significant association between asthma and ADHD (pooled OR = 1·66, 95% CI = 1·22 to 2·26), although heterogeneity was high (I2 = 99·47) and Egger’s test indicated the possibility of publication bias (p = 0·049). The pooled prevalence of asthma in individuals with and without ADHD was 16·9% (95% CI: 12·0 to 23·0) and 11·5% (95% CI: 9·8 to 13·4 %), respectively. The pooled prevalence of ADHD in individuals with and without asthma was 8·8% (95% CI: 6·2 to 12·2) and 5·6% (95% CI: 4·5 to 7·0 %), respectively. Results were substantially replicated in the analysis of the secondary outcome focusing on adjusted ORs (pooled OR = 1·53, 95% CI = 1·41 to 1·65); for this analysis heterogeneity was lower (albeit still elevated: I2 = 50·76) and Egger’s test was still indicative of publication bias (p = 0·026) (for all funnel plots, see appendix 9). Results pointing to a significant association between asthma and ADHD were also robust to all the 11 sensitivity analyses, except the one restricted to unadjusted ORs from clinical cross-sectional studies only. We also conducted a post hoc sensitivity analysis removing the study by Meyers et al.32, which was the only clinical conducted in an inpatient unit, as opposed to the other clinical studies from outpatient settings, and representing as possible outlier. After removing this study, the association between ADHD and asthma was significant in clinical studies. Of note, heterogeneity decreased to lower values in each of the following: when considering adjusted ORs, splitting cross-sectional studies reporting lifetime from those focused on current prevalence rates of asthma, and, additionally, when pooling separately adjusted ORs in clinical and population based cross-sectional. Importantly, the association between asthma and ADHD remained significant after removing studies based on Swedish samples (OR= 1·62, 95% CI: 1·18 to 2·23). In the post-hoc analysis combining the studies retrieved in our systematic review and our original Swedish population-based study presented in the next sections, we found a pooled unadjusted OR = 1·62 (95% CI: 1·23 to 2·12; I2= 99·62) and an adjusted pooled OR = 1·49 (95% CI: 1·41 to 1·57; I2= 51.05), thus confirming the results of the main analysis.

Results of the meta-regression analysis are reported in the appendix 10. Due to insufficient data, we could not include gender as a covariate. Study setting significantly influenced the pooled OR but, after removing the Meyers et al.32 study, this was not the case any more, consistently with the above mentioned sensitivity analyses. None of the other covariates significantly influenced the pooled OR. NOS ratings for each study are reported in detail in the appendix 11. There were a number of concerns around the quality of the studies, the most relevant one being the possible lack of appropriate representativeness of cases in 42 out of 49 datasets.

**Swedish population-based cohort study**

The overall cohort included 1, 575, 377 individuals (51·6% male). Among them, we identified 259, 253 (16·5%) individuals with asthma, and 57, 957 (3·7%) individuals with ADHD. The prevalence of asthma was significantly higher in individuals with ADHD than in those without [24·8% (95% CI: (24·4%-25·1%) *vs.* 16·1% (16·08%-16·20%), p < 0·001). Additionally, the prevalence of ADHD was significantly higher in individuals with asthma than in those without [5.53% (95% CI: 5·45%-5·62%) *vs.* 3·31% (3·28%-3·34%, p<0·001)].

Results of the evaluation and classification of the covariates via DAG are shown in the appendix table 5 and in Figure 1. In the crude model adjusting for sex and year of birth, asthma was significantly associated with ADHD (OR= 1·60, 95% CI: 1·57 to 1·63). The association remained statistically significant after adjusting for all covariates (adjusted OR= 1·45, 95% CI: 1·41 to 1·48).

For the sensitivity analysis in which asthma was more narrowly defined (i.e., clinical diagnosis of asthma in the NPR), the prevalence of asthma was still significantly higher in individuals with ADHD [n= 11426, 19.71% (19.39%-20.01%)] than in those without ADHD [n=186, 016, 12.26% (12.21%-12.31%)]. Additionally, the prevalence of ADHD was significantly higher in individuals with compared to those without asthma [5.79% (5.68%-5.89%) vs. 3.38% (3.35%-3.41%), p<0.001]. The association between asthma and ADHD was statistically significant in the crude model (OR=1·63, 95% CI: 1·60 to 1·67) as well as in the adjusted model (OR=1·44, 95% CI: 1·40 to 1·48).

**DISCUSSION**

This is the most comprehensive study available on the association between asthma and ADHD. By combining a meta-analysis, based on published and unpublished data, with a population-based cohort study, we were able to rigorously test the hypothesis of a significant association between asthma and ADHD controlling for possible confounders.

Our meta-analysis, comprising 49 datasets, found a significant cross-sectional association between ADHD and asthma, considering both unadjusted and adjusted ORs. Furthermore, our subgroup and meta-regression analyses showed that results were robust to study setting, year of study, age of participants, and continent where the study was carried out. Study quality ratings did not significantly impact on the results. Our findings extend two previous meta-analyses in the field 16, 17 that could not systematically control for confounding factors. Of note, by systematically contacting study authors and gathering unpublished data, we were able to include a substantially larger number of studies in comparison to these previous meta-analyses.

The results of our systematic review/meta-analysis should be considered in the light of its strengths and limitations. As for the strengths, we pre-registered the protocol in a publicly available repository (PROSPERO), reducing the risk of reporting bias. Furthermore, we performed a comprehensive and systematic search of several databases, with no restrictions in terms of language or document type, and we gathered unpublished data from study authors. Additionally, we used a state-of-the-art tool, the Newcastle-Ottawa scale, to assess the quality of the retained studies. However, the present meta-analysis could not fully address the issue of the role of possible confounders since, as reported in the appendix, most potential confounders were missing from several studies. Furthermore, heterogeneity, measured by I2, was significant and high for a number of analyses. Although this does not invalidate the results, it indicates that the pooled OR cannot appropriately summarise results from all datasets. Of note, heterogeneity decreased when splitting studies with lifetime and current prevalence of asthma, suggesting that the temporality in the diagnosis of asthma may be a factor impacting on the heterogeneity of the results. Additionally, heterogeneity decreased when focusing on adjusted ORs in clinical and population based cross-sectional separately, highlighting the relevance of the setting in contributing to the variability of the findings. Moreover, we found possible publication biases for some of our analyses. Finally, the study quality ratings indicated that, for the majority of included studies, poor representativeness was a potential concern.

Despite these limitations, the results of the meta-analysis were remarkably consistent with those from the population-based study. Indeed, the unadjusted OR, even when removing studies from Sweden (1·62, 95% CI: 1·18 to 2·23) from the meta-analysis was very similar to the one from the population-based study (1·60, 95% CI: 1·57 to 1·63). Additionally, the increase in the prevalence of asthma in individuals with vs. those without ADHD was quite similar in the meta-analysis (about 50%) and in the population-based study (about 60%, using clinical diagnosis of asthma in NPR) and these values suggest that our results are not only statistically, but also clinically meaningful.

Importantly, the population-based study allowed us to address the issue of the effects of confounders that we could not fully assess with our meta-analysis. After simultaneous adjustment for the measured confounders (identified based on previous studies on asthma and ADHD) the association between asthma and ADHD remained statistically significant. Of note, eczema was one of the covariates included in the model. This is of interest because some authors have asserted that the link between asthma and ADHD is fully accounted for by earlier eczema,31 which is not supported by our results.

The results of the Swedish population-based study should be considered in the light of possible limitations and should be cautiously interpreted for generalization. Linkage between national registers allowed us to extract information of various potential confounders, yet coverage of the outpatient register, which was initiated in 2001 and holds most of the ADHD diagnoses, is still imperfect.33 ADHD diagnosis was based on ICD codes and may only capture patients with relatively more severe symptoms compared with DSM based identification methods,34, 35 although false-negative misclassification is not likely to explain the observed association. Although both clinical diagnosis based on NPR and medication use based on PDR records were validated as suitable proxies of asthma identification with high quality,27 over-diagnosis of asthma might be possible to some degree in the main analysis where we referred to both NPR and PDR for identifying asthma prevalence. However, the sensitivity analysis where asthma diagnoses were identified only from National Patient Register reported similar values to the ones detected in the meta-analysis when comparing asthma prevalence in people with and without ADHD. Finally, we could not assess further to which extent medications used to treat asthma contributed to ADHD symptoms. However, a previous large population-based study has ruled out the role of asthma treatment as a factor contributing to the association between asthma and ADHD.30 This study confirmed the results of a previous report,36 that failed to find any significant difference in hyperactivity-impulsivity between asthmatic children with or without asthma medication. However, it is possible that the pharmacological treatment of asthma aggravates the severity of the ADHD symptoms.

Both our meta-analysis and the population-based study were not aimed to assess the longitudinal association between asthma and ADHD, which would provide insights into the causal relationship between the two disorders. As such, our study cannot provide insights into the causality of the association. Theoretically, it is possible that asthma contributes to ADHD, ADHD contributes to asthma, ADHD and asthma shares risk factors, or the association is determined by recursive interactions of risk factors and the clinical phenotypes. However, as mentioned, a previous meta-analysis16 focused specifically on longitudinal studies and concluded that childhood asthma significantly predicts future occurrence of ADHD, although the meta-analysis could not fully assess the role of possible confounders and could not test the alternative hypothesis that early ADHD is a predictor of subsequent asthma. Assuming that asthma predicts ADHD, inflammatory mechanisms may mediate this link. An increase in inflammatory cytokines following the allergic inflammation that characterizes asthma may impact specific regions in the prefrontal cortex and neurotransmitter systems that have been implicated in ADHD.31 Furthermore, sleep disruption associated with atopic mechanisms may contribute to ADHD symptoms, although there is evidence that the association remains significant even after controlling for loss of sleep.32

Regardless of the direction of the causality, the significant cross-sectional association that we found, even after controlling for a large number of possible confounders, has important clinical and scientific implications. Indeed, current guidelines for asthma (e.g.,37, 38) do not mention ADHD and available guidance on ADHD (e.g.,39-41) does not mention asthma. As a consequence, practitioners who are involved in the care of patients with ADHD tend to be unaware and do not inquire about asthma when they asses patients referred for ADHD and, vice-versa, professionals who treat individuals with asthma are generally unaware of its association with ADHD. Awareness of the association may lead practitioners who assess children with ADHD to promptly refer the patient to an asthma specialist when they detect early signs/symptoms of respiratory problems, rather than overlooking these signs/symptoms. Conversely, awareness of the association between these two conditions would prompt the asthma specialist to quickly refer their patients to an ADHD specialist when they become aware of problems of hyperactivity/impulsivity/inattention, rather than attributing these symptoms to an adjustment reaction to a chronic disorder or to the effect of the pharmacological treatment for asthma.

This may contribute to reduce the diagnostic delay, which is a concerning clinical and public health issue across many countries both for ADHD and asthma and results in individual and family strain as well as substantial additional health care costs, both for ADHD (e.g.,12, 13 ) and asthma (e.g.,14, 15). Furthermore, it is possible that the effective management of disruptive behaviours associated with ADHD symptoms improves adherence to the treatment of asthma, as reported for other somatic conditions, such as obesity.42

From a scientific perspective, the link between asthma and ADHD lends support to the possible involvement of inflammatory mechanisms in the pathophysiology of ADHD. Further longitudinal studies, rigorously controlling for possible confounders, confirming that asthma increases the risk of ADHD via inflammatory mechanisms, are needed. Overall, our study highlights the importance of considering associated systemic somatic dysfunctions in neurodevelopmental disorders such as ADHD and adds to the current debate around the integration of mental health and general medical care.43

**CONTRIBUTORS**

SC, HL, and SF were involved in the conception of the study, interpretation of the data, and writing the manuscript. SS, JZ, ES were involved data collection and analysis. ZC, RK-H and CA were involved in study conception and interpretation of the data. All authors were involved in revising the article critically for important intellectual content and final approval of the version to be published. SC and SV were responsible for the meta-analysis supervision. HL was responsible for the register-based study supervision and obtaining funding, along with SF. SC and SV are the guarantors of the meta-analysis. HL is the guarantor of the register-based study.

**DECLARATION OF INTERESTS**

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi\_disclosure.pdf (available on request from the corresponding authors) and declare: SF: Dr. Faraone reports grants from Shire, during the conduct of the study; other from Gilford Press, other from Lundbeck, personal fees and other from Rhodes, grants from Arbor, other from KenPharm, personal fees from Ironshore, grants from Shire, personal fees from Akili Interactive Labs, personal fees from Alcobra, personal fees from VAYA, grants from Sunovion, other from Neurovance, other from CogCube, other from NeurolifeSciences, personal fees from Genomind, outside the submitted work; In addition, Dr. Faraone has a patent US patent US20130217707 A1 issued to Upstate Medical University Dr. Faraone and In previous years, he received support from: Otsuka, McNeil, Janssen, Novartis, Pfizer and Eli Lilly. Dr. Faraone receives royalties from books published by Guilford Press: Straight Talk about Your Child's Mental Health, Oxford University Press: Schizophrenia: The facts and Elsevier: ADHD: Non-Pharmacologic Interventions. He is principle investigator of [www.adhdinadults.com](http://www.adhdinadults.com/).

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**Table 1. Summary of the results of the meta-analysis. The first row reports the result of the primary analysis; the other rows report the results of the sensitivity analyses (see text for further details).**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Type of analysis** | **N Datasets** | **N Subjects** | **OR** | **95%CI** | **P** | **Heterogeneity** |  | **Egger's Testpublication Bias** |
| **Q** | **df** | **p** | **I2** | **LLI2** | **ULI2** |  | **t** | **p** |
| Unadjusted ORs [lifetime or current (or not specified) asthma; if both available, lifetime was chosen], cross-sectional studies only  | 46 | 3,316,024 | 1.66 | 1.22-2.26 | 0.001 | 5097.97 | 27 | <0.001 | 99.47 | 99.41 | 99.53 |  | 2.068 | 0.049 |
| Unadjusted ORs [lifetime or current (or not specified) asthma; if both available, lifetime was chosen], cross-sectional studies only without Meyers(2010) | 45 | 597,764 | 1.68 | 1.52-1.86 | 0.000 | 205.841 | 26 | <0.001 | 87.37 | 82.81 | 90.72 |  | 0.017 | 0.987 |
| Unadjusted ORs (lifetime asthma only) from cross-sectional studies | 37 | 431,602 | 1.58 | 1.40-1.78 | <0.001 | 177.15 | 18 | <0.001 | 89.84 | 85.62 | 92.82 |  | 0.832 | 0.417 |
| Unadjusted ORs (current asthma only) from cross-sectional studies | 2 | 26,600 | 2.62 | 1.13-6.04 | 0.024 | 11.97 | 1 | 0.001 | 91.65 | 70.86 | 97.61 |  | - | - |
| Unadjusted ORs (current or past 12 months asthma only), from cross-sectional studies | 6 | 35,891 | 2.48 | 1.81-3.38 | <0.001 | 17.24 | 5 | 0.004 | 71.00 | 32.52 | 87.54 |  | 2.788 | 0.050 |
| Unadjusted ORs, clinical cross-sectional studies only | 7 | 6028 | 1.33 | 1.06-1.66 | 0.014 | 12.10 | 6 | 0.060 | 50.39 | 0.00 | 78.97 |  | 0.079 | 0.940 |
| Unadjusted ORs, population cross-sectional studies only  | 38 | 591,736 | 1.74 | 1.56-1.93 | <0.001 | 189.87 | 19 | 0.000 | 89.99 | 85.99 | 92.85 |  | 0.346 | 0.733 |
| Unadjusted ORs, cross-sectional studies with ADHD diagnosed with (semi)-structured interview only | 6 | 16,033 | 1.75 | 1.52-2.06 | <0.001 | 21.27 | 5 | 0.001 | 76.49 | 47.39 | 89.50 |  | 1.275 | 0.271 |
| Unadjusted ORs, cross-sectional plus longitudinal studies | 48 | 3,322,635 | 1.66 | 1.23-2.23 | <0.001 | 5152.85 | 29 | <0.001 | 99.44 | 99.37 | 99.49 |  | 2.199 | 0.036 |
| Unadjusted ORs, cross-sectional plus longitudinal studies(without Meyers 2010) | 47 | 604,375 | 1.67 | 1.52-1.84 | <0.001 | 206.22 | 28 | <0.001 | 86.42 | 81.61 | 89.98 |  | 0.030 | 0.976 |
| Unadjusted ORs, cross-sectional studies only, excluding studies in Swedish samples | 44 | 3,312,165 | 1.62 | 1.18-2.23 | 0.003 | 5076.21 | 25 | <0.001 | 99.50 | 99.45 | 99.56 |  | 1.975 | 0.059 |
| Unadjusted ORs, cross-sectional studies only, excluding studies in Swedish samples(without Meyers 2010) | 43 | 593,905 | 1.67 | 1.51-1.86 | <0.001 | 202.316 | 24 | <0.001 | 88.14 | 83.74 | 91.34 |  | 0.116 | 0.908 |
| Unadjusted ORs, including Swedish population-based study | 45 | 4,887,542 | 1.62 | 1.23-2.12 | <0.001 | 6930.68 | 26 | <0.001 | 99.62 | 99.59 | 99.66 |  | 0.605 | 0.551 |
| Unadjusted ORs, including Swedish population-based study (without Meyers 2010) | 44 | 2,169,282 | 1.65 | 1.53-1.79 | <0.001 | 207.62 | 25 | <0.001 | 87.97 | 83.58 | 91.17 |  | 0.284 | 0.779 |
| Adjusted ORs, [lifetime or current (or not specified) asthma; if both available, lifetime was chosen], cross-sectional studies only | 30 | 356,999 | 1.53 | 1.41-1.65 | <0.001 | 22.33 | 11 | 0.022 | 50.76 | 4.62 | 74.56 |  | 2.603 | 0.026 |
| Adjusted ORs, (lifetime asthma only) from cross-sectional studies | 27 | 336,737 | 1.46 | 1.41-1.51 | <0.001 | 8.28 | 8 | 0.407 | 3.38 | 0.00 | 66.23 |  | 1.241 | 0.255 |
| Adjusted ORs, (current asthma only) from cross-sectional studies | 4 | 23,158 | 2.40 | 1.84-3.14 | <0.001 | 3.40 | 3 | 0.333 | 11.89 | 0.00 | 88.61 |  | 1.005 | 0.421 |
| Adjusted ORs, clinical cross-sectional studies only | 3 | 17,570 | 3.02 | 1.93-4.72 | <0.001 | 1.50 | 2 | 0.473 | 0.00 | 0.00 | 95.53 |  | 1.315 | 0.414 |
| Adjusted ORs, population cross-sectional studies only | 28 | 356,814 | 1.53 | 1.41-1.65 | <0.001 | 21.19 | 9 | 0.012 | 57.53 | 14.20 | 78.98 |  | 2.593 | 0.032 |
| Adjusted ORs, cross-sectional plus longitudinal studies | 32 | 363,610 | 1.53 | 1.43-1.64 | <0.001 | 23.91 | 13 | 0.032 | 45.62 | 0.00 | 70.86 |  | 3.071 | 0.010 |
| Adjusted ORs, cross-sectional only, excluding studies in Swedish samples | 30 | 359,066 | 1.53 | 1.41-1.66 | <0.001 | 22.24 | 11 | 0.014 | 55.05 | 4.19 | 74.47 |  | 2.532 | 0.032 |
| Adjusted ORs, including Swedish population-based study | 31 | 1,934,443 | 1.49 | 1.41-1.57 | <0.001 | 22.47 | 12 | 0.021 | 51.05 | 0.00 | 71.96 |  | 2.509 | 0.015 |

**Table 2. Characteristics of individuals with and without ADHD in the Swedish population-based cohort study**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Covariates** | **Total****N (%)** | **ADHD****N (%)** | **Non-ADHD****N (%)** | ***p*** |
| Asthma of the child | 259,253 (16·5) | 14,347 (24·8) | 4,406 (16·1) | <0·001 |
| Male | 812,595 (51·6) | 40,348 (69·6) | 722,247 (50·9) | <0·001 |
| Year of birth\* |  |  |  |  |
|  1992-1996 | 565,014 (35·9) | 25,104 (43·3) | 539,910 (35·6) | <0·001 |
|  1997-2001 | 578,989 (36·8) | 24,372 (42·1) | 554,617 (36·6) |  |
|  2002-2006 | 431,374 (274) | 8,481 (14·6) | 422,893 (27·8) |  |
| Birth weight (g) |  |  |  |  |
|  <2500 | 66,035 (4·2) | 3,510 (6·1) | 62,525 (4·1) | <0·001 |
|  2500-3999 | 1,195,750 (75·9) | 42,848 (73·9) | 1,152,902 (76·0) |  |
|  ≥4000 | 313,592 (19·9) | 11,599 (20·0) | 301,993 (19·9) |  |
| Gestational age |  |  |  |  |
|  <=37 weeks | 22,151 (1·4) | 860 (1·5) | 21,291 (1·4) | <0·001 |
|  38-42 weeks | 1,145,754 (72·7) | 39,838 (68·7) | 1,105,916 (72·9) |  |
|  >=43 weeks | 407,472 (25·9) | 17,259 (29·8) | 390,213 (25·7) |  |
| Maternal age at birth\* |  |  |  |  |
|  <20 | 29,860 (1·9) | 2,564 (4·4) | 27,296 (1·8) | <0·001 |
|  20-29 | 784,328 (49·8) | 33,066 (57·1) | 751,262 (49·5) |  |
|  30-39 | 720,802 (45·8) | 21,070 (36·4) | 699,732 (46·1) |  |
|  ≥40 | 40,387 (2·6) | 1,257 (2·2) | 39,130 (2·6) |  |
| Mother’s birth country |  |  |  |  |
|  Sweden | 1,308,370 (83·1) | 51,250 (88·4) | 1,257,120 (82·8) | <0·001 |
|  Other | 267,007 (16·9) | 6,707 (11·6) | 260,300 (17·2) |  |
| Maternal smoking during pregnancy | 79,228 (5·0) | 6,019 (10·4) | 51,938 (8·96) | <0·001 |
| Maternal cohabitation at birth |  |  |  |  |
|  With father of the child | 1,398,943 (94·8) | 47,893 (82·6) | 1,351,050 (89·0) | <0·001 |
|  With other people | 44,410 (3·0) | 3,167 (5·5) | 41,243 (2·7) |  |
|  Living alone | 32,563 (2·2) | 2,782 (4·8) | 29,781 (2·0) |  |
| Parental education |  |  |  |  |
|  Primary and lower-secondary | 76,999 (4·9) | 3,695 (6·4) | 73,304 (4·8) | <0·001 |
|  Upper-secondary | 659,915 (41·9) | 32,614 (56·3) | 627,301 (41·3) |  |
|  Post-secondary  | 801,268 (50·9) | 21,048 (36·3) | 780,220 (51·4) |  |
|  Postgraduate | 37,195 (2·4) | 600 (1·0) | 36,595 (2·4) |  |
| Family disposable income (SEK/month) |  |  |  |  |
|  <5000 | 608,218 (38·6) | 31,333 (54·1) | 576,885 (38·0) | <0·001 |
|  5000-10000 | 835,143 (53·0) | 24,366 (42·0) | 810,777 (53·4) |  |
|  >=10000 | 132,016 (8·4) | 2,258 (3·9) | 129,758 (8·6) |  |
| Eczema of the child | 21,086 (13·4) | 10,179 (17·6) | 200,907 (13·2) | <0·001 |
| Overall | 1,575,377 (100·00) | 57,957 (100·00) | 1,517,420 (100·00) | ---- |

**FIGURE CAPTION**

**Figure 1. Directed acyclic graph for the association between asthma and ADHD**

Note: Age and sex are not presented in the figure.