

Association between childhood asthma and attention deficit hyperactivity or autism spectrum disorders: A systematic review with meta-analysis

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Abstract

Background: Children with asthma are at risk of depression and anxiety and growing evidence suggest they may also be at risk of attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD). Here, we conducted a systematic review with meta-analysis of studies investigating association between asthma and ADHD or ASD in children.

Methods: A comprehensive search using PubMed, EMBASE and Cochrane Library databases was completed in March 2019. Observational human studies published in English, clinic-based or population-based with a healthy comparator group, evaluating asthma-ADHD or asthma-ASD overlap in children 18 years or younger using categorical diagnoses (yes/no) were considered for inclusion. Random effects meta-analysis models were used to analyse data. The Newcastle Ottawa Scale was used to evaluate risk of bias.

Results: A total of 25 asthma-ADHD studies were included of which 17 showed significant positive associations and one a negative association: 17/25 studies were population-based, 19/25 were cross-sectional or cohort studies and 7/25 had a low risk of bias. We performed a meta-analysis of 23 of the studies, which showed a significant association between asthma and ADHD: odds ratio (OR) 1.52 (1.42-1.63), $P < .001$, $I^2 = 60\%$. All studies were adjusted for age and sex and a large proportion; that is, 19/23 were further adjusted for relevant confounders. Seventeen asthma-ASD studies were included, whereof 7 showed a positive association and 3 a negative association; 8/17 were population-based with a cross-sectional study design and 4/17 had a low risk of bias. We performed a meta-analysis of 14 of the studies, which did not show a significant association between asthma and ASD: OR 1.12 (0.93-1.34), $P = .24$, $I^2 = 89\%$. All studies were adjusted for age and sex and 10/14 were further adjusted for relevant confounders.

Conclusions: This systematic review with meta-analyses shows a significant overlap between asthma and ADHD, but not between asthma and ASD in children. Clinicians taking care of children with asthma or ADHD should be aware of such association to aid an early diagnosis and treatment of such comorbidity.

KEYWORDS

ADHD, asthma, autism, children, meta-analysis

1 | INTRODUCTION

Asthma often debuts in early childhood, where more boys than girls are affected.¹ The prevalence has increased in westernized societies² and asthma is considered the most common chronic respiratory disease.³ Children with asthma are at increased risk of depression and anxiety,⁴ which has a negative impact on asthma control⁵ and is recognized as comorbidities in the GINA guideline.⁶ However, growing evidence suggests that asthmatic children might be further burdened by poor mental health status, including attention deficit hyperactivity (ADHD) and autism spectrum disorder (ASD).^{7,8}

ADHD is the most common childhood psychiatric disorder affecting 7% before age 18 years⁹ and is characterized by inattention, impulsivity and hyperactivity with additional deficits in academic and social domains that may persist into adulthood, making early diagnosis and treatment important to decrease the negative effect on development.¹⁰ Three times more males than females are affected and an increase in prevalence is reported¹¹ in parallel with the increase in asthma prevalence.¹² ASD is characterized by persistent impairment in social communication and interaction, restricted and repetitive behaviour, and is also more prevalent in males.¹³ The estimated prevalence of ASD is 1% and also seems to be increasing.¹³

We hypothesized that asthma, ADHD and ASD in childhood are associated traits and the parallel increase in these disorders may be due to common environmental risk factors. A clarification of such association is important for clinical practice as it would highlight a need for early screening, diagnosis and simultaneous treatment of the conditions. We therefore conducted a systematic review with meta-analysis of available studies exploring the relationship between childhood asthma, ADHD and ASD.

2 | MATERIALS AND METHODS

The work is reported according to the PRISMA guidelines.

2.1 | Literature search

PubMed, Embase and Cochrane Library were searched for studies from the inception of each database until March 2019. Two separate searches were performed to examine the relation between childhood asthma and ADHD and asthma and ASD, respectively. The following search terms were used in combination and modified according to each database (see **Online Methods**):

- Asthma, reactive airway disease, wheeze or wheezing.
- Attention deficit disorder with hyperactivity, ADHD, attention deficit, attention deficit, attention deficit hyperactivity disorder, attention deficit hyperactivity disorder, hyperkinetic syndrome, hyperkinetic disorder, hyperactivity disorder or hyperactivity child syndrome.
- Autism spectrum disorder, ASD, autistic disorder, Asperger Syndrome or autism.

The literature searches were limited to papers in English. Both searches were screened and corrected for duplicates. The studies were first scanned on the titles and abstracts and irrelevant studies were excluded, for example, animal studies, studies in adults (≥ 18 years), and other interpretations of the abbreviation ASD. The remaining studies were retrieved as full text and reviewed for eligibility according to the predefined inclusion criteria. Systematic reviews and reference lists of the included papers were also examined to identify additional studies. Eligibility of the studies was evaluated by the authors THK and BC.

2.2 | Inclusion and exclusion criteria

Studies were included according to the following predefined inclusion criteria:

1. Studies about the association between asthma and ASD or ADHD, respectively.
2. Studies explicitly referring to the evaluation of asthma, defined either by parental reports, physician diagnosis, drug prescriptions, or diagnose codes from medical records.
3. Studies explicitly referring to the categorical diagnosis of ASD or ADHD, defined either by parental reports, physician diagnosis, drug prescriptions, or diagnose codes from medical records.
4. Studies concerning children and adolescents (< 18 years).
5. Meta-analyses or original studies.

Predefined exclusion criteria were:

1. Narrative reviews, case-reports, letters, editorials, conference abstracts, animal studies.
2. Studies concerning adults
3. Studies without a comparative reference group
4. No quantitative information available on the relation between asthma and ASD or ADHD for original studies
5. Overlapping studies, for example, studies using the same databases and conducted in the same time frame.

2.3 | Data extraction

Data was predominantly extracted directly from the studies and included information about the first author, year of publication, time and country of performance, study setting, study design, sample size, characteristics of the study population including neurodevelopmental condition, gender distribution, race/ethnicity and age, and methods used to assess the asthma, ADHD and ASD diagnoses. THK and RKV did the data extraction.

2.4 | Meta-analysis

Data on disease prevalence and the estimates of association (odds ratio (OR), prevalence ratio (PR), hazard ratio (HR), standard morbidity ratio (SMR)) were either extracted directly from the studies, calculated from data given in the studies or extracted from the meta-analyses, when data was not accessible elsewhere. The meta-analyses were conducted with R v 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria), using the metagen function from the "Meta" package. We analysed the data with a random effect model. Heterogeneity across the included studies was evaluated using I^2 statistics and publication bias by Funnel plots and Egger's test.

Risk of bias was evaluated using the Newcastle Ottawa Scale (NOS), defining a high-quality study with a low risk of bias by a score of 7-9. Stratified meta-analyses were done for studies with NOS score 0-6 vs. 7-9, clinic-vs. population-based studies, case-control vs. cross-sectional studies, and studies using doctor diagnosis (yes vs. no).

This systematic review with meta-analysis did not have a registered protocol on PROSPERO and did not include communication with study authors.

3 | RESULTS

3.1 | Asthma and ADHD literature search

A total of 1473 studies were identified whereof 355 were duplicates and 1025 were excluded on titles and abstract, leaving 93 papers for full text evaluation. Of these, 24 original studies, two meta-analyses and one additional study from the manual search of references were included^{8,14-39} (Figure S1).

3.2 | Asthma and ADHD study characteristics

Seventeen were population-based and eight were performed in clinical settings. The majority were cross-sectional or cohort studies (Table 1). Four^{8,23,30,33} examined ADHD in children with and without asthma, while the rest investigated asthma in children with and without ADHD. One study with a mean participant age

of 15.7 years did not specify an upper age limit,⁴⁰ whereas the remaining studies investigated participants below age 18. Two studies only included males,^{18,29} while the others had a proportion of males from 51%-86% among ADHD cases and 48%-86% among controls. Race/ethnicity was only reported in eight studies; two only included Caucasians, one only Han Chinese, four mixed ethnicities (mainly Caucasians), and one Australian study only investigated non-Aborigines.

Nine studies defined ADHD based on parental reports of a physician diagnosis, through interviews using questionnaires, for example, A-TAC, CBCL, the SNAP-IV 26 teacher and parent rating scale or a combination of these. Nine were based on a physician diagnosis with one including prescription of ADHD medication. Three were based on diagnose codes from medical records with one including ADHD medication. Two used records of drug prescription and one were based on medical and school records, diagnose codes, parent or teacher questionnaires and diagnostic criteria as defined by DSM-IV.

The diagnosis of asthma was in 13 studies based on a physician diagnosis, diagnose codes from health, medical or billing records or drug prescription. The remaining 12 studies relied on parental reports of physician-diagnosed asthma, using, for example, the ISAAC questionnaire. All of the studies were adjusted for sex and age and 19 of the 23 studies were further adjusted for relevant confounders.

3.3 | Asthma and ADHD overlap

A total of 17 of the 25 studies showed a significant positive association between asthma and ADHD with ORs ranging between 1.38 and 1.69 (Table 2). Of those, 15 were population-based studies, for example, nationwide health surveys and health insurance program, and two were from clinical settings. Most had a cross-sectional design, two were case-control and one a cohort study. Seven of the 17 studies showing positive associations based the ADHD diagnosis on parent information, whereas the rest used physician diagnoses, medical records or drug prescriptions. Half used an asthma diagnosis based on parental information and the rest physician diagnosis, drug prescriptions and/or diagnose codes from medical records or billing data.

Only one study found a negative association between asthma and ADHD, which was a cross-sectional study investigating the prevalence of asthma as a primary diagnosis in hospitalized 6 to 11-year-old children with ADHD.²⁶ The remaining 7 of the 25 studies did not report a significant association although the majority showed ORs above 1, that is, increased risk of asthma.

The meta-analysis by Schans³⁸ included six longitudinal studies and showed significant association between asthma and ADHD with an OR = 1.34 (1.24-1.44). Three of the studies^{8,28,29} were included in our study, all showing a significant positive association, whereas the remaining were excluded due to overlap in datasets or no categorical ADHD diagnosis. The meta-analysis by Miyazaki³⁹ including five

TABLE 1 Asthma-ADHD study characteristics

First author, Year	Country, Time conducted	Setting	Study design	Condition	Number of participants, Case/control	Case/control (Male %)	Race/Ethnicity	ADHD diagnostic method	Asthma diagnostic method	Age, (years)
Alabaf 2019	Sweden, 1992-2006	Nationwide population	Cross-sectional analysis of longitudinal twin study	ADHD	377/22,028	nr/52	nr	Parental telephone interview using A-TAC	Parent report of diagnosis	9 or 12
Yang 2018	Taiwan, 2010	Population	Cross-sectional	ADHD	28/2,744	nr/nr	nr	Parent-reported physician-diagnosed ADHD	Parent-reported physician-diagnosed asthma	3-6
Wang 2018	Taiwan, nr	Population	Case-control	ADHD	216/216	86.11/86.11	nr	Child psychiatrist-diagnosed ADHD according to DSM-IV-TR	Parent reported using the ISAAC questionnaire	8-10 (mean age 9.2)
Chen 2017	Taiwan, 1996-2010	Population	Cross-sectional	ADHD	8,201/32,804	76/76	nr	Psychiatrist-diagnosed by ICD-9-CM	Physician diagnosed by ICD-9-CM	Mean age 15.68
Jameson 2016	USA, 2001-2004	Population	Cross-sectional	ADHD	550/5,933	51.2/51.2	65.5% non-Hispanic White, 15.1% non-Hispanic Black, 14.4% Hispanics, 5% other race	Parent reported from questionnaire	Parent reported	13-18 (mean age 15.2)
Kline-Simon 2016	USA, 2014	Clinical	Cross-sectional	ADHD	11,888/11,888	69.9/69.9	43% White, 8% African American, 13% Asian, 29% Hispanic and 6% other.	ICD-9 codes from electronic health record	ICD-9 codes from electronic health record	11-18 (mean age 14.5)
van der Schans 2016	Netherlands, 1994-2013	Population	Retrospective nested case-control	ADHD	4,257/17,028	76.7/76.7	nr	Record of drug prescription	Record of drug prescription	6-12
Lin 2016	Taiwan, 2010-nr	Population	Cross-sectional	ADHD	176/2,720	nr/nr	Han Chinese	Parent reported using the Chinese version of the SNAP-IV 26 questionnaire	Parent report of diagnosis using the ISAAC questionnaire	9-10

(Continues)

TABLE 1 (Continued)

First author, Year	Country, Time conducted	Setting	Study design	Condition	Number of participants, Case/control	Case/control (Male %)	Race/Ethnicity	ADHD diagnostic method	Asthma diagnostic method	Age, (years)
Strom 2016	USA, 1997-2013	Population	Cross-sectional	ADD/ADHD	17,122/247,115	nr	nr	Parent report of physician diagnosis or just parent reported without physician's verification.	Parent reported	2-17
Turan Akvol 2015	Turkey, nr	Clinical	Nested case-control	ADHD	55/50	83.6/52	nr	Child psychiatrist-diagnosed by DSM-IV	Clinical diagnosis based on ISAAC questionnaire, physical examination, total IgE levels, total eosinophil count and skin prick testing.	7-12 (Mean age 10.1 in cases/8.1 in controls)
Kwon 2014	Korea, nr	Population	Cross-sectional	ADHD	549/3,564	75.2/47.9	nr	Child psychiatrist-diagnosed based on DSM-IV together with epidemiological questionnaires, Computerized Attention Deficit Hyperactivity Disorder Diagnostic System, the abbreviated Conner's Parent Rating Scale (CPRS), and DuPaul's ADHD Rating Scales	Parent reported using the ISAAC questionnaire	7-8 (mean age 7.78 in ADHD/ 7.83 in controls)
Silva 2014	Australia, 2003-2007	Population	Cross-sectional	ADHD	5,363/8,896	78.3/78.0	Non-Aboriginal	Paediatrician or psychiatrist diagnosis by DSM-IV/ICD-10 criteria and prescription of ADHD medication from records	ICD-9 codes from hospital discharge records	<18
James 2013	Australia, 2001-2005	Population	Cross-sectional	ADHD	89/17,296	50.75/50.75	nr	Parent reported from questionnaire	Parent reported using the ISAAC questionnaire	4-6 (mean age 5.03)

(Continues)

TABLE 1 (Continued)

First author, Year	Country, Time conducted	Setting	Study design	Condition	Number of participants, Case/control	Case/control (Male %)	Race/Ethnicity	ADHD diagnostic method	Asthma diagnostic method	Age, (years)
Hak 2013	United Kingdom, 1996-2006	Clinical	Nested case-control	ADHD	884/3,536	100/100	nr	Based on medical records of first-time diagnosis of ADHD and at least one recorded prescription of ADHD drug	Based on codes recorded in the medical history	4-14 (mean age 9.6)
Goodwin 2013	Australia, nr	Population	Cohort	ADHD	51/2,128 at year 5	nr	Population: 84% Caucasian, 4% Aboriginal, 12% other (primarily Asian)	Parent reported using the CBCL	Parent reported of physician-diagnosed asthma	5-17
Karlstad 2012	Norway, 2009-2010	Population	Cross-sectional	ADHD	585 male subjects, 223 female subjects with ADHD and asthma/reference is occurrence of ADHD in the general population by sex and age-specific group (nr)	nr	nr	ICD-10 or ICD-2 codes from reimbursed drug prescriptions	Filled prescription of asthma drugs with reimbursement codes	8-19
Saricoban 2011	Turkey, nr	Clinical	Cross-sectional	ADHD	14/552	nr	nr	Parental questionnaire	Diagnosed according to GINA 2006 guidelines and followed-up for asthma in allergy clinic	6-17
Suwan 2011	Thailand, 2010	Clinical	Case-control	ADHD	40/40	77.5/77.5	nr	Paediatrician-diagnosed according to DSM-IV criteria	Evaluated by history and physical examination	5-15 (mean age 9.0)

(Continues)

TABLE 1 (Continued)

First author, Year	Country, Time conducted	Setting	Study design	Condition	Number of participants, Case/control	Case/control (Male %)	Race/Ethnicity	ADHD diagnostic method	Asthma diagnostic method	Age, (years)
Meyers 2010	USA, 2000-2006	Clinical	Cross-sectional	ADHD	126,056/2,592,204	79.1/57.5	35.05%-46.01% White, 15.47%-17.06% Black, 7.07%-16.6% Hispanic, 25.97%-27.66% Missing, 3.79%-5.33% Other	ICD-9-CM codes extracted from hospital records	ICD-9-CM codes extracted from hospital records	6-11 (mean age 8.74 ADHD/8.28)
Romanos 2010	Germany, 2003-2006	Population	Cross-sectional	ADHD	653/12,665	79.6/48.4	nr	Parent report of ADHD diagnosis based on medical or psychological examination according to ICD-10 criteria.	Parent report of asthma diagnosis based on medical examination	3-17 (mean age 11.8 cases/9.8 controls)
Van den Heuvel 2007	Netherlands, 2001-2003	Clinical	Case-control	ADHD	146/133	80/80	nr	Diagnosed by a clinical psychologist according to DSM-IV	Diagnosed by a paediatrician according to ICD-10.	Mean age 8.7
Calam 2005	United Kingdom, 1999	Population	Cross-sectional	ADHD	122/9,712	nr	nr	Child and adolescent psychiatrist reviewed SDQ-domain (parent, self-, teacher-rated) hyperactivity/inattention and Development and Well-being Assessment	Parent reported	5-15 (mean age 9.87)

(Continues)

TABLE 1 (Continued)

First author, Year	Country, Time conducted	Setting	Study design	Condition	Number of participants, Case/control	Case/control (Male %)	Race/Ethnicity	ADHD diagnostic method	Asthma diagnostic method	Age, (years)
Leibson 2001	USA, 1987-1995	Population	Cross-sectional analysis of birth cohort	ADHD	309/3810	74.1/49.8	nr	Retrospective review based on a mix of clinical diagnosis of ADHD, parent or teacher questionnaires that assess ADHD symptoms and diagnostic criteria of ADHD as defined by DSM-IV.	Diagnosis of asthma documented by physician using diagnostic ICD-9 codes referred from billing data.	5-19 (mean age 15.2 ADHD/ 15.3 controls)
Biederman 1995	USA, nr	Clinical	Cross-sectional	ADHD	140/120	100/100	100% Caucasian, non-Hispanic	DSM-III-R ADHD based on interviews with parent and/or children using the Kiddie SADS-E	Parent-reported asthma	6-17
Flannery 1995	USA, 1959-1966	Population	Cross-sectional analysis of cohort study	ADD	394/9,462	nr	100% white mothers	Not specified, presumably coded data	Ascertained from a general paediatric exam	1-8

Abbreviations: nr, not reported.

TABLE 2 Summary of asthma-ADHD study results.

First author, year	Main result	Other outcomes of interest	Association between asthma and ADHD (95% CI)	Adjusted confounders
Alabaf 2019	Children with ADHD have a higher prevalence of asthma compared to controls, 26% vs. 13% respectively ($P < .001$). Prevalence of asthma in total population is 14.2%.	The co-existence of ASD and ADHD increased the odds for asthma, OR 2.6 (95% CI 1.7-3.9)	OR 2.1 (1.7-2.7)	nr
Yang 2018	Asthma with allergic sensitization is significantly associated with ADHD; asthma without allergic sensitization is not. Prevalence of asthma in total study population is 16.3%.		aOR 3.65 (1.07-12.49) for asthma with sensitization	Age, sex, maternal history of atopic disorders, birth weight, maternal education, duration of breastfeeding and diagnosis of atopic dermatitis at the age of 3 years.
Wang 2018	Higher prevalence of asthma in controls vs. ADHD cases, 28.2% vs. 24.5%. No association between asthma and ADHD.	Children with ADHD showed higher levels of IgE ($P < .001$) and eosinophil count ($P = .001$) than control children.	OR 1.21 (0.79-1.86)	Matched by age, sex, height, weight, BMI and grade level.
Chen 2017	Higher prevalence of asthma in ADHD children vs. controls, 25.2% vs. 18.1% ($P < .001$).		mOR 1.53 (1.44-1.63)	Age, sex and psychiatric comorbidities.
Jameson 2016	Prevalence of asthma in ADHD cases was 26.3% vs. 19.6% in controls. No significant association between ADHD and asthma was found when fully adjusted.		aOR 1.17 (0.80-1.71)	Age, sex, race/ethnicity, parental education, other medical disorders and other DSM-IV disorders.
Kline-Simon 2016	ADHD adolescents had significantly higher odds of having asthma compared to the matched controls.		OR 1.65 (1.53-1.78)	Matched by age, sex and medical facility.
van der Schans 2016	11.8% of cases and 8.7% of controls were exposed to asthma medication in the 3 years before index date. Asthma medication significantly associated with drug-treated ADHD.		aOR 1.4 (1.2-1.5)	Matched by age, sex, regional area code and presence of DM1, epilepsy or depression. Adjusted for allergic rhinitis and eczema.
Lin 2016	Children ever diagnosed with asthma had higher odds of having ADHD. Overall prevalence of lifetime asthma and ADHD in study participants was 9.7% and 6.1% respectively.		aOR 1.59 (1.27-1.99)	Age, sex, parental marriage status, family income, exposure to tobacco at home, maternal smoking during pregnancy, preterm status and city.
Strom 2016	Prevalence of asthma was 15.4% in ADHD cases and 8.7% in controls. Children with asthma had higher odds of ADD/ADHD.		aOR 1.41 (1.34-1.48)	Eczema, sex, age, race, household income, highest level of household education, US vs. foreign birthplace, insurance coverage and healthcare utilization in the past year.

(Continues)

TABLE 2 (Continued)

First author, year	Main result	Other outcomes of interest	Association between asthma and ADHD (95% CI)	Adjusted confounders
Turan Akyol 2015	Higher prevalence of asthma in ADHD group compared to controls, 27.3% vs. 8.0% respectively ($P = .03$).	No significant differences for elevated total IgE levels, eosinophil count and positive skin prick testing between the groups.	aOR 2.93 (0.82-10.47)	Sex and passive smoking.
Kwon 2014	Significantly higher prevalence of asthma in the ADHD group compared to controls, 36.6% vs. 24.3% ($P = .000$). Positive association between asthma life history and ADHD.		OR 1.60 (1.30-1.96)	nr
Silva 2014	Prevalence of asthma was 11.3% in both the ADHD and non-ADHD group. Admission for asthma in children < age 4 years was associated with an increased risk of subsequently being diagnosed with ADHD.		aOR 1.38 (1.24-1.53)	Age, sex, socioeconomic index of disadvantage for areas, marital status, maternal age, birth weight and gestational age.
James 2013	Prevalence of current asthma and ADHD in the study sample is 13.11% and 0.58 respectively. Current asthma is associated with an increased risk of ADHD.		aOR 3.39 (2.04-5.64)	Age, sex, usual general practitioner and BMI categories at school entry.
Hak 2013	Higher prevalence of asthma in ADHD group compared to controls, 34.2% vs. 24.6%. History of asthma was associated with ADHD.		aOR 1.4 (1.2-1.7)	Age, low birth weight and/or preterm delivery, comorbid allergic diseases and general practice.
Goodwin 2013	17.8% of the cohort had an asthma diagnosis at age 5. ADHD prevalence was around 2% at ages 5-14 years and only 1% at age 17 years. Significantly increased odds from ages 5-17 years for ADHD for children with asthma at age 5 years compared to those without.	Moderate asthma was significantly associated with increased odds for ADHD problems ($P < .05$). Remitted asthma, later onset asthma and persistent asthma were all associated with ADHD problems.	aOR 1.84 (1.11-3.02)	Maternal age, maternal education, maternal smoking in pregnancy, maternal smoking at age 5, maternal history of mental health problems at age 8 and family functioning at age 5 years.

(Continues)

TABLE 2 (Continued)

First author, year	Main result	Other outcomes of interest	Association between asthma and ADHD (95% CI)	Adjusted confounders
Karlstad 2012	Higher than expected occurrence of ADHD in people with asthma for both 8- to 19-year-old males and females with the reference being the occurrence of ADHD in the general population by gender and 1-year age-specific groups.		SMR 1.2 (1.1-1.4) for 8- to 19-year-old males and 1.7 (1.5-2.0) for 8- to 19-year-old females.	nr
Saricoban 2011	No significant difference in prevalence of ADHD in children with asthma compared to controls without asthma, 2.7% vs. 1.9% ($p = \text{non-significant}$)		OR 1.42 (0.39-5.15) ^a	-
Suwan 2011	Higher prevalence of asthma in ADHD cases compared to controls, 15.0% vs. 12.5% $P = .75$. Asthma is not significantly associated with ADHD.		aOR 1.37 (0.35-5.33)	Matched by age and sex. Adjusted confounders nr
Meyers 2010	Higher prevalence of asthma in cases with a secondary ADHD diagnosis compared to controls, 4.73% vs. 3.39%.			
Romanos 2010	Increased lifetime prevalence of allergic asthma in children with ADHD compared to non-ADHD children, 8.1% vs. 5.0%, $P < .001$.		aOR 1.23 (0.87-1.72)	Family income, social status, breastfeeding, postnatal health problems, maternal smoking during pregnancy, exposure to tobacco smoke at home, number of siblings, parental history of atopy, the living environment
Van Den Heuvel 2007	Higher prevalence of asthma in the control group compared to the ADHD group, 40% vs. 32%.		OR 0.72 (0.44-1.17) ^a	Matched by age and sex.
Calam 2005	Asthma prevalence was 15.3% in all the participants. Higher prevalence of ADHD in asthmatic children than non-asthmatic children, 2.0% vs. 1.1%, $P = .004$.		OR 1.82 (1.2-2.76) ^a	-
Leibson 2001	Significant higher prevalence of asthma in ADHD group vs. non-ADHD group, 22% vs. 13%, $P < .001$.		OR 1.85 (1.39-2.46) ^a	-
Biederman 1995	No significant higher prevalence of asthma in ADHD group vs. normal controls, 13% vs. 10%, $P = .53$.		OR 1.33 (0.61-2.88) ^a	-
Flannery 1995	Higher prevalence of asthma in children with ADHD compared to normal controls, 6.9% vs. 4.2%.		OR 1.68 (1.12-2.51) ^a	

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; mOR, modified odds ratio, nr, not reported; OR, odds ratio; SMR, Standardized morbidity ratio.

^a Calculated from data available in the study

studies also showed significant association: OR = 1.80 (1.57-2.07). Four of the studies^{22,29,31,35} were included in our study, all reporting increased ORs, but only one reaching significance.³⁵ The fifth study was excluded due to overlap in datasets.

We conducted a meta-analysis of 23 of the 25 included studies, excluding the studies by Karlstad and Meyers, where an OR could not be calculated, showing a significant OR = 1.52 (1.42-1.63), $P < .001$, $I^2 = 60\%$ (Figure 1). A Funnel plot of the study results (Figure 2) did not show publication bias ($P = .30$).

Risk of bias evaluation using NOS showed that 5 of the 23 studies had a low risk of bias (Figure 3). The most common risk concerns were ascertainment of exposure; case/control definition and non-response rate. Stratified meta-analyses of studies with NOS score 0-6 vs. 7-9 showed similar, significant results in both strata with similar I^2 -values. However, excluding the study by Van den Heuvel in the low risk of bias strata resulted in an insignificant heterogeneity ($P = .35$) and a much lower $I^2 = 9\%$ (Figure S2).

Stratified analyses of clinic-vs. population-based studies, case-control vs. cross-sectional studies, and studies using doctor diagnosis (yes vs. no) showed similar, significant results, except for the case-control strata, which included 6 studies (Figures S3-S5).

3.4 | Asthma and ASD literature search

The search yielded 988 studies; 228 were duplicates and 703 were excluded on titles and abstracts, leaving 57 papers for full text evaluation. Of those, 18 studies were included:^{14-16,41-55} 16 original studies, one meta-analysis and one additional study from the references in the included papers (Figure S6).

3.5 | Asthma and ASD study characteristics

Eight studies were population-based using national health survey data, health insurance programs or twin registers, whereas the rest were performed in clinical settings (Table 3). Eight were cross-sectional, seven case-control, and one retrospective and one prospective cohort study were identified. Two studies examined ASD in children with and without asthma,^{43,50} whereas the remaining examined asthma in children with and without ASD. One study¹⁴ with a mean participant age of 17.5 years did not specify an upper age limit and another study⁴² included participants aged 3-26 years. One study only included males in the ASD group,⁵⁴ whereas the other studies included both males and females with the proportion of males ranging from 57% to 88% among ASD cases and from 49% to 83% among controls. Race/ethnicity was given in seven studies, where the majority were Caucasians.

The assessment of ASD varied across the included studies: six were physician-based and four specified that the diagnosis was based on clinical evaluation meeting DSM-IV-TR or DSM-IV criteria and/or using ADOS, ADI-R, Filipek's criteria or CARS. Four studies used parental reports of ASD and one used A-TAC questionnaire in

a parental telephone interview. Two studies used diagnoses from health records.

The assessment of asthma was mostly reported as physician-based, extracted from physician's records, diagnoses from health records or based on a clinical evaluation. Seven studies relied on parental reports of either physician-diagnosed asthma or without further specification.

All of the studies were adjusted for sex and age and 10 of the 14 studies were further adjusted for relevant confounders.

3.6 | Asthma and ASD overlap

Seven of the 17 studies showed a significant positive association between asthma and ASD. Of those, two studies examined the prevalence of ASD in children with and without asthma showing a PR of 1.40 and a HR of 2.01. The remaining five studies showed significant OR ranging between 1.19 and 1.90. All seven studies reporting a significant positive association between asthma and ASD were based on national health surveys, health insurance data or twin registers, five were cross-sectional, one a case-control study and one a cohort study. Four relied on parental reports of both ASD and asthma and three relied on physician diagnoses.

Three studies showed a significant negative association between asthma and ASD. Jónsdóttir⁴⁶ used an electronic health records database in a retrospective longitudinal analysis of children without asthma showing that ASD was protective for new asthma, Zerbo⁴² a case-control study based on diagnose codes from medical records, and Bakkaloglu⁴⁹ a small cross-sectional clinical study where none of 30 children with ASD had asthma compared to 11 with asthma of 39 controls. The remaining 7 studies did not show significant associations between asthma and ASD (Table 4).

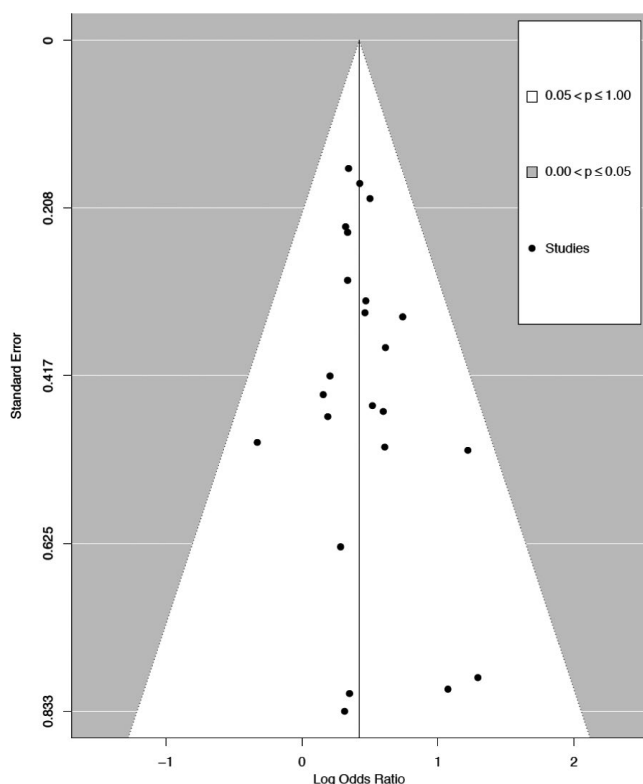
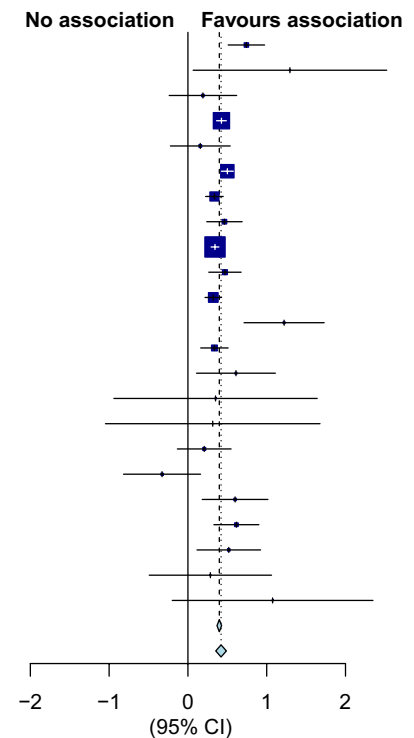
One meta-analysis⁵⁵ from 2016 of ten studies was identified, which showed an increased non-significant risk of asthma among children with ASD: OR of 1.10 (95% CI 0.85-1.43). An analysis stratified by study design showed that for the five cross-sectional studies in the meta-analysis the OR was 1.26 (0.98-1.61), whereas OR was 0.98 (0.68-1.43) for the five case-control studies. Nine of the ten studies in the meta-analysis were included in our study and the missing one was excluded due to overlap in the study groups. Of the eight additional studies we included, four showed a significant positive association, one a negative association and three no association.

We conducted a meta-analysis of 14 of the 17 included studies, excluding two studies by Patel and Tsai where an OR could not be calculated and the study by Jónsdóttir, which estimated the risk of new asthma in children with ASD. The meta-analysis showed a non-significant OR of 1.12 (0.93-1.34), $P = .24$, $I^2 = 89\%$ (Figure 4). A Funnel plot of the study results (Figure 5) did not show publication bias ($P = .26$).

The risk of bias evaluation showed that 4 of the 17 studies had a low risk of bias; that is, NOS score 7-9 (Figure 6). The most common risk concerns were ascertainment of exposure; case/control definition and non-response rate. Stratified meta-analyses of studies with

FIGURE 1 Asthma-ADHD meta-analysis

Source	(95% CI)
Alabaf, 2019	0.74 [0.51; 0.97]
Yang, 2018	1.29 [0.07; 2.52]
Wang, 2018	0.19 [-0.24; 0.62]
Chen, 2017	0.43 [0.36; 0.49]
Jameson, 2016	0.16 [-0.22; 0.54]
Kline-Simon, 2016	0.50 [0.43; 0.58]
van der Schans, 2016	0.34 [0.22; 0.45]
Lin, 2016	0.46 [0.24; 0.69]
Strom, 2016	0.34 [0.29; 0.39]
Kwon, 2014	0.47 [0.26; 0.68]
Silva, 2014	0.32 [0.22; 0.43]
James, 2013	1.22 [0.71; 1.73]
Hak, 2013	0.34 [0.16; 0.51]
Goodwin, 2013	0.61 [0.11; 1.11]
Saricoban, 2011	0.35 [-0.94; 1.64]
Suwan, 2011	0.31 [-1.05; 1.68]
Romanos, 2010	0.21 [-0.13; 0.55]
Van Den Heuvel, 2007	-0.33 [-0.82; 0.16]
Calam, 2005	0.60 [0.18; 1.02]
Leibson, 2001	0.62 [0.33; 0.90]
Flannery, 1995	0.52 [0.12; 0.92]
Biederman, 1995	0.29 [-0.49; 1.06]
Turan Akyol, 2015	1.08 [-0.20; 2.35]
Total (fixed effect)	0.40 [0.37; 0.43]
Total (random effects)	0.42 [0.35; 0.49]
Heterogeneity: $\chi^2_{22} = 54.96$ ($P < .001$), $I^2 = 60\%$	

**FIGURE 2** Funnel plot of asthama-ADHD studies

NOS score 0-6 vs. 7-9 showed similar, non-significant results in both strata with similar, high I^2 -values (Figure S7).

Stratified analyses of clinic-vs. population-based studies, case-control vs. cross-sectional studies, and studies using doctor diagnosis (yes vs. no) showed similar, non-significant results, except for

population-based studies and studies not using doctor diagnoses, where a significant overlap between asthma and ASD was shown (Figures S8-S10).

4 | DISCUSSION

4.1 | Primary Findings

This systematic review of 25 studies investigating the association between asthma and ADHD and 17 studies investigating the association between asthma and ASD in children showed a significant overlap between asthma and ADHD, whereas there was no such overlap between asthma and ASD. This suggests a shared origin of childhood asthma and ADHD and that an increased awareness of behavioural problems should be directed towards children with symptoms of asthma and vice versa to facilitate early diagnosis and treatment of comorbidities.

4.2 | Asthma and ADHD overlap

The results of the 25 identified studies investigating the relationship between asthma and ADHD were quite consistent with 17 showing a significant overlap between the diseases and only one study showing a negative association.²⁶ The results from our meta-analysis of 23 studies confirmed a significant overlap between asthma and ADHD in children, which was also apparent in analyses stratified by low risk of bias, clinic-vs. population-based studies, case-control vs. cross-sectional studies, and studies using doctor diagnoses. The study by Van den Heuvel, which is

The Newcastle Ottawa Scale for quality assessment of observational asthma-ADHD studies																					
		Authors																			
Item		Alabaf, 2019	Yang, 2018	Wang, 2018	Chen, 2017	Jameson, 2016	Kline-Simon, 2016	Van der Schans, 2016	Lin, 2016	Strom, 2016	Turan Akyol, 2015	Kwon, 2014	Silva, 2014	James, 2013	Hak, 2013	Saricoban, 2011	Suwan, 2011	Romanos, 2010	Van den Heuvel, 2007	Calam, 2005	Leibson, 2001
A Selection – case-control																					
Adequate Case Definition		✓	x	✓	x	✓	x	x	✓	x	✓	✓	x	x	✓	✓	✓	x	✓	x	✓
Representativeness of the Cases		✓	✓	✓	✓	✓	✓	✓	✓	✓	x	✓	✓	x	x	x	x	✓	✓	x	x
Selection of Controls		✓	✓	✓	✓	✓	x	✓	✓	✓	x	✓	✓	✓	✓	x	x	✓	x	✓	✓
Definition of Controls		✓	x	✓	✓	x	✓	✓	x	x	x	✓	x	✓	✓	✓	x	✓	✓	✓	✓
A Selection – cohort																					
Representativeness of the Exposed Cohort																					✓
Selection of the Non-Exposed Cohort																					✓
Ascertainment of Exposure																					x
Demonstraion of No Outcome of Interest at Start of Study																					✓
B Comparability																					
Study controls for other variables		x	✓✓	✓✓	✓✓	✓✓	✓✓	✓✓	✓✓	✓✓	✓	x	✓✓	✓✓	✓✓	✓	✓✓	x	✓✓	x	x
C Exposure – case-control																					
Ascertainment of Exposure		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Same method of ascertainment for cases and controls		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Non-Response Rate		x	x	x	✓	x	✓	✓	x	x	x	x	x	x	✓	x	✓	x	✓	x	x
C Outcome – cohort																					
Assessment of Outcome																					x
Follow-Up Long Enough for Outcomes to Occur																					✓
Adequacy of Follow Up of Cohort																					x
Score		5	5	7	7	6	6	7	6	5	3	5	5	6	7	4	5	4	7	3	4

FIGURE 3
 Newcastle Ottawa Scale risk of bias assessment of asthma-ADHD studies

a large sample, clinic-based, case-control study, where ADHD diagnosis was done by a psychiatrist and asthma by a paediatrician, contributed with statistical heterogeneity despite the study had an overall low risk of bias (NOS score of 7). The only limitation of the study is that the control group was children admitted to a paediatric outpatient clinic due to various somatic complaints; that is, not healthy controls, which may have resulted in an increased proportion of asthma diagnoses in the control group. Further, our findings align with the findings from two previous meta-analyses in children^{38,39} that included six and five studies, respectively. A recent meta-analysis including studies of children, adolescents and adults also supported an association between asthma and ADHD.⁵⁶

4.3 | Asthma and ASD overlap

The results of the identified studies examining the relationship between asthma and ASD were inconsistent with several studies showing a significant overlap between the diseases,^{14,15,43,50-52,57}

one study showing that ASD protects against developing asthma,⁴⁶ one showing that asthma protects against developing ASD,⁴² and the remaining studies showing no association. The studies showing a significant overlap between the diseases were all large population-based studies with a total number of participants above 5,000, which may indicate that the lack of association in the remaining studies was a power issue. However, the two studies showing a significant negative association^{42,46} were both based on diagnoses from medical records and had sample sizes above 1,000. The conflicting findings were confirmed in our meta-analysis, which did not support an overall association across the 14 included studies, which is in agreement with the only other meta-analysis investigating this in 10 studies of children.⁵⁵ Our analyses stratified by low risk of bias, clinic-vs. population-based studies, case-control vs. cross-sectional studies, and studies using doctor diagnoses showed similar, non-significant results except for the population-based studies and studies relying on parental reporting, that is, not using doctor diagnoses.

TABLE 3 Asthma-ASD study characteristics

First author, Year	Country, Time conducted	Setting	Study design	Condition	Number of participants, Case/control	Gender, Case/control (Male %)	Race/Ethnicity	ASD diagnostic method	Asthma diagnostic method	Age, (years)
Croen 2019	USA, 2003-2006	Clinical	Case-control	ASD	663/915	82.3/54.2	nr	Clinical evaluation based on ADOS and ADI-R	Parent reported through telephone interview	2-5 at enrolment
Alabaf 2019	Sweden, 1992-2006	Nationwide population	Cross-sectional analysis of longitudinal twin study	ASD	91/22,028	nr/52	nr	Parental telephone interview using A-TAC	Parent report of diagnosis	9 or 12
Jónsdóttir 2017	USA, 2008-2016	Clinical	Retrospective cohort	ASD	464/912	78.7/77.9	69%-69.4% White, 15.8%-16.2% Black, 3.1%-3.2% Asian, 9.1%-9.3% Hispanic/Latino, 11.6%-11.7% Other	ICD-9 and ICD-10 codes from electronic health records	ICD-9 and ICD-10 codes from electronic health records	Mean age 3.4 at entry, 10.2 at completion
Alexeeff 2017	USA, 2000-2012	Clinical	Case-control	ASD	3,911/38,609	81.8/50.7	40.9%-44% White, 7.2%-7.6% Black, 16.9%-19.1% Asian, 21.1%-24% Hispanic, 0.4% Native American, 8.2%-10.2% Other	Physician diagnosed with an ASD case validation exercise	ICD-9 codes from electronic medical records	2-12
Zerbo 2015	USA, 1995-2006	Clinical	Case-control	ASD	5,565/27,825	82/82	nr	ICD-9-CM codes recorded in medical records between the ages of 3 and 18 years	ICD-9 codes recorded in medical records between the ages of 2 and 26 years	3-26 (mean age in 2006 12.15)
Patel 2015	USA, 2007-2012	Population	Cross-sectional	Autism	6,350 with asthma/60,298 controls	56.8/50.7	70.7% White, 17.1% Black, 6.2% Asian, 4.6% Multiple race, 1.4% Other	Parent report of physician diagnosis	Parent report of physician/health professional diagnosis	0-17 (mean age 9.7 for cases, 8.5 for controls)

(Continues)

TABLE 3 (Continued)

First author, Year	Country, Time conducted	Setting	Study design	Condition	Number of participants, Case/control	Gender, Case/control (Male %)	Race/Ethnicity	ASD diagnostic method	Asthma diagnostic method	Age, (years)
Lyall 2015	USA, nr	Clinical	Case-control	ASD	560/391	86/83	nr	Clinical evaluation using ADOS and ADI-R	Parent report of medical history and use of questionnaire and a survey	2-5
Tsai 2014	Taiwan, 2002-2010	Population	Prospective cohort	ASD	2,134 with asthma/8,536 controls	58.9/58.9	nr	Psychiatrist-diagnosed based on ICD-9-CM codes	Physician diagnosed based on ICD-9-CM codes	0-3 (mean age 1.35 at enrolment)
Lin 2014	Taiwan, nr	Population	Cross-sectional	ASD	578/25,688	81/79.4	nr	Psychiatrist-diagnosed based on ICD-9-CM codes	Physician diagnosed based on ICD-9-CM codes	<18 (mean age 12.95 for cases, 13.17 for controls)
Kotey 2014	USA, 2007-2008	Population	Cross-sectional	Autism	1,412/76,545	77.9/51.5	68.6%-71.4% Caucasian, 9.2%-10.1% African American, 8.5%-11.3% Hispanic, 9.9%-10.8% Other	Parent report of diagnosis	Parent reported	3-18 (mean age 10.47 for cases, 10.58 for controls)
Mrozek-Budzyn 2013	Poland, nr	Clinical	Case-control	Childhood or atypical autism	96/192	83.3/80.2	nr	Child psychiatrist-diagnosed based on ICD-10 criteria	Extracted from physician's records	≤ 14 (mean age 7.5)
Chen 2013	Taiwan, 1996-2010	Population	Case-control	ASD	1,598/6,392	79.7/79.7	nr	Diagnoses by board-certified psychiatrist identified by ICD-9-CM codes	Physician diagnosed identified by ICD-9-CM codes	Mean age 17.51 (no range reported)
Schieve 2012	USA, 2006-2010	Population	Cross-sectional	Autism	375/35,775	77.9/48.8	56.9%-68.9% Non-Hispanic White, 11.1%-15.4% Non-Hispanic Black, 13.2%-21.8% Hispanic, 5.9%-6.7% Asian/Other	Parent report of physician diagnosis	Parent reported	3-17

(Continues)

TABLE 3 (Continued)

First author, Year	Country, Time conducted	Setting	Study design	Condition	Number of participants, Case/control	Gender, Case/control (Male %)	Race/Ethnicity	ASD diagnostic method	Asthma diagnostic method	Age, (years)
Magalhaes 2009	Brazil, 2006-2008	Clinical	Cross-sectional	Asperger's Syndrome	15/30	100/nr	nr	Clinical diagnosis meeting DSM-IV-TR and Filipek's review criteria	Clinical evaluation	7-18
Jyonouchi 2008	USA, 2005-2008	Clinical	Case-control	ASD	133/43	88/72.1	72.1%-76% Caucasian, 7%-8.3% African American, 6%-14% Hispanic, 7%-7.5% Asian, 2.3% Other	Diagnosed by paediatricians and/or paediatric neurologists/psychiatrists based on DSM-IV criteria, ADI-R and/or ADOS	NIH guideline criteria	1-17.3
Bakkaloglu 2008	Turkey, nr	Clinical	Cross-sectional	Autism	30/39	nr	nr	Clinical diagnosis based on DSM-IV criteria and rated by using CARS	Physician-filled questionnaire	2-4
Gurney 2006	USA, 2003-2004	Population	Cross-sectional	Autism	483/84,789 Extrapolation to the general paediatric population of the US; 324,000/61,100,000	79/51	67.3%-79% White, 15%-15.3% Black, 1.6%-3.2% Multiracial, 2.6%-4.6% Other, 6.7%-9.9% Missing	Parent report of diagnosis by physician or other health professional	Parent report of diagnosis by physician or other health professional	3-17

Abbreviation: nr, not reported.

TABLE 4 Summary of asthma-ASD study results

First author, Year	Main result	Other outcomes of interest	Association between asthma and ASD (95% CI)	Adjusted confounders
Croen 2019	Prevalence of asthma was 13.09% and 10.33% in ASD cases and controls, respectively. ASD children were not more likely to have a history of asthma.	Maternal asthma at delivery was more prevalent in ASD children vs. control ($P = .05$), aOR 1.26 (95% CI 0.99-1.60). Likewise with maternal lifetime history of asthma, aOR 1.29 (95% CI 1.01-1.64)	aOR 0.98 (0.70-1.39)	Child sex, household income, maternal age, race and education.
Alabaf 2019	Asthma prevalence was 23.1% and 13% in ASD children and controls, respectively ($P < .001$). Prevalence of asthma in total population is 14.2%.	The co-existing of ASD and ADHD increased the odds for asthma, OR 2.6 (95% CI 1.7-3.9)	OR 1.9 (1.1-3.0)	nr
Jónsdóttir 2017	Prevalence of asthma ever was 7.5% vs. 14.5% in children with ASD at entry compared to children without. Odds of an asthma diagnosis is reduced in children with ASD		aOR 0.44 (0.28-0.69)	Matching by age, date of initial visit, sex, race/ethnicity, insurance status and geographic location. Adjusted for observation period and clinical site.
Alexeeff 2017	Prevalence of asthma in children later diagnosed with ASD was 25.93% vs. 24.77% in controls. Children later diagnosed with ASD are not more likely than controls to be diagnosed with asthma in years preceding ASD diagnosis.		aOR 0.94 (0.86-1.01)	Matching by site and age. Adjusted for sex, maternal race, level of education and household income.
Zerbo 2015	Asthma was less frequently diagnosed in ASD children vs. controls (13.7% vs. 15.9%)		OR 0.83 (0.76-0.90)	Matched for age, sex and total membership months.
Patel 2015	Children with asthma had higher prevalence of autism than children with no asthma (1.5% vs. 0.9%). Prevalence of asthma in the total study sample was 10%.		Adj. PR 1.4 (1.2-1.7)	Age, sex, race and socioeconomic status.
Lyall 2015	No difference in prevalence of asthma in cases and controls (16% in both, $P = .93$)		OR 0.86 (0.57-1.30)	Matched by age, sex and geographic area. Adjusted by child recurrent infections in early life and maternal smoking.
Tsai 2014	Asthmatic infants and children had a significantly higher incidence of ASD in the 8-year follow-up period compared to non-asthmatic controls (1.3% vs. 0.7%, $P = .007$)		Adj. HR 2.01 (1.19-3.40) for developing ASD among asthmatic children.	Age, sex, level of urbanization and allergic comorbidities.
Lin 2014	Significantly higher prevalence of asthma in ASD children compared to controls (25.3% vs. 20.7%, $P < .001$)	The co-existing of ASD and ADHD showed increased prevalence of asthma compared to controls (33% vs. 20.7%, $P < .001$)	OR 1.29 (1.07-1.56) ^a	Age, sex and level of urbanization.

(Continues)

TABLE 4 (Continued)

First author, Year	Main result	Other outcomes of interest	Association between asthma and ASD (95% CI)	Adjusted confounders
Kotey 2014	Autistic children were more likely to have asthma compared to non-autistic children. 14.52% and 1.81% of the study population had asthma and autism, respectively.		aOR 1.19 (1.03-1.36)	Age, sex, body mass index, race, history of brain injury, exposure to second-hand smoke and socio-economic status.
Mrozek-Budzyn 2013	No significantly higher prevalence of asthma in autistic children compared to controls (5.2% vs. 4.7%, $p = \text{non-significant}$)		OR 1.12 (0.36-3.43) ^a	Matched by age, sex and physician's practice.
Chen 2013	Significantly higher prevalence of asthma in ASD cases compared to controls (23.3% vs. 15.3%, $P < .001$). The mean age was 17.51 and included both children and adults		Modified OR 1.74 (1.51-1.99)	Age and sex.
Schieve 2012	Increased prevalence of asthma in autistic cases compared to controls (21.6% vs. 13.8%)		aOR 1.6 (1.2-2.2)	Age, sex, race/ethnicity and maternal education.
Magalhaes 2009	High prevalence of allergic symptoms including asthma in Asperger cohort, but no association between asthma individually and Asperger's Syndrome.	Total serum IgE was elevated in 13 Asperger patients and they had significantly different level when compared to normal group ($P < .001$), but not when compared to atopic group ($P = .6582$). Same picture observed when looking at the eosinophil count.	OR 0.31 (0.06-1.64) ^b	Age, sex and socio-economic status.
Jyonouchi 2008	14.3% of children with ASD had asthma compared to 18.6% in controls. No association between autism and asthma.		OR 0.73 (0.29-1.81)	Age and sex.
Bakkaloglu 2008	Fewer autistic children had symptoms of respiratory allergy (wheezing or asthma) compared to controls, 0% vs. 28%, $P < .005$.		OR 0.04 (0.00-0.72) ^b	Age and sex.
Gurney 2006	Higher prevalence of asthma in children with autism compared to children without, 17.6% vs. 13.5% respectively. No association between asthma and autism		aOR 0.9 (0.6-1.4)	Age, sex, primary language spoken in the home, insurance status and household educational attainment.

Abbreviation: aOR, adjusted odds ratio; CI, confidence interval; HR, hazard ratio; nr, not reported; OR, odds ratio; PR, prevalence ratio.

^a Calculated from data available in the study

^bOR and 95% CI as found in the meta-analysis from Zheng et al[45]

Source	(95% CI)
Croen, 2019	-0.02 [-0.36; 0.32]
Alabaf, 2019	0.64 [0.14; 1.14]
Alexeeff, 2017	-0.06 [-0.14; 0.02]
Zerbo, 2015	-0.19 [-0.27; -0.10]
Lyall, 2015	-0.15 [-0.56; 0.26]
Lin, 2014	0.25 [0.07; 0.44]
Kotey, 2014	0.17 [0.03; 0.31]
Mrozek-Budzyn, 2013	0.11 [-1.01; 1.24]
Chen, 2013	0.55 [0.42; 0.69]
Schieve, 2012	0.47 [0.17; 0.77]
Magalhaes, 2009	-1.17 [-2.83; 0.48]
Jyonouchi, 2008	-0.31 [-1.23; 0.60]
Bakkaloglu, 2008	-3.22 [-6.51; 0.07]
Gurney, 2006	-0.11 [-0.53; 0.32]
Total (fixed effect)	0.03 [-0.01; 0.08]
Total (random effects)	0.11 [-0.07; 0.29]
Heterogeneity: $\chi^2_{13} = 116.47$ ($P < .001$), $I^2 = 89\%$	

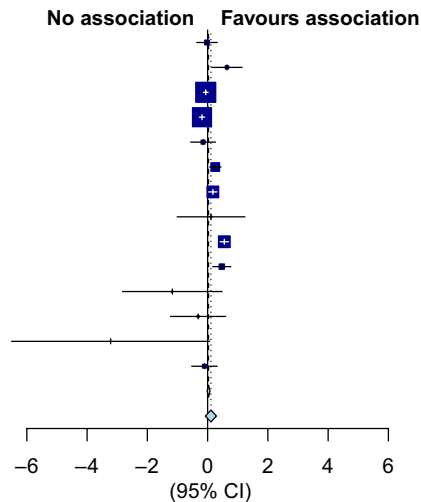


FIGURE 4 Asthma-ASD meta-analysis

4.4 | Strengths and limitations

The conflicting results particularly in the asthma-ASD studies might be attributable to different methods to assess the diagnoses, different study settings, design, sample size, age range of the patients and adjustments for possible confounders. Importantly, not all studies were designed to investigate the association between childhood asthma and ASD, which was therefore added as post-hoc analyses, for example, Croen⁴⁵ focused on maternal immune disorders and offspring ASD while Jyonouchi⁵³ focused on innate immunity in a subset of children with ASD and neither of the studies showed a significant

association between asthma and ASD. The asthma-ADHD association analyses were also post-hoc in some of the included studies, which had a primary focus on, for example, atopic dermatitis and ADHD,^{25,31} use and cost of medical care among children with ADHD,²⁷ and immune disorders among children with neurodevelopmental disorders, special talents and non-right handedness^{17,18}; however, most of these studies showed a significant overlap between asthma and ADHD.

The methods to define the diagnoses of asthma, ADHD and ASD varied widely among the studies ranging from register data on diagnoses and medical treatment, parental reporting, and various clinical approaches, which were not all consistent with gold standard diagnostic procedures. These differences constitute a risk of misclassification that may have affected the association analyses. It is well-known that parental reporting of their child's health status are subject to recall bias, misclassification and underestimation of both asthma⁵⁸ and hyperactivity.⁵⁹ The included studies may be subject to diagnostic heterogeneity as only two of the studies using a physician diagnosis of asthma specified following recognized international guidelines.^{23,53} Further, not subgrouping the asthmatics as atopic vs. non-atopic may be a limitation since Kohlboeck⁶⁰ found that the association between asthma and emotional symptoms depended on atopic status. Interestingly, we observed a significant overlap between asthma and ASD in the strata of studies not using a doctor diagnosis of ASD, for example, studies relying on parental report alone or diagnosis based on prescription record, which might be influenced by inherited behavioural traits or health-seeking behaviour that could confound the relationship between reported health conditions.

The diagnosis of both ADHD and ASD can only be made by a psychiatrist or a paediatrician with sufficient expertise based on a full clinical, psychosocial and developmental assessment combined with observer reports from parents and schools. Screening instruments are considered useful but cannot stand alone, which challenge the reliability of some included studies.^{8,15,45,47,53} Including prescriptions of ADHD medication is a strength as this is restricted to specialists in many countries; however, not all children with ADHD receive pharmacological treatment. In general, studies performed in clinical settings are less prone to misclassification compared to

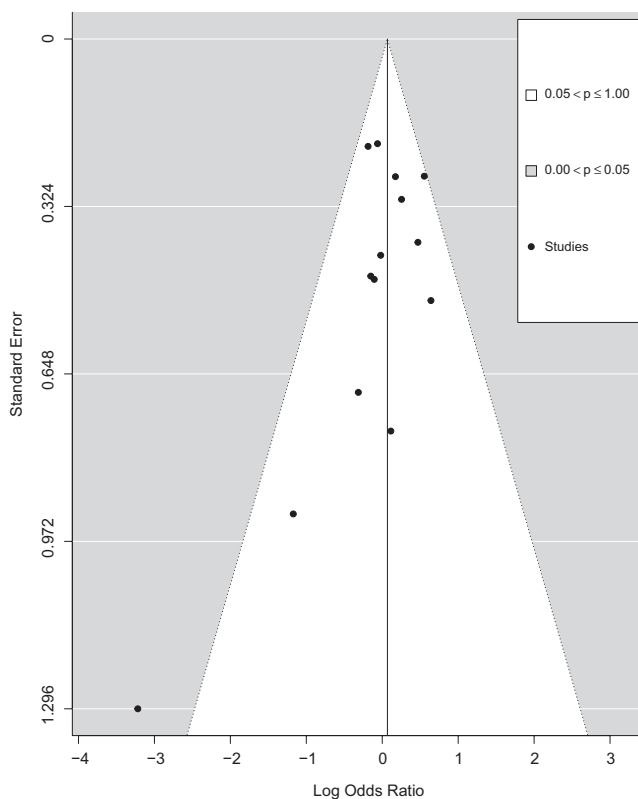


FIGURE 5 Funnel plot of asthma-ASD studies

The Newcastle Ottawa Scale for quality assessment of observational asthma-ASD studies															
		Authors													
	Item	Croen, 2019	Alabaf, 2019	Alexeef, 2017	Zerbo, 2015	Lyall, 2015	Lin, 2014	Kotey, 2014	Mrozek-Budzyn, 2013	Chen, 2013	Schieve, 2012	Magalhaes, 2009	Jyonouchi, 2008	Bakkaloglu, 2008	Gurney, 2006
A	Selection														
	Adequate Case Definition	✓	✓	✓	✗	✓	✗	✗	✓	✗	✗	✓	✓	✓	✗
	Representativeness of the Cases	✓	✓	✓	✓	✓	✓	✓	✗	✓	✓	✗	✗	✗	✓
	Selection of Controls	✓	✓	✓	✗	✓	✓	✓	✗	✓	✓	✗	✗	✗	✓
	Definition of Controls	✓	✓	✓	✓	✓	✓	✓	✗	✓	✓	✗	✗	✗	✓
B	Comparability														
	Study controls for other variables	✓	✗	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
C	Exposure														
	Ascertainment of Exposure	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✓	✓	✓	✗
	Same method of ascertainment for cases and controls	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Non-Response Rate	✗	✗	✓	✓	✗	✓	✗	✗	✓	✗	✓	✗	✗	✗
	Score	6	5	8	6	7	7	6	4	7	6	5	5	5	6

FIGURE 6 Newcastle Ottawa Scale risk of bias assessment of asthma-ASD studies

population-based register studies, but may not be able to detect a significant disease overlap due to smaller sample sizes that reduce statistical power,^{18,32,35,48,53,54} which may have been the case for the asthma-ASD analysis as we found a significant overlap in the strata of population-based studies.

Many of the studies included children and adolescents in a wide age range, which is important to note since asthma and ASD often debut in early childhood, whereas the ADHD diagnosis usually is established later in childhood and adolescence, which could be a limitation to asthma-ADHD studies only including younger children. The change in gender distribution during puberty concerning asthma requires inclusion of both males and females as pure male studies might have over- or underestimated the asthma prevalence, which could compromise analysis of disease overlap.^{18,29,54}

Some studies managed potential confounders through matching of cases and controls and others adjusted for these in multivariable regression analyses. There was no clear consistency across the studies regarding confounders, which included, for example, maternal age at birth, smoking during pregnancy, gestational age and birth weight. Many studies did not deal with this, which is a major limitation for

investigating disease overlap as common risk or protective factors could explain both overlap and lack of overlap. All of the abovementioned limitations might be the reason for significant heterogeneity between studies, which was observed for both the ADHD and ASD analyses.

Although the methods of this systematic review with meta-analysis were predefined, it is a limitation that it did not have a registered protocol on PROSPERO.

4.5 | Interpretation

The significant association between childhood asthma and ADHD in our meta-analysis may be due to a shared disease mechanism related to a perturbed immune response in early life. The airway inflammation seen in asthma is often a type 2 inflammation, involving T-helper 2 cells, mast cells and eosinophils and is characterized by cytokines such as interleukin (IL)4, IL5, IL13 and elevated immunoglobulin E (IgE) levels. In children with ADHD, it has been shown that symptom scores of the major symptom clusters are associated with levels of

proinflammatory cytokines, suggesting that a dysregulated inflammatory pathway is involved in the pathophysiology.⁶¹ In the same study it was shown that the total ADHD symptom score was associated with increasing levels of IL13⁶¹ and another study demonstrated increased levels of IgE and eosinophils in ADHD cases compared to controls;²⁰ that is, markers of type 2 inflammation characteristic of asthma. Further, studies have shown overlap between ADHD and early-onset, severe atopic dermatitis,^{25,31} which is also often characterized by type 2 inflammation. Finally, systemic low-grade inflammation has been demonstrated in children with atopic diseases,⁶² and also appears to affect neurodevelopment and cognitive function.⁶³

The shared propensity to develop inflammation seen in asthma, neurodevelopment and ADHD may be caused by common risk factors such as preterm delivery and other inflammatory insults, deficient micronutrient supply during pregnancy and infancy and the composition and development of the gut microbiome in early life. A perturbed gut microbiome during the first year of life has been associated with immune dysregulation and risk of asthma⁶⁴ and the gut microbiome also seems to affect the brain and behaviour, possibly leading to neuropsychiatric disorders like ADHD via the gut-brain axis.⁶⁵ Supply of micronutrients like vitamin D and n-3 long-chained polyunsaturated fatty acids may constitute a common risk factor for asthma and ADHD since studies have shown the importance of these in both early childhood asthma^{66,67} and neurological development.^{63,68} Shared genetic factors may also contribute to the observed overlap between asthma and ADHD.^{69,70}

Our demonstration of a likely association between asthma and ADHD across 23 studies should encourage clinicians to pay special attention to early symptoms of such comorbidity. Further, asthma and ADHD guidelines should acknowledge such comorbidity. An increased attention to the overlap between asthma and ADHD may lead to faster referrals, diagnostic clarification and treatment initiation, leading to less impairments, better symptom control, prognosis and quality of life for the affected children. Caregivers of children with both asthma and ADHD reported lower quality of life compared to caregivers of children with a similar asthma severity but without ADHD.⁷¹ The recognition of association between ADHD and asthma may be important for the child's future mental health as adolescents with ADHD have an increased risk of developing both unipolar and bipolar depression later in life with a further increased risk from comorbid asthma.⁷² Overall, our findings support the existence of a broad overlap between asthma and mental health disorders, which currently includes both depression, anxiety and ADHD.

4.6 | Conclusion

This systematic review with meta-analysis shows a greater likelihood of children with asthma also having ADHD and vice versa, but there was no evidence of an association between childhood asthma and ASD. These findings should lead to an increased awareness among clinicians taking care of children with asthma or ADHD to facilitate early diagnosis and treatment of such

comorbidity, which should be implemented in asthma and ADHD guidelines.

CONFLICT OF INTEREST

All authors declare no potential, perceived, or real conflict of interest regarding the content of this manuscript. The funding agencies did not have any role in design and conduct of the study; collection, management, and interpretation of the data; or preparation, review, or approval of the manuscript. No pharmaceutical company was involved in the study.

AUTHOR CONTRIBUTIONS

The guarantor of the study is BC, from conception and design to conduct of the study and acquisition of data, data analysis and interpretation of data. THK and RKV have analysed the data and written the first draft of the manuscript. All co-authors have provided important intellectual input and contributed considerably to the analyses and interpretation of the data. All authors guarantee that the accuracy and integrity of any part of the work have been appropriately investigated and resolved and all have approved the final version of the manuscript. The corresponding author had full access to the data and had final responsibility for the decision to submit for publication. No honorarium, grant, or other form of payment was given to any of the authors to produce this manuscript.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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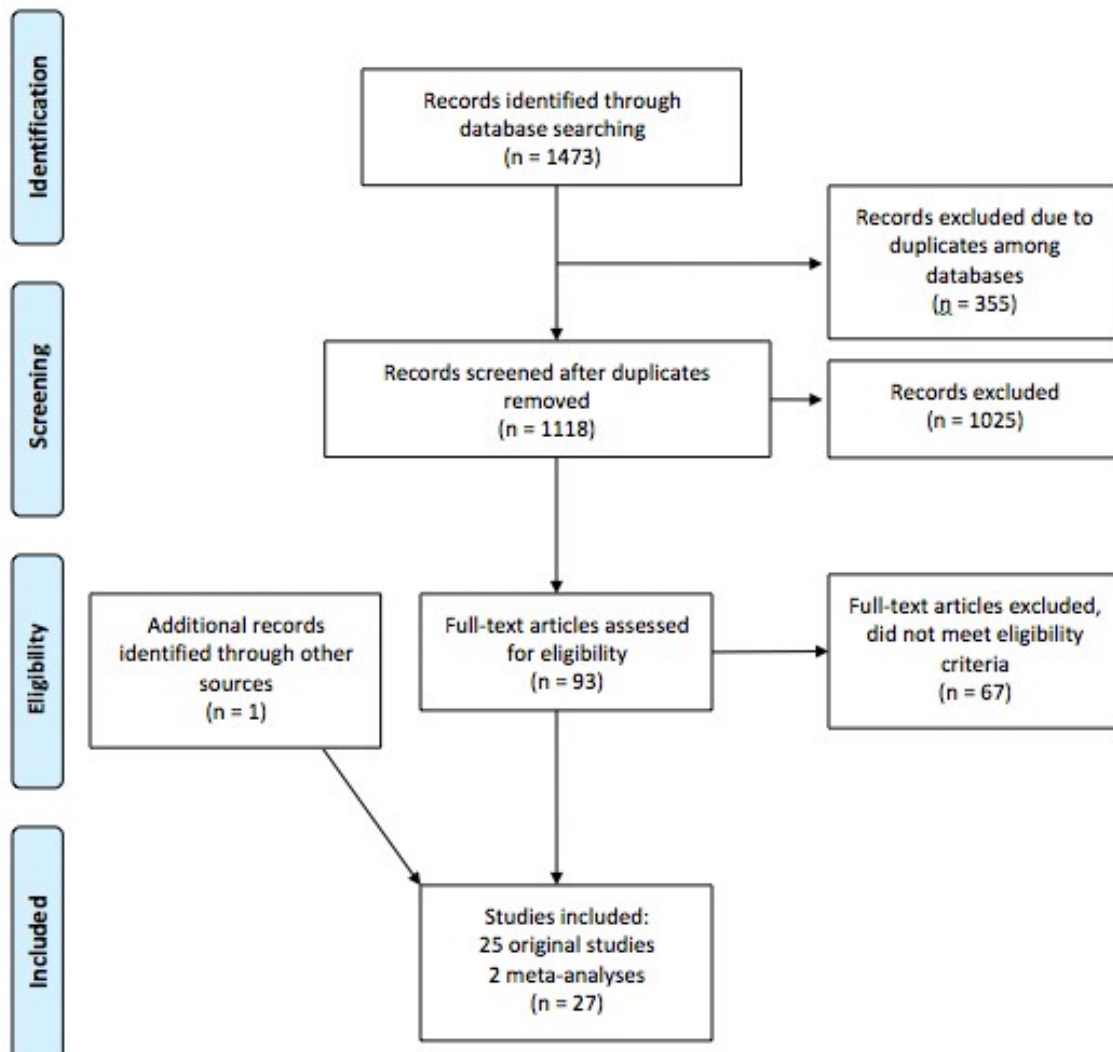
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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

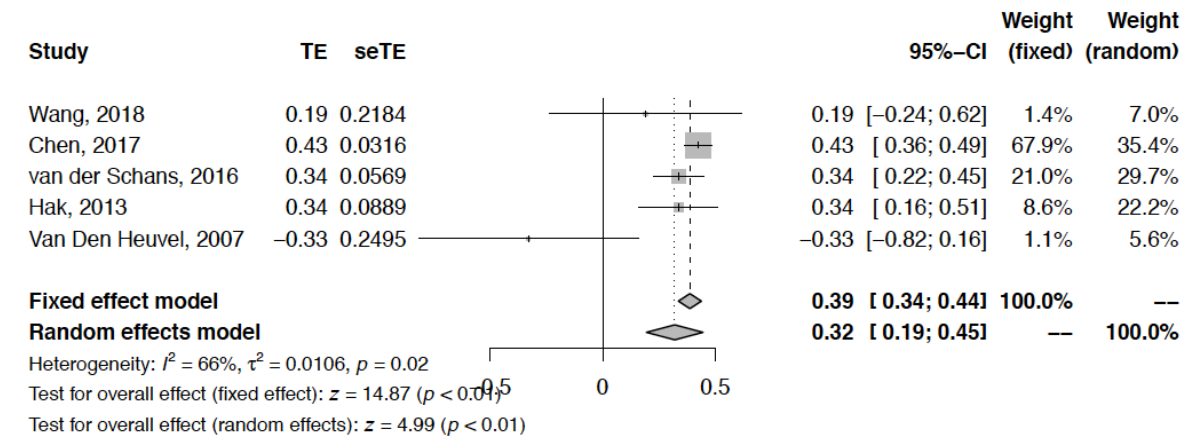
How to cite this article: Kaas TH, Vinding RK, Stokholm J, Bønnelykke K, Bisgaard H, Chawes BL. Association between childhood asthma and attention deficit hyperactivity or autism spectrum disorders: A systematic review with meta-analysis. *Clin Exp Allergy*. 2020;00:1–25. <https://doi.org/10.1111/cea.13750>

eFigure 1

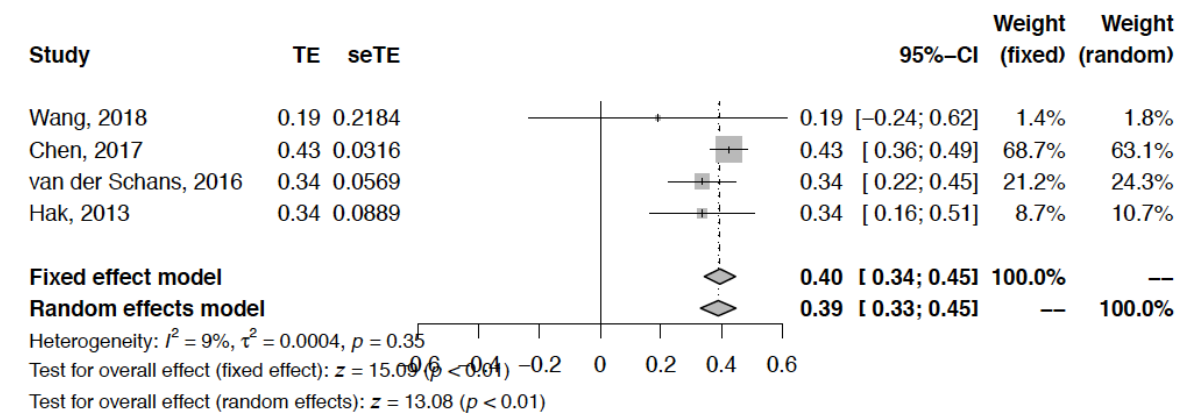


eFigure 2

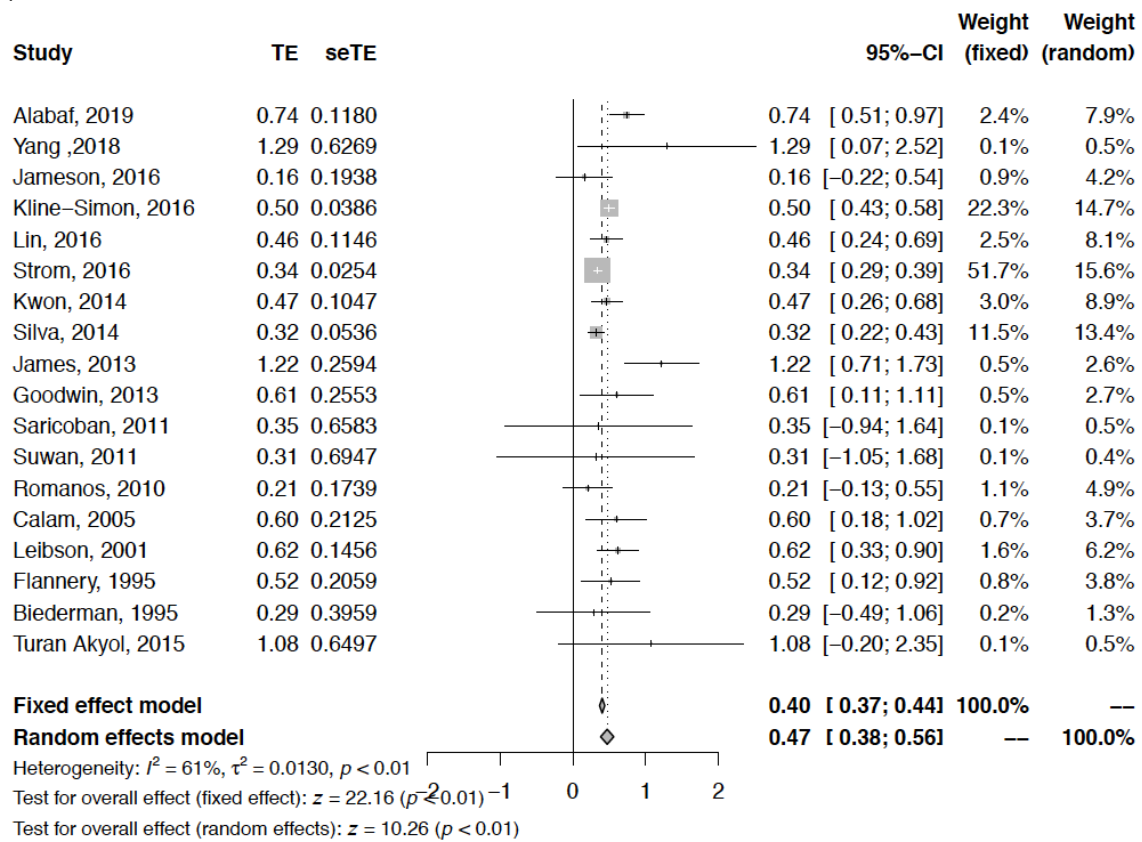
A)



B)

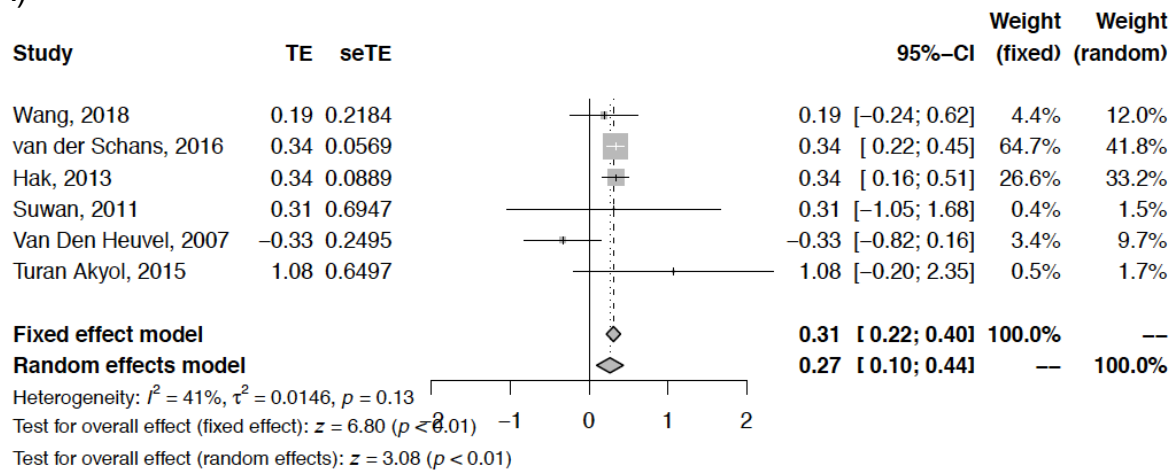


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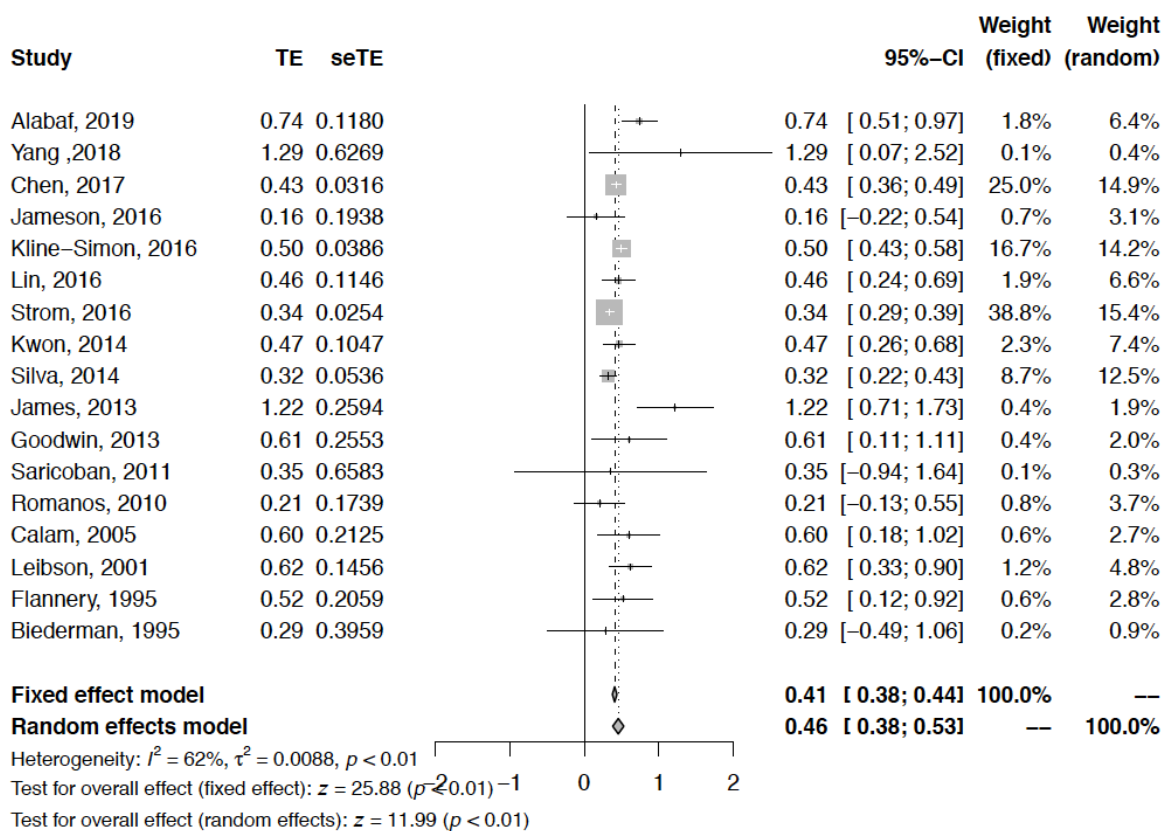


eFigure 3

A)

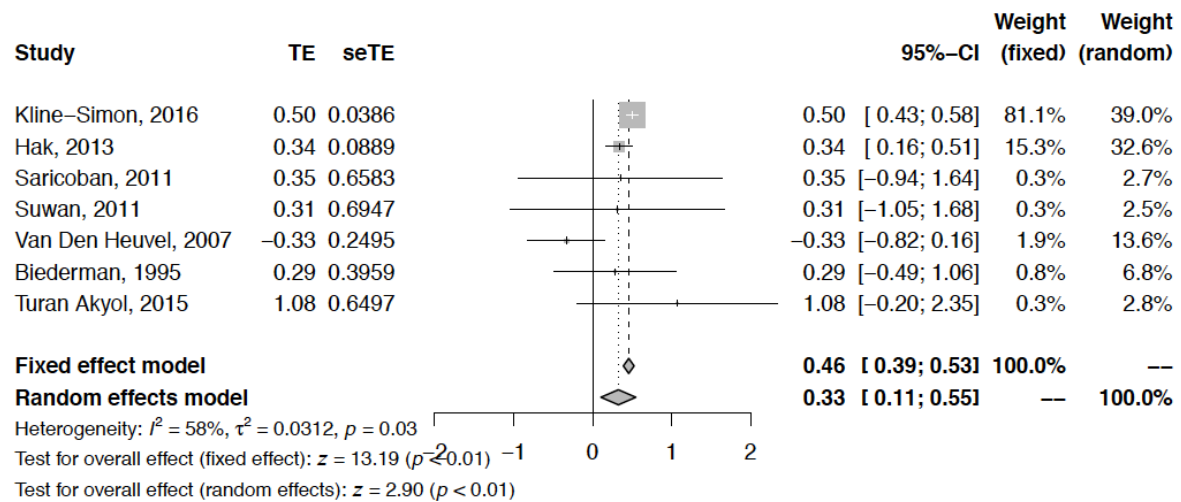


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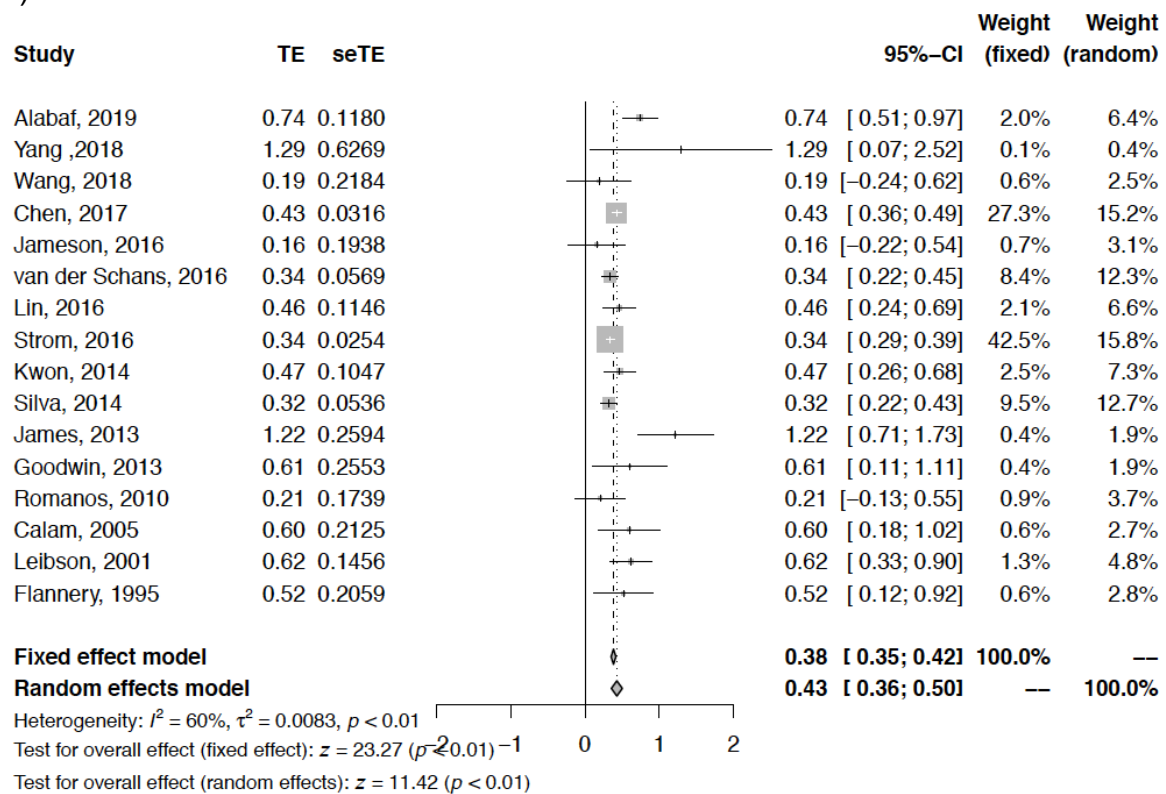


eFigure 4

A)

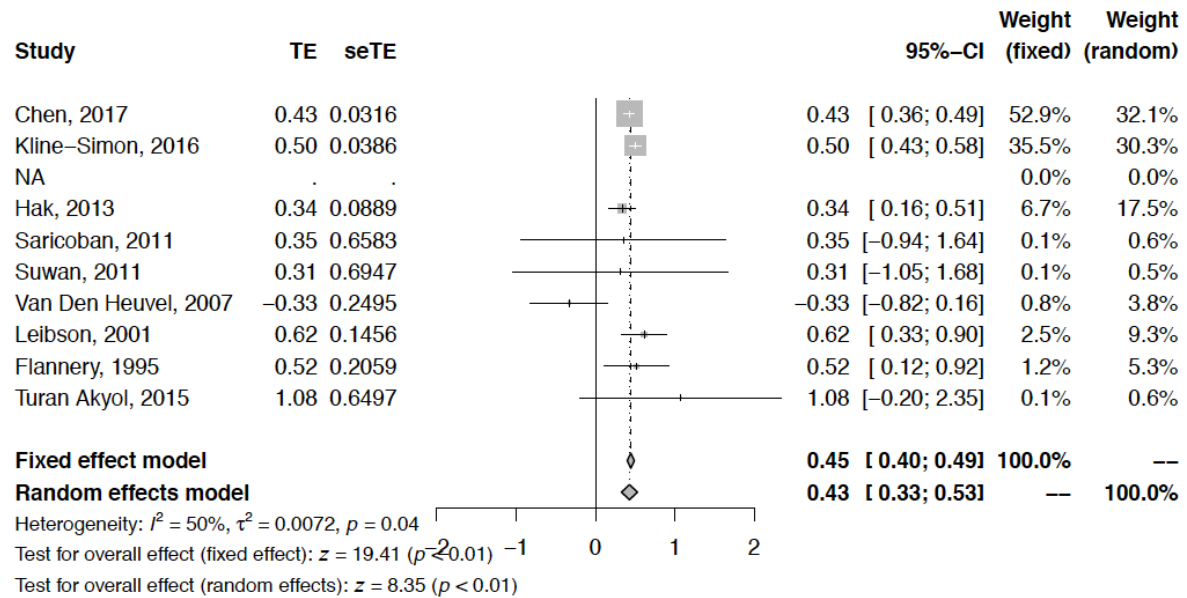


B)

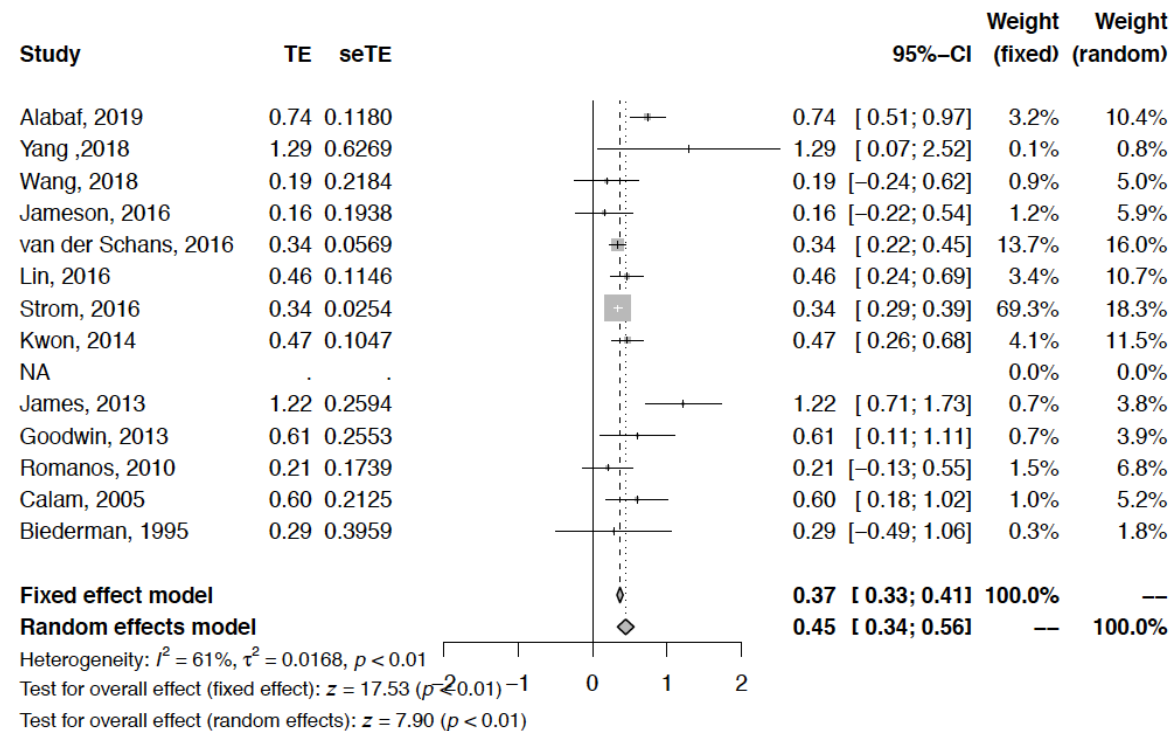


eFigure 5

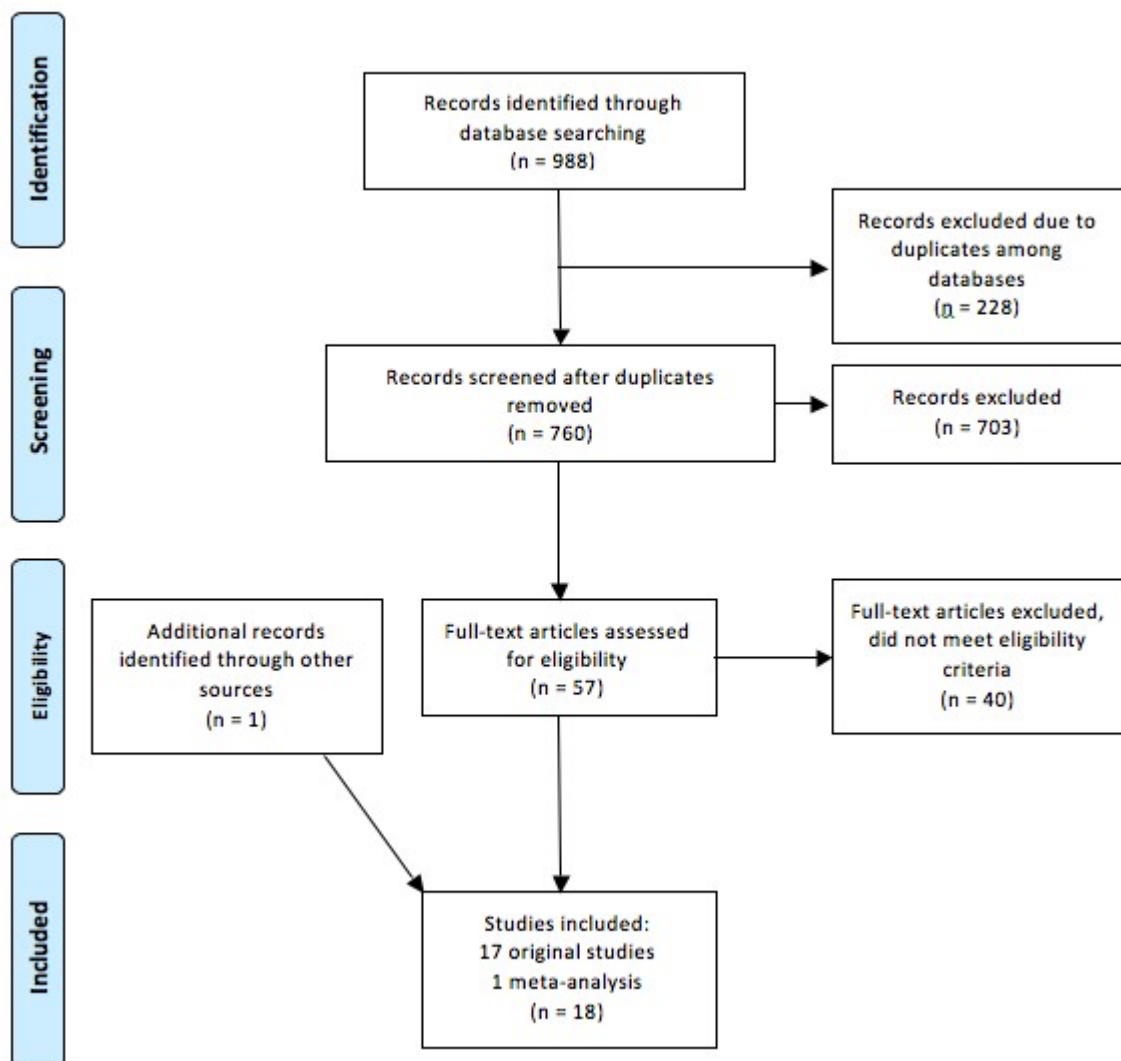
A)



B)

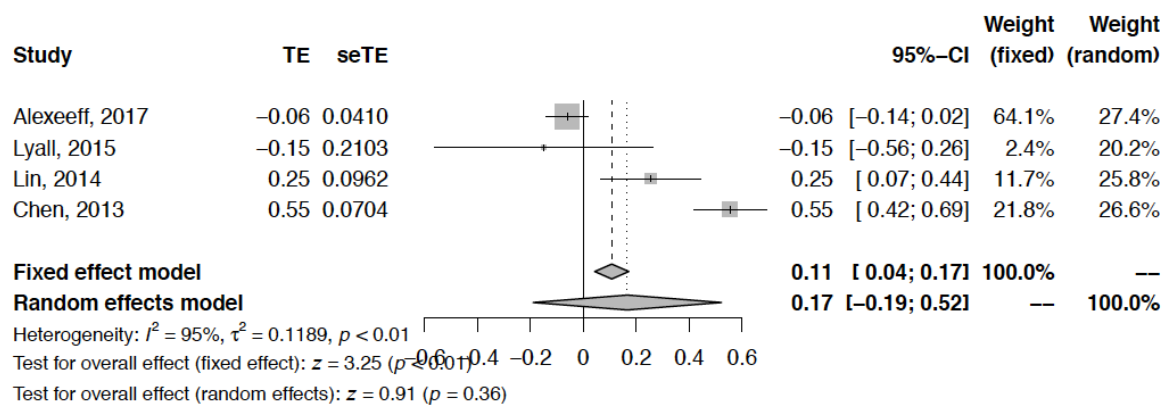


eFigure 6

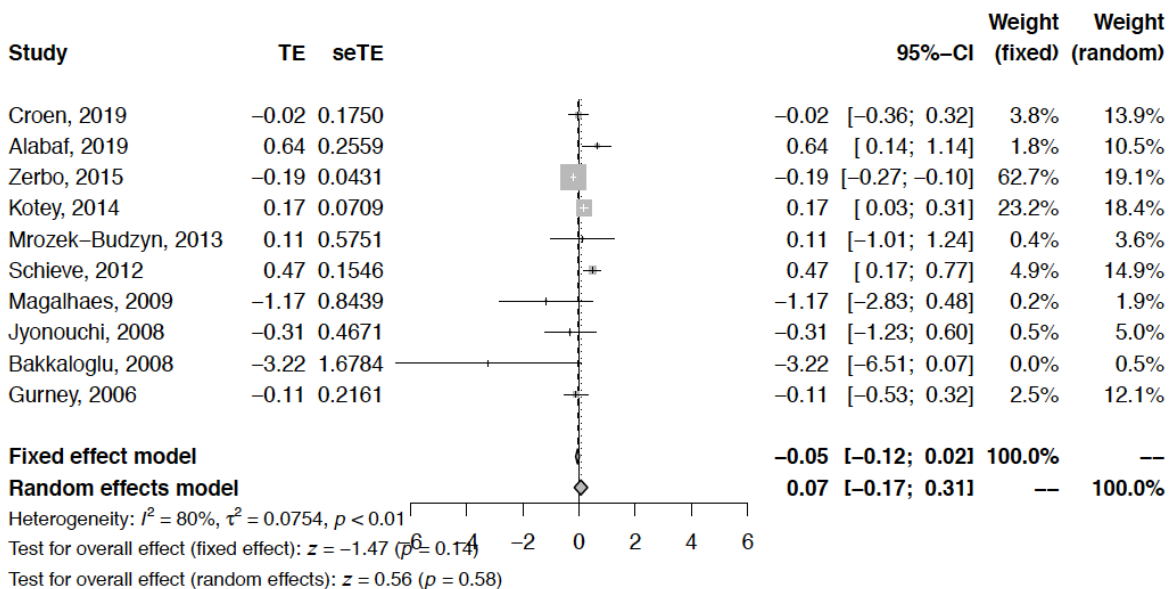


eFigure 7

A)

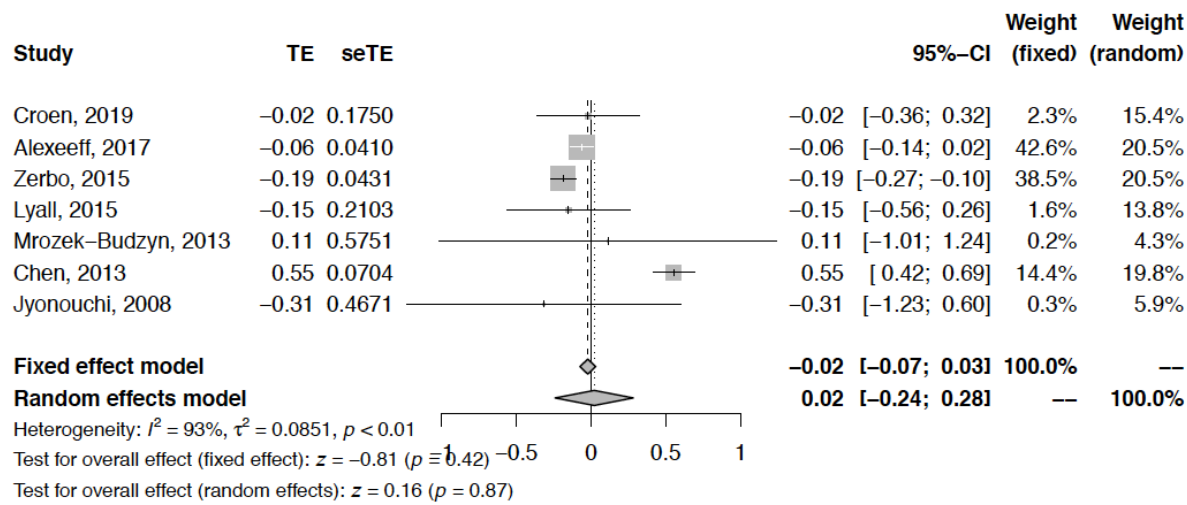


B)

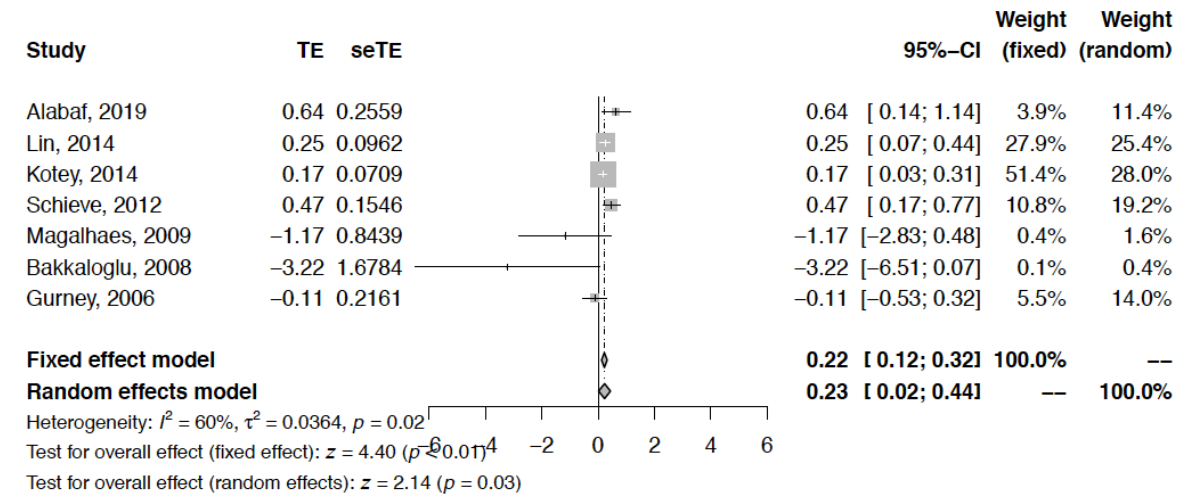


eFigure 8

A)

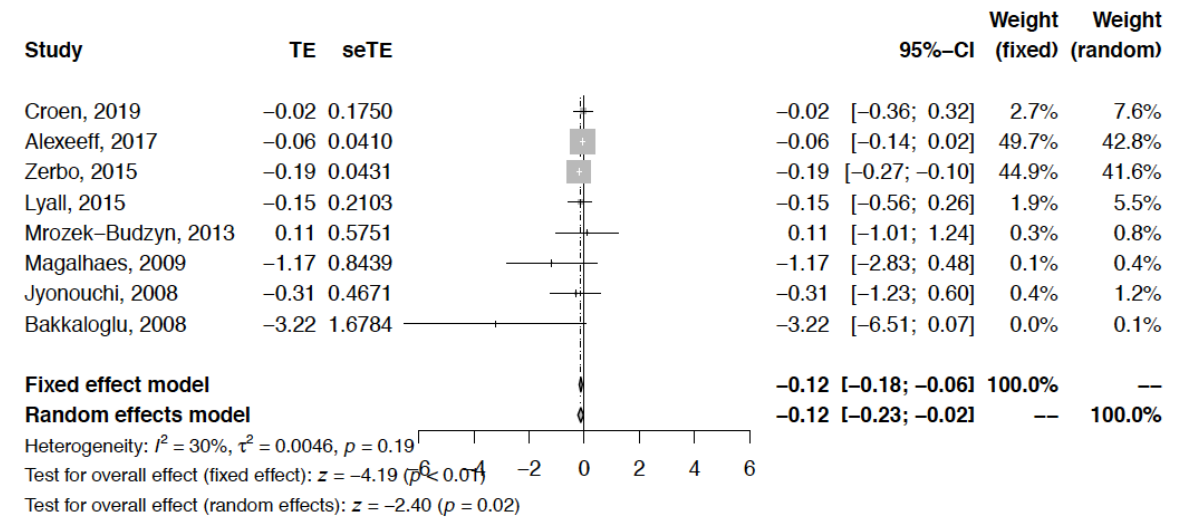


B)

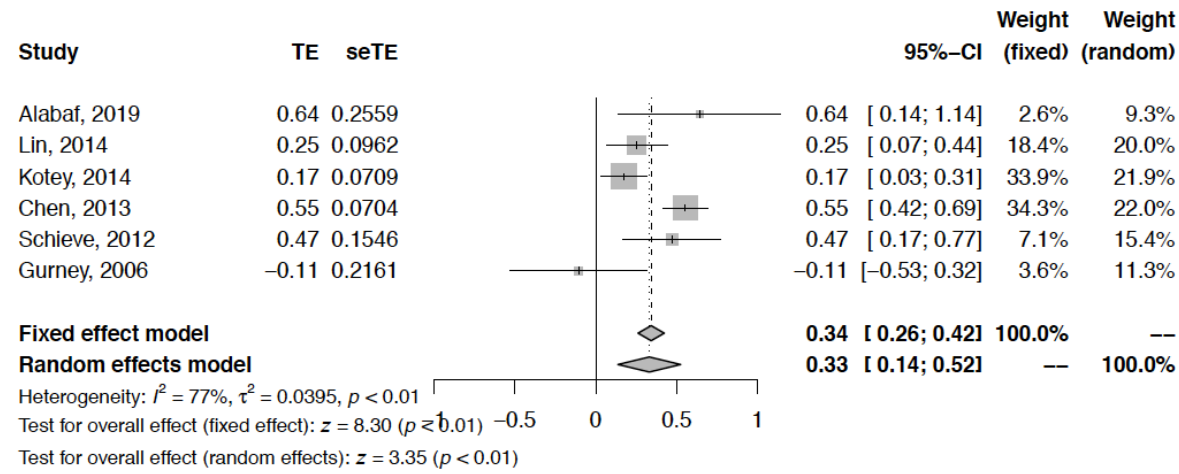


eFigure 9

A)

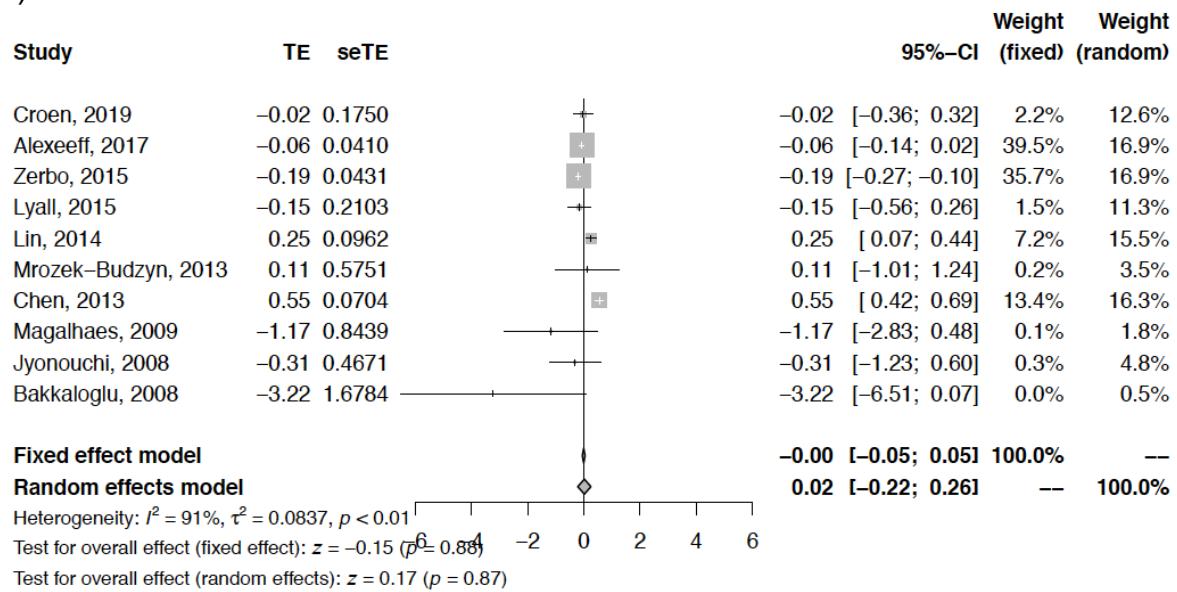


B)

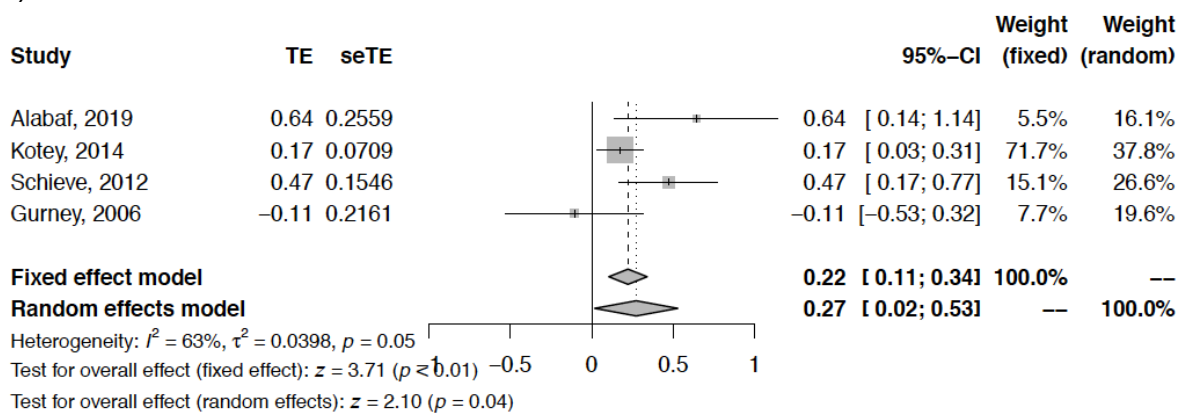


eFigure 10

A)



B)



ONLINE SUPPLEMENT

SEARCH PROTOCOLS

Asthma and ASD

Databases	Search strategy	Hits
PubMed 1966- Date: 28/3-2019	#1: (("Asthma"[Mesh]) OR (asthma* OR "reactive airway disease" OR wheeze OR wheezing))	195095
	#2: ("Autism Spectrum Disorder"[Mesh]) OR (asd OR "autism spectrum disorder" OR "autistic disorder" OR "Asperger Syndrome" OR autism)	53280
	#3: #1 AND #2	251
	Limits: English	238
Embase 1974- Date: 28/3-2019	#1: exp asthma/	239503
	#2: (asthma* or "reactive airway disease" or wheeze or wheezing).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	284231
	#3: #1 OR #2	284422
	#4: exp autism/ or exp asperger syndrome/	60505
	#5: (asd or "autism spectrum disorder" or "autistic disorder" or "Asperger Syndrome" or autism).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	74259
	#6: #4 OR #5	78966
	#7: #3 AND #6	749
	Limits: English	729
Cochrane Library Date: 28/3-2019	#1: MeSH descriptor: [Asthma] explode all trees	10870
	#2: (asthma* OR "reactive airway disease" OR wheeze OR wheezing):ti,ab,kw	28843
	#3: #1 OR #2	28843
	#4: MeSH descriptor: [Autism Spectrum Disorder] explode all trees	1127
	#5: (asd OR "autism spectrum disorder" OR "autistic disorder" OR "Asperger Syndrome" OR autism):ti,ab,kw	2593
	#6: #4 OR #5	2604
	#7: #3 AND #5	21

Asthma and ADHD

Databases	Search strategy	Hits
PubMed 1966- Date: 28/3-2019	#1: (("Asthma"[Mesh]) OR (asthma* OR "reactive airway disease" OR wheeze OR wheezing))	195095
	#2: (("Attention Deficit Disorder with Hyperactivity"[Mesh]) OR (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 "hyperactivity child syndrome"))	44201
	#3: #1 AND #2	440
	Limits: English	419
Embase 1974- Date: 28/3-2019	#1: exp asthma/	239503
	#2: (asthma* or "reactive airway disease" or wheeze or wheezing).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	284231
	#3: #1 OR #2	284422
	#4: exp attention deficit disorder/	54753
	#5: ("Attention Deficit Disorder with Hyperactivity" or 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 "hyperactivity child syndrome").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	61148
	#6: #4 OR #5	61148
	#7: #3 AND #6	1075
	Limits: English	1036
Cochrane Library Date: 28/3-2019	#1: MeSH descriptor: [Asthma] explode all trees	10870
	#2: (asthma* OR "reactive airway disease" OR wheeze OR wheezing):ti,ab,kw	28843
	#3: #1 OR #2	28843
	#4: MeSH descriptor: [Attention Deficit Disorder with Hyperactivity] explode all trees	2411
	#5: (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 "hyperactivity child syndrome"):ti,ab,kw	4547
	#6: #4 OR #5	4547

	#7: #3 AND #6	18
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eFIGURE LEGENDS

eFIGURE 1: PRISMA flow diagram for asthma-ADHD studies.

eFIGURE 2: Stratified asthma-ADHD meta-analysis for studies with A) Newcastle Ottawa Scale 7-9, B) Newcastle Ottawa Scale 7-9, excluding Van den Heuvel, C) Newcastle Ottawa Scale 0-6.

eFIGURE 3: Stratified asthma-ADHD meta-analysis for A) case-control studies, B) cross-sectional studies.

eFIGURE 4: Stratified asthma-ADHD meta-analysis for A) clinic-based studies, B) population-based studies.

eFIGURE 5: Stratified asthma-ADHD meta-analysis for studies using A) doctor diagnoses, B) other types of diagnoses such as parental reporting.

eFIGURE 6: PRISMA flow diagram for asthma-ASD studies.

eFIGURE 7: Stratified asthma-ASD meta-analysis for studies with A) Newcastle Ottawa Scale 7-9, B) Newcastle Ottawa Scale 0-6.

eFIGURE 8: Stratified asthma-ASD meta-analysis for A) case-control studies, B) cross-sectional studies.

eFIGURE 9: Stratified asthma-ASD meta-analysis for A) clinic-based studies, B) population-based studies.

eFIGURE 10: Stratified asthma-ASD meta-analysis for studies using A) doctor diagnoses, B) other types of diagnoses such as parental reporting.