TIMESPAN

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Abbreviations

T2D	Type-2 Diabetes
CVD	cardiovascular disease
ADHD	Attention Deficit Hyperactivity Disorder
NOS	Newcastle-Ottawa Scale
GRACE	Good Research for Comparative Effectiveness

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1. Executive Summary

Cardiometabolic disease, including Obesity, Type-2 Diabetes (T2D) and cardiovascular disease (CVD) are well-known chronic conditions that frequently co-occurs. Each of these conditions are associated with premature death, as well as high levels of health care costs. Attention Deficit Hyperactivity Disorder (ADHD) is a common neurodevelopmental condition, characterized by hyperactivity, inattention, impulsivity, that often persist from childhood into adulthood. It is a costly disorder that often co-occurs with substance use disorders bipolar disorder, and depression. It is associated with criminality, occupational problems, and premature death, including suicide.

Research on psychiatric comorbidity in ADHD has informed clinical treatment guidelines to help mental health teams to build up an expertise in the diagnosis and treatment of individuals with ADHD and co-occurring psychiatric disorders. In contrast, due to a lack of research, guidelines about the management of cardiometabolic disease in individuals with ADHD is scarce.

To guide clinical practice and prevention strategies, we have conducted three systematic reviews and meta-analysis:

i) Li L, Yao H, Zhang L, Garcia-Argibay M, Du Rietz E, Brikell I, Solmi M, Cortese S, Ramos-Quiroga JA, Ribasés M, Chang Z, and Larsson H (In press). Attention-deficit/hyperactivity disorder is associated with increased risk of cardiovascular diseases: a systematic review and meta-analysis. JCPP Advances.

ii) Zhang L, Yao H, Li L, Du Rietz E, Andell P, Garcia-Argibay M, D'Onofrio BM, Cortese S, Larsson H, Chang Z. Risk of Cardiovascular Diseases Associated With Medications Used in Attention-Deficit/Hyperactivity Disorder: A Systematic Review and Meta-analysis. JAMA Netw Open. 2022 Nov 1;5(11):e2243597.

iii) Garcia-Argibay M, Li L, Du Rietz E, Zhang L, Yao H, Jendle J, Ramos-Quiroga JA, Ribasés M, Chang Z, Brikell I, Cortese S, Larsson H. The association between type 2 diabetes and attention- deficit/hyperactivity disorder: A systematic review, meta-analysis, and population-based sibling study. Neurosci Biobehav Rev. 2023 Apr;147:105076.

2. Deliverable report

To guide clinical practice and prevention strategies, we have conducted three systematic reviews and meta-analysis:

i) ADHD as a risk factor for CVD

To systematically review, quantitatively synthesize, and appraise available evidence on the link between ADHD with CVDs, we searched relevant articles in PubMed, Embase, PsycINFO, and Web of Science from inception to May 1, 2022. Study quality was assessed by using the Newcastle-Ottawa Scale (NOS), and random-effects model meta-analyses were performed. A total of 18,391,169 (ADHD: n=421,224) individuals from 11 studies were included in our systematic review and 8,196,648 (ADHD=332,619) individuals from five studies were included in the main meta-analysis of adjusted estimates. Pooled estimates showed that ADHD was significantly associated with an increased risk of CVDs in analyses based on adjusted effect size (OR=1.96; 95% CI =1.19-2.23, Q=140.74, P_Q<0.001, I^2=97.2%). When restricted among adults, the heterogeneity declined to null (OR=1.73; 95% CI =1.14-2.62, Q=6.28, P_Q=0.10, I^2=6.28%), suggesting age might be the main source of heterogeneity. In

subgroup analyses, we found increased risk of CVDs associated with ADHD across age groups, type of CVDs, and data sources. This systematic review and meta-analyses indicate that ADHD is associated with increased risk for CVDs, but further studies with various study designs are warranted to advance the understanding of the underlying mechanisms for the observed association between ADHD and CVDs. Additional research is also needed to resolve the role of ADHD medications which remains unclear due to the limited number of primary studies exploring this issue.

Reference: Li L, Yao H, Zhang L, Garcia-Argibay M, Du Rietz E, Brikell I, Solmi M, Cortese S, Ramos-Quiroga JA, Ribasés M, Chang Z, and Larsson H (In press). Attention-deficit/hyperactivity disorder is associated with increased risk of cardiovascular diseases: a systematic review and meta-analysis. JCPP Advances.

ii) ADHD medication and the risk of CVD

To provide an updated synthesis of evidence on whether ADHD medications are associated with the risk of a broad range of CVDs, we searched relevant articles in PubMed, Embase, PsycINFO, and Web of Science up to May 1, 2022. We included observational studies investigating the association between ADHD medications (including stimulants and nonstimulants) and risk of CVD. Independent reviewers extracted data and assessed study quality using the Good Research for Comparative Effectiveness (GRACE) checklist. Nineteen studies (with 3 931 532 participants including children, adolescents, and adults; 60.9%male), of which 14 were cohort studies, from 6 countries or regions were included in the meta-analysis. Median follow-up time ranged from 0.25 to 9.5 years (median, 1.5 years). Pooled adjusted relative risk (RR) did not show a statistically significant association between ADHD medication use and any CVD among children and adolescents (RR, 1.18; 95%CI, 0.91-1.53), young or middle-aged adults (RR, 1.04; 95%CI, 0.43-2.48), or older adults (RR, 1.59; 95%CI, 0.62-4.05). No significant associations for stimulants (RR, 1.24; 95%CI, 0.84-1.83) or nonstimulants (RR, 1.22; 95% CI, 0.25-5.97) were observed. For specific cardiovascular outcomes, no statistically significant association was found in relation to cardiac arrest or arrhythmias (RR, 1.60; 95%CI, 0.94-2.72), cerebrovascular diseases (RR, 0.91; 95%CI, 0.72-1.15), or myocardial infarction (RR, 1.06; 95%CI, 0.68-1.65). There were no associations with any CVD in female patients (RR, 1.88; 95%CI, 0.43-8.24) and in those with preexisting CVD (RR, 1.31; 95%CI, 0.80-2.16). Heterogeneity between studies was high and significant except for the analysis on cerebrovascular diseases. This meta-analysis suggests no statistically significant association between ADHD medications and the risk of CVD across age groups, although a modest risk increase could not be ruled out, especially for the risk of cardiac arrest or tachyarrhythmias. Further investigation is warranted for the cardiovascular risk in female patients and patients with preexisting CVD as well as long-term risks associated with ADHD medication use.

Reference: Zhang L, Yao H, Li L, Du Rietz E, Andell P, Garcia-Argibay M, D'Onofrio BM, Cortese S, Larsson H, Chang Z. Risk of Cardiovascular Diseases Associated With Medications Used in Attention-Deficit/Hyperactivity Disorder: A Systematic Review and Meta-analysis. JAMA Netw Open. 2022 Nov 1;5(11):e2243597.

iii) ADHD as a risk factor for TD2

We conducted a systematic review and a meta-analysis to quantitatively summarize evidence on the association between ADHD and T2D. Moreover, a register-based sibling study was conducted to simultaneously control for confounding factors. A systematic search identified four eligible observational studies (N = 5738,287). The meta-analysis showed that individuals with ADHD have a

more than doubled risk of T2D when considering adjusted estimates (OR=2.29 [1.48–3.55], *d*=0.46). Results from the register-based Swedish data showed a significant association between ADHD and T2D (HR=2.35 [2.14–2.58]), with substance use disorder, depression, and anxiety being the main drivers of the association, and cardiovascular and familiar risk playing a smaller role. While results from the meta-analysis provide evidence for an increased risk of T2D in individuals with ADHD, the register-based analyses show that the association between ADHD and T2D is largely explained by psychiatric comorbidities. Pending further evidence of causal association, our findings suggest that early identification and treatment of ADHD comorbidities might greatly reduce the risk of developing T2D in individuals with ADHD.

Reference: Garcia-Argibay M, Li L, Du Rietz E, Zhang L, Yao H, Jendle J, Ramos-Quiroga JA, Ribasés M, Chang Z, Brikell I, Cortese S, Larsson H. The association between type 2 diabetes and attention-deficit/hyperactivity disorder: A systematic review, meta-analysis, and population-based sibling study. Neurosci Biobehav Rev. 2023 Apr;147:105076.

3. Conclusion

We have used state-of-the-art methods to synthesize and appraise the available evidence on ADHD and cardiometabolic disease with a focus on CVDs and T2D.

APPENDIX: TIMESPAN publications for systematic review covering the available evidence on ADHD and cardiometabolic disease

i) Li L, Yao H, Zhang L, Garcia-Argibay M, Du Rietz E, Brikell I, Solmi M, Cortese S, Ramos-Quiroga JA, Ribasés M, Chang Z, and Larsson H (In press). Attention-deficit/hyperactivity disorder is associated with increased risk of cardiovascular diseases: a systematic review and meta-analysis. JCPP Advances.

ii) Zhang L, Yao H, Li L, Du Rietz E, Andell P, Garcia-Argibay M, D'Onofrio BM, Cortese S, Larsson H, Chang Z. Risk of Cardiovascular Diseases Associated With Medications Used in Attention-Deficit/Hyperactivity Disorder: A Systematic Review and Meta-analysis. JAMA Netw Open. 2022 Nov 1;5(11):e2243597.

iii) Garcia-Argibay M, Li L, Du Rietz E, Zhang L, Yao H, Jendle J, Ramos-Quiroga JA, Ribasés M, Chang Z, Brikell I, Cortese S, Larsson H. The association between type 2 diabetes and attention- deficit/hyperactivity disorder: A systematic review, meta-analysis, and population-based sibling study. Neurosci Biobehav Rev. 2023 Apr;147:105076.

Attention-deficit/hyperactivity disorder is associated with increased risk of cardiovascular diseases: a systematic review and meta-analysis

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Abstract

Attention-deficit/hyperactivity disorder (ADHD) often co-occurs with other psychiatric and physical diseases. However, available evidence on associations between ADHD and cardiovascular diseases (CVDs) is mixed. To systematically review, quantitatively synthesize, and appraise available evidence on the link between ADHD with CVDs, we searched relevant articles in PubMed, Embase, PsycINFO, and Web of Science from inception to May 1, 2022. Study quality was assessed by using the Newcastle-Ottawa Scale (NOS), and random-effects model meta-analyses were performed. A total of 18,391,169 (ADHD: n=421,224) individuals from 11 studies were included in our systematic review and 8,196,648 (ADHD=332,619) individuals from five studies were included in the main meta-analysis of adjusted estimates. Pooled estimates showed that ADHD was significantly associated with an increased risk of CVDs in analyses based on adjusted effect size (OR=1.96; 95% CI =1.19-2.23, Q=140.74, P_Q<0.001, I^2=97.2%). When restricted among adults, the heterogeneity declined to null (OR=1.73; 95% CI =1.14-2.62, Q=6.28, P_Q=0.10, I^2=6.28%), suggesting age might be the main source of heterogeneity. In subgroup analyses, we found increased risk of CVDs associated with ADHD across age groups, type of CVDs, and data sources. This systematic review and meta-analyses indicate that ADHD is associated with increased risk for CVDs, but further studies with various study designs are warranted to advance the understanding of the underlying mechanisms for the observed association between ADHD and CVDs. Additional research is also needed to resolve the role of ADHD medications which remains unclear due to the limited number of primary studies exploring this issue.

Introduction

Cardiovascular diseases (CVDs) are the leading cause of morbidity, mortality, and rising health care costs worldwide.(1, 2) CVDs caused an estimated 18.6 million deaths in 2019 worldwide, corresponding to almost 400 million years of life lost and another 34.4 million years lived with disability.(3) It is therefore a public health priority to gain further insight into the factors that contribute to CVDs in order to guide prevention and clinical practice. Besides traditional CVD risk factors, such as overweight/obesity, diabetes, and smoking, concerns around the risk for CVDs in individuals with psychiatric disorders are growing.(4-8)

Attention-deficit/hyperactivity disorder (ADHD) is one of the most prevalent psychiatric disorders, affecting around 5% of children and 2.5% of adults.(9, 10) It is characterized by developmentally inappropriate, pervasive and impairing inattention and/or hyperactivity-impulsivity. In addition to the core clinical symptoms of ADHD, co-occurring poor mental and physical comorbidities are prevalent in individuals with ADHD.(11) However, compared with the extensive research of psychiatric comorbidities in ADHD,(12) physical comorbidities (13), such as CVDs, have received less attention, particularly among adults. (14)

There are several reasons why individuals with ADHD could be at increased risk for CVDs. First, previous research suggests that the link between ADHD and cardiovascular diseases is biologically plausible via immune system abnormalities,(15, 16) neuromodulator dysregulation, (17, 18) and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis. (19, 20) Second, individuals with ADHD are at increased risk for unhealthy lifestyle factors (e.g., smoking, obesity, poor physical activity), (21-23) which are all well-established risk factors for CVDs. (24-26) Third, previous studies indicate that several psychiatric comorbidities of ADHD, for example, depression,(27, 28), substance use disorders, (29, 30) schizophrenia,(31) bipolar disorder,(32) and anxiety disorder, (33) are associated with CVDs. Fourth, even though findings are inconclusive, there has been a long-standing concern around a potential increased risk of cardiovascular events due to the use of stimulant medications to treat ADHD. (34, 35) However, the available epidemiological findings are mixed, despite the potential hypotheses for an increased risk of CVDs in ADHD.

The aim of the current study was to conduct a systematic review and meta-analysis was to provide a quantitative summary of observational studies on the associations between ADHD and CVDs. A second aim was to evaluate the impact of study design and confounder adjustment (e.g., sociodemographic factors, traditional risk factors for

CVDs, and use of medications) on the observed associations, in order to provide insights into underlying mechanisms.

Methods

The study was conducted and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (36) and Conducting Systematic Reviews and Meta-Analyses of Observational Studies of Etiology (COSMOS-E). (37) This protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO: CRD42021274367). (38)

Search Strategy

A systematic search for observational studies was conducted in PubMed, Embase, PsycINFO, and Web of Science databases, up to May 1, 2021, with no language and article type restrictions. We used various combinations of the following keywords "cardiovascular disease", "coronary heart disease", "heart disease", "sudden death", "ischemic heart disease", "hypertension", "cerebrovascular disease", "stroke", "transient ischemic attack", "attention-deficit hyperactivity disorder", "central nervous system stimulants" and "observational study". The complete search strategy is presented in Table S1. In addition, we performed manual searches through the reference lists of original publications and reviewed articles to identify further pertinent studies.

Inclusion criteria

We included all types of observational (cross-sectional or prospective) studies providing data on the strength of the association between ADHD and CVDs in children, adolescents, or adults. Eligible definitions of ADHD were as follows: 1) a categorical diagnosis of ADHD according to the DSM-III, DSM-III-R, DSM-IV, DSM-IV-TR, DSM-5, ICD-9, or ICD-10; 2) ADHD-medication prescriptions as a proxy for ADHD diagnosis; 3) ADHD symptoms based on value above cut-off on a validated self/parents/teacher-reported ADHD questionnaire; 4) ADHD diagnosed via a structured psychiatric interview or positive answer by self/parents/teachers to the question 'Did your doctor ever tell you that you/the child have ADHD?' Titles, abstracts, and full text of included studies were screened independently by two authors. Discrepancies were resolved through discussion with a senior investigator.

The main outcome was the maximally adjusted odds ratio (OR), risk ratio (RR), and hazard ratio (HR), with their corresponding 95% confidence interval (CI) ratio expressing the association between ADHD and CVDs. The secondary outcome was the unadjusted estimate of the associations. When sufficient data (i.e., sample size,

prevalence of ADHD, CVDs) was available, crude ORs were manually calculated or obtained by contacting the original authors, if not reported in the original paper. The choice of primary and secondary outcomes was made because adjusted estimates are more informative and potentially less prone to biased derived from the selection of the participants.(39)

Data extraction

The following information was extracted from each study for the qualitative and quantitative synthesis: name of the first author, year of publication, sample size, data source, study country, age and sex for participants, study design, years of original data collection, the definition of ADHD and CVDs, effect size (ORs, RRs and HRs) and information on confounding adjustment. We extracted both adjusted and unadjusted ratios if available, and we used the maximally adjusted ratios in the analyses. Unadjusted effect sizes were calculated based on the information provided in the paper when necessary. Two authors conducted the data extraction process separately, and any disagreements were resolved by discussing with a third investigator.

The quality assessment of eligible studies was performed using the Newcastle-Ottawa Scale (NOS) by two independent authors, and the discrepancies were solved by consensus. This 9-star scale consists of three parts: selection of participants and the measurement of exposure (4 stars), comparability (2 stars), and assessment of outcomes and adequate follow-up (3 stars). (40) A higher score on the NOS represents a higher-quality study, and generally, a score of 0 to 3, 4 to 6, or 7 to 9 is regarded as low-, moderate-, or high-quality, respectively. (40)

Statistical analysis

We first described the characteristics of the included studies and various confounding adjustment strategies to provide an overall picture of the current evidence. Meta-analyses were conducted using random-effects models in order to take into account heterogeneity between studies, and the results were summarized in forest plots. When there were several studies from the same population, only the one with the largest sample size was included in the meta-analysis to avoid overrepresentation bias. (41) ORs from logistic regression and HRs from Cox regression were combined because they closely approximate each other. (42) We then meta-analyzed adjusted and unadjusted ORs across all studies. Additionally, several subgroups and sensitivity analyses were conducted to investigate whether the main results were robust across (1) age groups (adults and children separately) (2) specific types of CVD (hypertension and other types of CVDs), and (3) different data sources (registers and research

samples).

Heterogeneity across studies was described by Cochran's Q test and the inconsistency index (I^2). If significant heterogeneity was detected by the Q test, we considered I^2 values greater than 75% as high heterogeneity.(43) Restricted maximum likelihood method was used to estimate between-study variability, with Hartung-Knapp-Sidik-Jonkman confidence interval for the summary effect. To evaluate each study's effect on the overall effect size, a leave-one-out analysis was also conducted. The publication bias was first assessed through visual inspection of the funnel plot and then tested quantitatively with Egger's test. All analyses were performed with Stata 16.0 (StataCorp L.P., College Station, TX).

Results

Study Characteristics

The study selection process is shown in **Figure 1,** and the list of excluded articles (with reasons) after the full-text screen is presented in **Table S2**. **Table 1** shows the main characteristics of the eleven original studies included in the systematic review.(44-54) Among the 18,391,169 participants from six countries, a total of 421,214 individuals were with ADHD. The age of participants ranged from 5 to 81 years old, and 9,889,671 (53.8%) participants were men. The publication years were between 2011 and 2022. The most common study design included in the meta-analysis were cross-sectional (n=4), (44, 47, 49, 52), cohort (n=4) (46, 48, 50, 54), followed by case-control (n=3) (45, 51, 53) studies. These studies were conducted in the United States, Sweden, Germany, Turkey, Netherlands, and Canada. Of the 11 studies, five (44, 46, 47, 50, 54) obtained data from healthcare/insurance registries, five (45, 48, 49, 51, 53) obtained data from research samples, and one (52) used data from a specific national cohort. Therefore, register-based or electronic health care databases comprising large numbers of participants were the most commonly used data source for the studied associations. The definition of ADHD varied across studies, self/teacher/parent-reported ADHD symptoms (46, 48, 49, 52, 53) were the most widely used measurements, followed by electronic health records based on codes in the ICD codes or the DSM-IV (44, 45, 47, 50, 54). With regards to the CVD outcomes, various measurements were used, including CVD diagnosis based on ICD codes and several specific recommendations/guidance for hypertension (e.g. Recommendations of the American Heart Association). The most commonly studied CVD outcomes were hypertension (44-47, 50, 51) and any type of CVDs (48, 49, 52-54) .

As shown in **Table 2**, seven (44, 46, 47, 49, 50, 52, 54) studies (64%) accounted

for potential confounders by adjusting for a number of measured covariates. However, inadequate adjustment for confounding was commonly found among included studies. Four studies (47, 49, 50) only adjusted for age and gender, while the other three studies (46, 52, 54) also included sociodemographic characteristics (e.g., ethnicity, education), psychiatric comorbidities, lifestyle factors (e.g., smoking, alcohol use, and physical activity), and metabolic conditions (e.g., obesity, type 2 diabetes, and hyperlipidemia). However, these lifestyle factors, psychiatric comorbidities, and metabolic conditions are more likely mediators in the pathways linking ADHD to CVDs (**Figure 2**) rather than confounders. The potential role of familial factors was only explored in one Swedish study. (50) Of particular importance, only one study examined the contribution of ADHD medication to the association between ADHD and CVDs in a sensitivity analysis, and suggested null effect of ADHD medication. (54)

The quality scores based on the NOS ranged from 2 to 9 stars (Median: 5), suggesting an overall moderate quality of the included studies. As shown in **Table S3**, the number of stars represented the score of each item. Generally, most studies used well-defined exposures and outcomes, but some included studies with one or no star in relation to 'Comparability' did not adjust for sex, age, and other sociodemographic characteristics.

Meta-analysis

In the main analysis, we first explored the associations between ADHD and CVDs among seven studies that provided adjusted effect sizes (44, 46-48, 50, 52, 54). The three Swedish register-based studies (47, 50, 54) involved similar population, therefore only the largest one was included in the main analysis. (47) A total of 8,196,648 (ADHD=332,619) individuals from five studies were included in the main meta-analysis of adjusted estimates. We found that ADHD was associated with a significantly increased risk of CVDs (pooled odds ratio (OR) =1.96; 95% confidence interval (CI) =1.19-2.23) (**Figure 3**). However, heterogeneity was high and significant (Q=140.74, P_Q<0.001, I^2=97.2%) and the between-study standard variance was not high (tau^2 is 0.09, 95%CI=0.03-0.44) but with wide confidence interval. The effect size was robust in the leave-one-out sensitivity analysis (**Figure S1**), and the effect size was not driven by one single study. There was no evidence of publication bias for the primary outcomes (Egger test: P=.81) (**Figures S2 and S3**).

When we repeated the analysis among six studies (44-46, 48, 51, 53) with unadjusted associations (five of six estimates were manually calculated), a positive association was found for CVDs in individuals with ADHD compared to controls (OR=

1.48, 95% CI =0.97-2.26; Q=188.57, P_Q< 0.001, $I^{2=}$97.3%) but this was not statistically significant (**Figure S4**).

Table 3 summarizes the results from subgroup and sensitivity analyses based on adjusted estimates. First, in the analysis limited to adults, the association between ADHD and CVDs was significant among six studies (pooled OR =1.73; 95% CI =1.14-2.62) without significant heterogeneity (Q=6.28, P_Q=0.10, I^2=6.28%), while the only study in children reported a stronger association between ADHD and CVD (hypertension as main outcome) than adults (OR =3.26; 95% CI =3.00-3.55; $Q_{between-group}$ = 86.74, P <0.0001). As age was a main factor affecting the heterogeneity of the results, we restricted the following sensitivity analyses on type of CVDs and data sources among adults. Second, among four studies with adjusted data on specific types of CVDs, we found that ADHD was associated with a higher risk of hypertension (OR=1.55; 95% CI =0.75-3.21, Q=5.89, P_Q=0.06, I^2=66.0%) and other CVDs (OR=1.73; 95% CI =1.19-2.68, Q=3.20, P_Q=0.20, I^2=37.7%), even though the association between ADHD and Hypertension was not statistically significant.

Discussion

The meta-analysis provided evidence that ADHD was significantly associated with an increased risk of CVDs, after adjusting for potential confounders. However, due to the limited number of available studies and lack of information in the original studies, it is currently unclear whether these associations can be explained by other confounders. Therefore, there is a critical need for future studies on this understudied topic to advance the understanding of the underlying mechanism for the observed association between ADHD and CVDs, especially the role of ADHD medications and other mediating factors, as mental comorbid conditions (i.e. substance use disorders or depression). A better understanding of major mediating factors may inform clinical guidelines about how to intervene on CVDs in ADHD.

Compared with evidence from meta-analysis for well-established risk factors for CVDs (i.e., smoking, obesity, physical activity/sedentary behavior, diabetes, dyslipidemia and sleep disorders) among adults, the observed magnitude of association between ADHD and CVDs was slightly smaller than the magnitude of association for sedentary behavior, (26) diabetes, (55) and smoking, (24) but stronger than the magnitude for dyslipidemia, (56) obesity (25) and sleep disorders (57) (**Table 4**). When comparing with other psychiatric disorders, the observed strength of associations between ADHD and CVDs is largely similar to estimates of associations of

schizophrenia (58) and substance use disorders (59) with CVDs, but stronger than stress-related disorder, (60) depression, (61) bipolar disorder, (58) and anxiety disorders (**Table 4**). (62) Therefore, it is important to call for enhanced clinical awareness of cardiovascular risk among adults with ADHD.

In the original studies, the type and number of possible confounding factors adjusted for varied across studies, and few studies provided a clear rationale for their covariate selection, which is a common problem in contemporary observational research on mental health. (63) Therefore, the significant adjusted association should also be interpreted with caution. In addition, inadequate adjustment for confounding was found in most studies (e.g., only four studies (44, 46, 52, 54) considered other potential confounders except for age and sex), and only one of the included studies adjusted for ADHD medication, (54) which may contribute to increased risk of CVDs. (64, 65) Only one of the previous studies used a sibling comparison design (50) and suggested that the observed associations could also be partly explained by shared familial factors. Therefore, it is currently unclear whether any of the observed association reflect a causal effect or confounding. Clearly, more research using different designs, such as within-family analysis or instrumental variable design, are needed to systematically adjust for a broad set of possible confounders and further explore the underlying mechanisms. Support for a potential causal association of ADHD with coronary heart disease (66) and stroke (67) has been observed in a recent Mendelian Randomization study. In addition, to identify critical intervention targets, more research is also needed on potential mediating factors, such as ADHD medication use, other psychiatric comorbidities and metabolic diseases.

Heterogeneity was high and significant for the main analyses, indicating that the pooled OR cannot appropriately summarize results from all the included individuals' studies, but it has limited effect on the conclusion of a positive association between ADHD and CVDs. (68, 69) When we restricted the analyses to different age group (children and adults), the associations remained stable, but the degree of heterogeneity substantially decreased to null, suggesting that age might be an important factor affecting the heterogeneity of the results.

Using subgroup meta-analyses, we clarified the differences in associations between ADHD and different types of CVD outcomes. The available studies indicate that individuals with ADHD had a 73% higher risk of a broad range of CVDs than those without ADHD. (54) suggested that the strength of the associations was more pronounced for cardiac arrest, hemorrhagic stroke, and peripheral vascular

disease/arteriosclerosis. (54) However, research from independent samples is needed to replicate their findings. On the other hand, previous studies indicating that ADHD-related traits such as impulsivity, hostility, and time urgency/impatience, are associated with increased risk for hypertension.(46, 70) Consistently, we also found a potential elevated risk of hypertension among adults with ADHD, but this was not statistically significant. Therefore, more studies are needed to further explore the associations between ADHD and specific types of CVDs.

Strengths and Limitations

This is the first systematic review and meta-analysis, with 421,224 individuals having ADHD, to assess the relationship between ADHD and CVDs. Additionally, we also conducted sensitivity and subgroup analyses to further evaluate the findings from the main analyses. However, our results should be considered in the context of some limitations. First, we reported unadjusted ORs as secondary outcomes, but most (83.3%) of the unadjusted ORs were from manually calculated effect sizes based on available information in the original studies, as these studies did not generate unadjusted effect size of the association between ADHD and CVDs. Second, we attempted to reduce publication bias by including both published and unpublished studies, but bias cannot be ruled out completely. Third, most of the included studies were conducted in Europe and the U.S., which limits the generalizability of the findings to other populations across the world. Therefore, more studies are needed to examine the associations between ADHD and CVDs using samples from different settings and regions. Fourth, the definition and measurements of ADHD and CVDs from original studies varied substantially. Due to the limited number of included studies, it is not possible to assess the associations among different definitions, which need to be evaluated in future systematic reviews and meta-analyses on this topic.

Future perspective

Compared with other psychiatric disorders (e.g., schizophrenia, major depression), the risk of CVDs in individuals with ADHD is largely understudied. A number of important research questions, therefore, need to be addressed in future research. First, except for studies with a specific focus on hypertension, the most commonly used measure of CVDs was a broad category, encompassing a wide range of circulatory system diseases. Future studies are needed to explore the associations between ADHD and specific types of CVDs, which is critical to enabling risk reductions via targeted intervention and preventative efforts. Second, future research should also consider

careful adjustments for a wide range of possible confounders of the observed associations between ADHD and CVDs, including but not limited to early life risk factors (e.g., preterm birth (71, 72) and birth weight,(72, 73)) and socioeconomic status, (74, 75) as well as unmeasured familial factors. (50) To further identify critical intervention targets, future research also needs to explore the role of potential mediating factors, such as smoking,(76, 77) sleep problems,(78, 79) metabolic conditions (80) (e.g., obesity,(81) types 2 diabetes mellitus (T2DM),(82) dyslipidemia, (83) and in particular obesity given that a recent Mendelian Randomization study suggested that obesity may mediate the causal association between ADHD and coronary heart disease. (66) Third, only one study has explored the role of psychiatric comorbidities and the use of psychotropic medications in the studied associations. This is an important limitation given that ADHD is frequently comorbid with other psychiatric disorders (e.g., mood disorder and substance use disorder), and these conditions and related medications are in turn associated with increased risk of CVDs. (54, 84) Future studies should examine to what extent the observed associations between ADHD and CVDs could be explained by ADHD medications, other psychiatric disorders and related medications. Fourth, research is also needed to test the potential sex- and age differences in the associations of ADHD with CVDs, which is helpful for risk stratification and individualized treatment recommendations in clinical practice. Taken together, more studies on this topic are needed, especially using different study designs, such as matched-cohort studies,(46, 50) genetically-informed studies (e.g., sibling comparison studies and Mendelian Randomization studies) (66) and advanced statistical methods (e.g. propensity score methods) to account for confounding.

Conclusion

This systematic review and meta-analysis suggest a significant positive association between ADHD and CVDs. More efforts are needed to this substantially understudied research field. In particular, mediation effects by psychiatric comorbidities and related medications, as well as the causal mechanisms underlying the association, deserve further attention because of their important public health implications.

Conflict of Interest Disclosures

Dr Larsson has served as a speaker for Medice, Evolan Pharma and Shire/Takeda and has received research grants from Shire/Takeda; all outside the submitted work. EDR has served as a speaker for Shire Sweden AB outside the submitted work. Dr. Solmi

received honoraria/has been a consultant for Angelini, Lundbeck, Otsuka. S Cortese declares honoraria and reimbursement for travel and accommodation expenses for lectures from the following non- profit associations: Association for Child and Adolescent Central Health (ACAMH), Canadian ADHD Alliance Resource (CADDRA), British Association of Pharmacology (BAP), and from Healthcare Convention for educational activity on ADHD. Dr. J. Antoni was on the speakers' bureau and/or acted as consultant for Janssen-Cilag, Novartis, Shire, Takeda, Bial, Shionogi, Sincrolab, Novartis, BMS, Medice, Rubió, Uriach, Technofarma and Raffo in the last 3 years. He also received travel awards (air tickets + hotel) for taking part in psychiatric meetings from Janssen-Cilag, Rubió, Shire, Takeda, Shionogi, Bial and Medice. The Department of Psychiatry chaired by him received unrestricted educational and research support from the following companies in the last 3 years: Janssen- Cilag, Shire, Oryzon, Roche, Psious, and Rubió. No other disclosures were reported.

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References

1. Vos T, Lim SS, Abbafati C, Abbas KM, Abbasi M, Abbasifard M, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. The Lancet. 2020;396(10258):1204-22.
2. Mensah GA, Roth GA, Fuster V. The global burden of cardiovascular diseases and risk factors: 2020 and beyond. American College of Cardiology Foundation Washington, DC; 2019. p. 2529-32.
3. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990–2019: Update From the GBD 2019 Study. Journal of the American College of Cardiology. 2020;76(25):2982-3021.
4. Everson-Rose SA, Lewis TT. Psychosocial factors and cardiovascular diseases. Annu Rev Public Health. 2005;26:469-500.
5. Pedersen SS, von Känel R, Tully PJ, Denollet J. Psychosocial perspectives in cardiovascular disease. European Journal of Preventive Cardiology. 2017;24(3_suppl):108-15.
6. Solmi M, Fiedorowicz J, Poddighe L, Delogu M, Miola A, Høye A, et al. Disparities in Screening and Treatment of Cardiovascular Diseases in Patients With Mental Disorders Across the World: Systematic Review and Meta-Analysis of 47 Observational Studies. The American journal of psychiatry. 2021;178(9):793-803.
7. Correll CU, Solmi M, Veronese N, Bortolato B, Rosson S, Santonastaso P, et al. Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: a large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls. World Psychiatry. 2017;16(2):163-80.
8. Correll CU, Solmi M, Croatto G, Schneider LK, Rohani-Montez SC, Fairley L, et al. Mortality in people with schizophrenia: a systematic review and meta-analysis of relative risk and aggravating or attenuating factors. World Psychiatry. 2022;21(2):248-71.
9. Faraone SV, Asherson P, Banaschewski T, Biederman J, Buitelaar JK, Ramos-Quiroga JA, et al. Attention-deficit/hyperactivity disorder. Nat Rev Dis Primers. 2015;1:15020.
10. Davidson MA. Literature Review: ADHD in Adults: A Review of the Literature. Journal of Attention Disorders. 2007;11(6):628-41.
11. Angold A, Costello EJ, Erkanli A. Comorbidity. J Child Psychol Psychiatry. 1999;40.
12. Gnanavel S, Sharma P, Kaushal P, Hussain S. Attention deficit hyperactivity disorder and comorbidity: A review of literature. World J Clin Cases. 2019;7(17):2420-6.
13. Arrondo G, Solmi M, Dragioti E, Eudave L, Ruiz-Goikoetxea M, Ciaurriz-Larraz AM, et al. Associations between mental and physical conditions in children and adolescents: An umbrella review. Neurosci Biobehav Rev. 2022;137:104662.
14. Instanes JT, Klungsoyr K, Halmoy A, Fasmer OB, Haavik J. Adult ADHD and Comorbid Somatic Disease: A Systematic Literature Review. J Atten Disord. 2018;22(3):203-28.
15. Fernández-Ruiz I. Immune system and cardiovascular disease. Nature Reviews Cardiology. 2016;13(9):503-.
16. Hoekstra PJ. Attention-deficit/hyperactivity disorder: is there a connection with the immune system? European child & adolescent psychiatry. 2019;28(5):601-2.
17. Ahmad Banday A, Lokhandwala MF. Defective renal dopamine D1 receptor function contributes to hyperinsulinemia-mediated hypertension. Clinical and experimental hypertension. 2006;28(8):695-705.
18. Misener V, Luca P, Azeke O, Crosbie J, Waldman I, Tannock R, et al. Linkage of the dopamine receptor D1 gene to attention-deficit/hyperactivity disorder. Molecular psychiatry. 2004;9(5):500-9.

19. Corominas M, Ramos-Quiroga J, Ferrer M, Sáez-Francàs N, Palomar G, Bosch R, et al. Cortisol responses in children and adults with attention deficit hyperactivity disorder (ADHD): a possible marker of inhibition deficits. ADHD Attention Deficit and Hyperactivity Disorders. 2012;4(2):63-75.
20. Jokinen J, Nordström P. HPA axis hyperactivity and cardiovascular mortality in mood disorder inpatients. Journal of affective disorders. 2009;116(1-2):88-92.
21. van Amsterdam J, van der Velde B, Schulte M, van den Brink W. Causal Factors of Increased Smoking in ADHD: A Systematic Review. Substance Use & Misuse. 2018;53(3):432-45.
22. Cortese S, Moreira-Maia CR, St. Fleur D, Morcillo-Peñalver C, Rohde LA, Faraone SV. Association Between ADHD and Obesity: A Systematic Review and Meta-Analysis. American Journal of Psychiatry. 2015;173(1):34-43.
23. Cook BG, Li D, Heinrich KM. Obesity, Physical Activity, and Sedentary Behavior of Youth With Learning Disabilities and ADHD. Journal of Learning Disabilities. 2014;48(6):563-76.
24. Mons U, Müezzinler A, Gellert C, Schöttker B, Abnet CC, Bobak M, et al. Impact of smoking and smoking cessation on cardiovascular events and mortality among older adults: meta-analysis of individual participant data from prospective cohort studies of the CHANCES consortium. BMJ : British Medical Journal. 2015;350:h1551.
25. Dwivedi AK, Dubey P, Cistola DP, Reddy SY. Association Between Obesity and Cardiovascular Outcomes: Updated Evidence from Meta-analysis Studies. Curr Cardiol Rep. 2020;22(4):25.
26. Wilmot EG, Edwardson CL, Achana FA, Davies MJ, Gorely T, Gray LJ, et al. Sedentary time in adults and the association with diabetes, cardiovascular disease and death: systematic review and meta-analysis. Diabetologia. 2012;55(11):2895-905.
27. Nicholson A, Kuper H, Hemingway H. Depression as an aetiologic and prognostic factor in coronary heart disease: a meta-analysis of 6362 events among 146 538 participants in 54 observational studies. Eur Heart J. 2006;27(23):2763-74.
28. Hare DL, Toukhsati SR, Johansson P, Jaarsma T. Depression and cardiovascular disease: a clinical review. European Heart Journal. 2014;35(21):1365-72.
29. Aldridge RW, Story A, Hwang SW, Nordentoft M, Luchenski SA, Hartwell G, et al. Morbidity and mortality in homeless individuals, prisoners, sex workers, and individuals with substance use disorders in high-income countries: a systematic review and meta-analysis. Lancet. 2018;391(10117):241-50.
30. Roerecke M, Rehm J. Alcohol consumption, drinking patterns, and ischemic heart disease: a narrative review of meta-analyses and a systematic review and meta-analysis of the impact of heavy drinking occasions on risk for moderate drinkers. BMC Med. 2014;12:182.
31. Hennekens CH, Hennekens AR, Hollar D, Casey DE. Schizophrenia and increased risks of cardiovascular disease. The American heart journal. 2005;150(6):1115-21.
32. Swartz HA, Fagiolini A. Cardiovascular Disease and Bipolar Disorder: Risk and Clinical Implications. The Journal of clinical psychiatry. 2012;73(12):1563-5.
33. Tully PJ, Harrison NJ, Cheung P, Cosh S. Anxiety and Cardiovascular Disease Risk: a Review. Current Cardiology Reports. 2016;18(12):120.
34. Liu H, Feng W, Zhang D. Association of ADHD medications with the risk of cardiovascular diseases: a meta-analysis. European Child & Adolescent Psychiatry. 2019;28(10):1283-93.
35. Zhang L, Yao H, Li L, Du Rietz E, Andell P, Garcia-Argibay M, et al. Risk of Cardiovascular Diseases Associated With Medications Used in Attention-Deficit/Hyperactivity Disorder: A Systematic Review and Meta-analysis. JAMA Network Open. 2022;5(11):e2243597-e.
36. Boutron I, Hoffmann T, Mulrow C, Shamseer L, Tetzlaff J, Akl E, et al. The PRISMA 2020 statement:

538 an updated guideline for reporting systematic reviews. BMJ (Clinical research ed). 2021;372(n71).
539 37. Dekkers OM, Vandenbroucke JP, Cevallos M, Renehan AG, Altman DG, Egger M. COSMOS-E:
540 Guidance on conducting systematic reviews and meta-analyses of observational studies of etiology.
541 PLoS medicine. 2019;16(2):e1002742.
542 38. Lin Li LZ, Honghui Yao, Miguel Garcia-Argibay, Ebba Du Rietz, Isabell Brikell, Samuele Cortese,
543 Zheng Chang, Henrik Larsson. The associations between ADHD and cardiovascular diseases: a
544 systematic review and meta-analysis. 2021.
545 39. Cortese S, Gabellone A, Marzulli L, Iturmendi-Sabater I, de La Chica-Duarte D, Piqué IM, et al.
546 Association between autism spectrum disorder and diabetes: systematic review and meta-analysis.
547 Neuroscience & Biobehavioral Reviews. 2022:104592.
548 40. Wells G, Shea B, O'Connell D, Peterson j, Welch V, Losos M, et al. The Newcastle–Ottawa Scale
549 (NOS) for Assessing the Quality of Non-Randomized Studies in Meta-Analysis. . 2000; .
550 41. Li L, Lagerberg T, Chang Z, Cortese S, Rosenqvist MA, Almqvist C, et al. Maternal pre-pregnancy
551 overweight/obesity and the risk of attention-deficit/hyperactivity disorder in offspring: a systematic
552 review, meta-analysis and quasi-experimental family-based study. International Journal of Epidemiology.
553 2020;49(3):857-75.
554 42. D'Agostino RB, Lee ML, Belanger AJ, Cupples LA, Anderson K, Kannel WB. Relation of pooled logistic
555 regression to time dependent Cox regression analysis: the Framingham Heart Study. Statistics in
556 medicine. 1990;9(12):1501-15.
557 43. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med.
558 2002;21(11):1539-58.
559 44. Akmatov MK, Ermakova T, Bätzing J. Psychiatric and Nonpsychiatric Comorbidities Among Children
560 With ADHD: An Exploratory Analysis of Nationwide Claims Data in Germany. Journal of Attention
561 Disorders. 2019;25(6):874-84.
562 45. Nilgün ÇÖL CG, Beltinge DEMİRCİOĞLU KILIÇ, Mehmet KARADAĞ. Prevalence of
563 obesity/hypertension in children and adolescents with ADHD and evaluation of total body composition.
564 Anatolian Journal of Psychiatry 2018.
565 46. Fuemmeler BF, Østbye T, Yang C, McClernon FJ, Kollins SH. Association between attention-
566 deficit/hyperactivity disorder symptoms and obesity and hypertension in early adulthood: a population-
567 based study. International Journal of Obesity. 2011;35(6):852-62.
568 47. Chen Q, Hartman CA, Haavik J, Harro J, Klungsøyr K, Hegvik TA, et al. Common psychiatric and
569 metabolic comorbidity of adult attention-deficit/hyperactivity disorder: A population-based cross-
570 sectional study. PLoS One. 2018;13(9):e0204516.
571 48. Ramos Olazagasti MA, Klein RG, Mannuzza S, Belsky ER, Hutchison JA, Lashua-Shriftman EC, et al.
572 Does childhood attention-deficit/hyperactivity disorder predict risk-taking and medical illnesses in
573 adulthood? J Am Acad Child Adolesc Psychiatry. 2013;52(2):153-62.e4.
574 49. Semeijn EJ, Kooij JJ, Comijs HC, Michielsen M, Deeg DJ, Beekman AT. Attention-deficit/hyperactivity
575 disorder, physical health, and lifestyle in older adults. J Am Geriatr Soc. 2013;61(6):882-7.
576 50. Du Rietz E, Brikell I, Butwicka A, Leone M, Chang Z, Cortese S, et al. Mapping phenotypic and
577 aetiological associations between ADHD and physical conditions in adulthood in Sweden: a genetically
578 informed register study. The Lancet Psychiatry. 2021;8.
579 51. Grisaru S, Yue M, Samuel SM, Chaput KH, Hamiwka LA. Blood pressure in children with attention
580 deficit/hyperactivity disorder. Paediatr Child Health. 2018;23(6):e102-e8.
581 52. Xu G, Snetselaar LG, Strathearn L, Ryckman K, Nothwehr F, Torner J. Association between history

582 of attention-deficit/hyperactivity disorder diagnosis and cardiovascular disease in U.S. adults. Health
583 Psychology. 2022:No Pagination Specified-No Pagination Specified.
584 53. Spencer TJ, Faraone SV, Tarko L, McDermott K, Biederman J. Attention-deficit/hyperactivity
585 disorder and adverse health outcomes in adults. J Nerv Ment Dis. 2014;202(10):725-31.
586 54. Li L, Chang Z, Sun J, Garcia-Argibay M, Du Rietz E, Dobrosavljevic M, et al. Attention-
587 deficit/hyperactivity disorder as a risk factor for cardiovascular diseases: a nationwide population-based
588 cohort study. World Psychiatry. 2022;21(3):452-9.
589 55. Garcia-Argibay M. The association between type 2 diabetes and attention- deficit/hyperactivity
590 disorder: a systematic review, meta-analysis, and population-based sibling study. Unpublished
591 manuscript. 2022.
592 56. Sniderman AD, Williams K, Contois JH, Monroe HM, McQueen MJ, de Graaf J, et al. A meta-analysis
593 of low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, and apolipoprotein B
594 as markers of cardiovascular risk. Circ Cardiovasc Qual Outcomes. 2011;4(3):337-45.
595 57. Li M, Zhang XW, Hou WS, Tang ZY. Insomnia and risk of cardiovascular disease: a meta-analysis of
596 cohort studies. Int J Cardiol. 2014;176(3):1044-7.
597 58. Lambert AM, Parretti HM, Pearce E, Price MJ, Riley M, Ryan R, et al. Temporal trends in associations
598 between severe mental illness and risk of cardiovascular disease: A systematic review and meta-analysis.
599 PLOS Medicine. 2022;19(4):e1003960.
600 59. Gan WQ, Buxton JA, Scheuermeyer FX, Palis H, Zhao B, Desai R, et al. Risk of cardiovascular diseases
601 in relation to substance use disorders. Drug and Alcohol Dependence. 2021;229:109132.
602 60. Song H, Fall K, Fang F, Erlendsdóttir H, Lu D, Mataix-Cols D, et al. Stress related disorders and
603 subsequent risk of life threatening infections: population based sibling controlled cohort study. BMJ.
604 2019;367:l5784.
605 61. Emdin CA, Odutayo A, Wong CX, Tran J, Hsiao AJ, Hunn BH. Meta-Analysis of Anxiety as a Risk
606 Factor for Cardiovascular Disease. Am J Cardiol. 2016;118(4):511-9.
607 62. Batelaan NM, Seldenrijk A, Bot M, van Balkom AJ, Penninx BW. Anxiety and new onset of
608 cardiovascular disease: critical review and meta-analysis. Br J Psychiatry. 2016;208(3):223-31.
609 63. Larsson H. Transparent and complete reporting of confounding in observational research. JCPP
610 Advances. 2022;2(2):e12086.
611 64. Habel LA, Cooper WO, Sox CM, Chan KA, Fireman BH, Arbogast PG, et al. ADHD medications and
612 risk of serious cardiovascular events in young and middle-aged adults. Jama. 2011;306(24):2673-83.
613 65. Levin CJ, Goodman DW, Adler LA. Review of cardiovascular effects of ADHD medications.
614 Psychiatric Annals. 2018;48(7):323-7.
615 66. Leppert B, Riglin L, Wootton RE, Dardani C, Thapar A, Staley JR, et al. The Effect of Attention
616 Deficit/Hyperactivity Disorder on Physical Health Outcomes: A 2-Sample Mendelian Randomization
617 Study. American Journal of Epidemiology. 2021;190(6):1047-55.
618 67. Du R, Zhou Y, You C, Liu K, King DA, Liang Z-S, et al. Attention-deficit/hyperactivity disorder and
619 ischemic stroke: A Mendelian randomization study. International Journal of Stroke.
620 2022:17474930221108272.
621 68. Cortese S, Sun S, Zhang J, Sharma E, Chang Z, Kuja-Halkola R, et al. Association between attention
622 deficit hyperactivity disorder and asthma: a systematic review and meta-analysis and a Swedish
623 population-based study. Lancet Psychiatry. 2018;5(9):717-26.
624 69. Imrey PB. Limitations of Meta-analyses of Studies With High Heterogeneity. JAMA Network Open.
625 2020;3(1):e1919325-e.

70. Yan LL, Liu K, Matthews KA, Daviglus ML, Ferguson TF, Kiefe CI. Psychosocial Factors and Risk of HypertensionThe Coronary Artery Risk Development in Young Adults (CARDIA) Study. Jama. 2003;290(16):2138-48.
71. Bavineni M, Wassenaar TM, Agnihotri K, Ussery DW, Lüscher TF, Mehta JL. Mechanisms linking preterm birth to onset of cardiovascular disease later in adulthood. European Heart Journal. 2019;40(14):1107-12.
72. Franz AP, Bolat GU, Bolat H, Matijasevich A, Santos IS, Silveira RC, et al. Attention-Deficit/Hyperactivity Disorder and Very Preterm/Very Low Birth Weight: A Meta-analysis. Pediatrics. 2018;141(1):e20171645.
73. Mohseni R, Mohammed SH, Safabakhsh M, Mohseni F, Monfared ZS, Seyyedi J, et al. Birth Weight and Risk of Cardiovascular Disease Incidence in Adulthood: a Dose-Response Meta-analysis. Current Atherosclerosis Reports. 2020;22(3):12.
74. Clark AM, DesMeules M, Luo W, Duncan AS, Wielgosz A. Socioeconomic status and cardiovascular disease: risks and implications for care. Nature Reviews Cardiology. 2009;6(11):712-22.
75. Russell AE, Ford T, Williams R, Russell G. The Association Between Socioeconomic Disadvantage and Attention Deficit/Hyperactivity Disorder (ADHD): A Systematic Review. Child psychiatry and human development. 2016;47(3):440-58.
76. Ambrose JA, Barua RS. The pathophysiology of cigarette smoking and cardiovascular disease: an update. Journal of the American college of cardiology. 2004;43(10):1731-7.
77. McClernon FJ, Kollins SH. ADHD and smoking: from genes to brain to behavior. Annals of the New York Academy of Sciences. 2008;1141(1):131-47.
78. Fan M, Sun D, Zhou T, Heianza Y, Lv J, Li L, et al. Sleep patterns, genetic susceptibility, and incident cardiovascular disease: a prospective study of 385 292 UK biobank participants. European Heart Journal. 2019;41(11):1182-9.
79. Owens JA. The ADHD and sleep conundrum: a review. Journal of Developmental & Behavioral Pediatrics. 2005;26(4):312-22.
80. Landau Z, Pinhas-Hamiel O. Attention deficit/hyperactivity, the metabolic syndrome, and type 2 diabetes. Current diabetes reports. 2019;19(8):1-9.
81. Powell-Wiley TM, Poirier P, Burke LE, Després J-P, Gordon-Larsen P, Lavie CJ, et al. Obesity and cardiovascular disease: a scientific statement from the American Heart Association. Circulation. 2021;143(21):e984-e1010.
82. Einarson TR, Acs A, Ludwig C, Panton UH. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007–2017. Cardiovascular Diabetology. 2018;17(1):83.
83. Hedayatnia M, Asadi Z, Zare-Feyzabadi R, Yaghooti-Khorasani M, Ghazizadeh H, Ghaffarian-Zirak R, et al. Dyslipidemia and cardiovascular disease risk among the MASHAD study population. Lipids in Health and Disease. 2020;19(1):42.
84. Vancampfort D, Stubbs B, Mitchell AJ, De Hert M, Wampers M, Ward PB, et al. Risk of metabolic syndrome and its components in people with schizophrenia and related psychotic disorders, bipolar disorder and major depressive disorder: a systematic review and meta-analysis. World psychiatry : official journal of the World Psychiatric Association (WPA). 2015;14(3):339-47.

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670

671 **FIGURES**

672 **Figure 1** PRISMA flow diagram for inclusion of the studies examining the association
673 between ADHD and cardiovascular diseases
674 *PRISMA = Preferred Reporting Items for Systematic Review and Meta-Analyses*
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677 **Figure 2** Casual diagram representing the potential pathways of the association ADHD
678 and CVDs
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681 **Figure 3** Forest plot of all studies describing associations between ADHD and CVDs
682 with adjusted estimates
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Table 1 Overview of studies included in the systematic review

Study	Country	Data sources and year of original data collection	Study design	Sample size	N (CVD)/N(ADHD)	N (CVD)/N(NON-ADHD)	Male (%)	Mean age or age range	Exposure		Outcomes		NOS
									ADHD Definition	Age at assessment	Definition	Diseases	
Akmatov (2019) *	Germany	Insurance claims data, 2017	cross-sectional	2,586,620	4,837/258,662	16,519/2,327,958	75.6	5-14	ICD-10	5-14	ICD-10	Hypertension	7
Chen (2018) *	Sweden	National medical registers,1968-2013	cross-sectional	5,551,807	2,072/61,129	247,870/5,490,678	50.8	40.55±13.49; 18-64	ICD-9 and 10	18-64	ICD-8, 9 and 10	Hypertension	6
Du Rietz (2021)	Sweden	National medical registers,1932-2013	Cohort (follow for 47years)	4,789,799	NA/61,960	NA/4,727,839	51.0	18-81	ICD-9 and 10, ADHD medication prescription	N/A	ICD-8, 9 and 10	Hypertension, ischaemic heart disease, pulmonary disease, atrial fibrillation, heart failure, stroke, peripheral vascular disease	8
Fuemmeler (2011) *	United States	National Longitudinal Study of Adolescent Health, 1995-2009	Cohort (follow for 33years)	11,015	46/262	NA/10,753	51.0	28.80±0.12	Self-report	N/A	7th report of the Joint National Committee on Prevention Detection, Evaluation, and Treatment of High Blood Pressure: SBP ≥ 160 mm Hg and DBP ≥ 100	Hypertension	7
Grisaru (2018)	Canada	Research sample,2007-	case-control	3,804	3/55	53/3,749	51.1	6-19	Medical record	6-19	The fourth report on the diagnosis evaluation and	Hypertension	2

		2013								treatment of high blood pressure in Children and adolescents			
Li (2022)	Sweden	National medical registers,1941-2013	Cohort (follow11.8 years)	5,389,519	663/37,027	62,089/5,352,492	48.9	38.44±12.32; 18-73	ICD-9 and 10	3-73	ICD-8, 9 and 10	CVD	9
Nilgün (2019)	Turkey	Research sample, 2012	case-control	177	10/77	9/100	24.3	8.95±2.68; 5-15	DSM-IV	N/A	Recommendations of the American Heart Association	Hypertension	3
Olazagasti (2013)	United States	Research sample	cohort	271	37/135	37/136	100.0	41.4±2.9	Teacher and parent rating	41.4±2.9	N/A	CVD	3
Semeijn (2013) *	Netherlands	Research sample,2008-2009	cross-sectional	231	7/23	67/208	40.7	71.6±7.7	Semi-structured diagnostic interview	N/A	Self-report	CVD	5
Spencer (2014)	United States	Research sample	case-control	198	1/98	1/100	45.5	31±11	the adult ADHD self-reportscale (ASRS) v1.1 Symptom Checklist	N/A	Self-report	Heart attack	5
Xu (2021) *	United States	National Health Interview Survey, 2007 and 2012	cross-sectional	57,728	256/1,790	7,650/55,938	47.7	18 or older	Self-report	N/A	Self-report	All CVD Coronary heart disease Stroke	5

*****_Included in the adjusted meta-analysis_

Table 2 Adjusted covariates in studies of ADHD and CVDs

	Covariates adjusted in each included study												
Study	Gender	Age/Year of birth	Region/race/ethnicity	Education achieved	Metabolic conditions [a]	Family income	Depression	Other psychiatric comorbidities [b]	Smoking	Alcohol	Psychiatric medications	Family history of CVD	Physical activity
Akmatov (2019)	×	×	×										
Chen (2018)	×	×											
Du Rietz (2021)	×	×											
Fuemmeler (2011)	×	×	×	×			×		×	×			×
Grisaru (2018)	N/A												
Li (2022)	×	×	×	×	×		×	×	×		×	×	
Nilgün (2019)	N/A												
Olazagasti (2013)	N/A												
Semeijn (2013)	×	×											
Spencer (2014)	N/A												
Xu (2021)	×	×	×	×		×			×	×			

Metabolic conditions include obesity, type 2 diabetes, dyslipidemia

B Other psychiatric comorbidities include anxiety disorder, autism spectrum disorder, bipolar disorder, conduct disorder, depressive disorder, eating disorder, intellectual disability, personality disorder, schizophrenia and substance use disorder

Table 3 Summary of results of subgroups analyses

Study	Number of studies	Pooled ORs	Q	P_Q	I^2
Adults	4	1.73(1.14-2.62)	6.28	0.1	6.28%
Children	1	3.26(3.00-3.55)	N/A	N/A	N/A
Adults:					
Hypertension	3	1.55 (0.75-3.21)	5.89	0.06	66.0%
Other CVDs	3	1.73(1.19-2.68)	3.2	0.201	37.7%

P_Q: p-value associated to the Q statistic of heterogeneity

Table 4 The magnitude of associations between ADHD, well-established risk factors for CVDs, and psychiatric disorders with CVDs among adults

	OR/HR/RR (95% CI)	Type of evidence
ADHD	1.73(1.14-2.62)	Meta-analysis of observational studies
Well-established risk factors for CVD		
Sedentary behavior (26)	2.47 (1.44-4.24)	Meta-analysis of observational studies
Diabetes (55)	2.29 (1.48-3.55)	Meta-analysis of observational studies
Smoking (24)	2.07 (1.82-2.36)	Meta-analysis of observational studies
Dyslipidemia (56)	1.43 (1.35- 1.51)	Meta-analysis of observational studies
Obesity (25)	1.43 (1.33-1.54)	Meta-analysis of observational studies
Sleep disorders (57)	1.33 (1.13-1.57)	Meta-analysis of observational studies
Psychiatry comorbidities		
Schizophrenia (58)	1.91 (1.52–2.41)	Meta-analysis of observational studies

Substance use disorder (59)	1.70 (1.6 - 1.9)	Cohort study
Stress-related disorders (60)	1.64 (1.45-1.84)	Cohort study
Depression (61)	1.64 (0.84, 3.19)	Meta-analysis of observational studies
Bipolar disorder (58)	1.61 (1.34–1.94)	Meta-analysis of observational studies
Anxiety disorders (62)	1.52 (1.36 - 1.71)	Meta-analysis of observational studies

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Risk of Cardiovascular Diseases Associated With Medications Used in Attention-Deficit/Hyperactivity Disorder

A Systematic Review and Meta-analysis

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Abstract

IMPORTANCE Use of attention-deficit/hyperactivity disorder (ADHD) medications has increased substantially over the past decades, but there are concerns regarding their cardiovascular safety.

OBJECTIVE To provide an updated synthesis of evidence on whether ADHD medications are associated with the risk of a broad range of cardiovascular diseases (CVDs).

DATA SOURCES PubMed, Embase, PsycINFO, and Web of Science up to May 1, 2022.

STUDY SELECTION Observational studies investigating the association between ADHD medications (including stimulants and nonstimulants) and risk of CVD.

DATA EXTRACTION AND SYNTHESIS Independent reviewers extracted data and assessed study quality using the Good Research for Comparative Effectiveness (GRACE) checklist. Data were pooled using random-effects models. This study is reported according to the Meta-analyses of Observational Studies in Epidemiology guideline.

MAIN OUTCOMES AND MEASURES The outcome was any type of cardiovascular event, including hypertension, ischemic heart disease, cerebrovascular disease, heart failure, venous thromboembolism, tachyarrhythmias, and cardiac arrest.

RESULTS Nineteen studies (with 3 931 532 participants including children, adolescents, and adults; 60.9% male), of which 14 were cohort studies, from 6 countries or regions were included in the meta-analysis. Median follow-up time ranged from 0.25 to 9.5 years (median, 1.5 years). Pooled adjusted relative risk (RR) did not show a statistically significant association between ADHD medication use and any CVD among children and adolescents (RR, 1.18; 95% CI, 0.91-1.53), young or middle-aged adults (RR, 1.04; 95% CI, 0.43-2.48), or older adults (RR, 1.59; 95% CI, 0.62-4.05). No significant associations for stimulants (RR, 1.24; 95% CI, 0.84-1.83) or nonstimulants (RR, 1.22; 95% CI, 0.25-5.97) were observed. For specific cardiovascular outcomes, no statistically significant association was found in relation to cardiac arrest or arrhythmias (RR, 1.60; 95% CI, 0.94-2.72), cerebrovascular diseases (RR, 0.91; 95% CI, 0.72-1.15), or myocardial infarction (RR, 1.06; 95% CI, 0.68-1.65). There was no associations with any CVD in female patients (RR, 1.88; 95% CI, 0.43-8.24) and in those with preexisting CVD (RR, 1.31; 95% CI, 0.80-2.16). Heterogeneity between studies was high and significant except for the analysis on cerebrovascular diseases.

CONCLUSIONS AND RELEVANCE This meta-analysis suggests no statistically significant association between ADHD medications and the risk of CVD across age groups, although a modest risk increase

(continued)

Key Points

Question Are attention-deficit/hyperactivity disorder (ADHD) medications associated with the risk of cardiovascular disease (CVD)?

Findings This systematic review and meta-analysis based on 19 observational studies with more than 3.9 million participants suggested that there was no statistically significant association between ADHD medications and the risk of cardiovascular events among children and adolescents, young and middle-aged adults, or older adults.

Meaning Despite no statistically significant association between ADHD medications and CVD, more evidence is needed for the potential risk of cardiac arrest and tachyarrhythmias, the cardiovascular risk in female patients and in those with preexisting CVD, and long-term risk.

+ Invited Commentary

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Abstract (continued)

could not be ruled out, especially for the risk of cardiac arrest or tachyarrhythmias. Further investigation is warranted for the cardiovascular risk in female patients and patients with preexisting CVD as well as long-term risks associated with ADHD medication use.

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Introduction

Attention-deficit/hyperactivity disorder (ADHD), one of the most common neurodevelopmental disorders, is characterized by developmentally inappropriate inattention and/or hyperactivity-impulsivity symptoms starting in childhood.[1] The symptoms often persist into adulthood,[2,3] and even into older age for a substantial number of patients.[4] ADHD medications, including both stimulants and nonstimulants, are recommended for pharmacological treatment of ADHD, and the prevalence of ADHD medication use among both children and adults has increased substantially in many countries.[5]

While evidence from randomized clinical trials (RCTs) suggests ADHD medications are efficacious in reducing core ADHD symptoms,[6] there are concerns about their cardiovascular safety.[7] As ADHD medications are sympathomimetic agents that exert dopaminergic and noradrenergic effects, increasing heart rate and blood pressure is biologically plausible.[8] A previous Cochrane review of RCTs found that the stimulant methylphenidate was associated with increased pulse or heart rate.[7] However, as these RCTs could only evaluate short-term effects, it remains uncertain whether these changes led to a clinically significant risk of cardiovascular disease (CVD) over time. Longitudinal observation studies evaluating serious cardiovascular outcomes associated with ADHD medication use have emerged during the last decade, but with mixed findings.[9-12] A review paper incorporating five large population-based studies in the US reported no association between stimulants and serious cardiovascular events in children.[13] A meta-analysis of only 3 studies[14] found no increased risk of arrhythmic and ischemic cardiac events but a decreased risk of stroke. A more recent meta-analysis of 10 studies[15] showed a positive association between ADHD medications and risk of sudden death or arrhythmia but not for stroke, myocardial infarction, or all-cause mortality. However, it had several methodology limitations (eg, not preregistered, narrow outcome definition, and missing several important studies). Moreover, several new original studies have been published after these meta-analyses.[16-20] Thus, an updated synthesis is needed to address those limitations as well as to include a broader range of cardiovascular events (eg, hypertension, heart failure, and transient ischemic attack that have not been included in previous meta-analyses) and conduct sub-analyses by type of cardiovascular events and ADHD medications. In addition, observational studies that evaluate the benefits or risks of medical treatments are prone to bias (eg, immortal time bias, prevalent user bias, confounding by indication) if not conducted appropriately. It is therefore critical to make a rigorous quality assessment of the available studies and discuss common problems that future studies need to address. Understanding whether, and to what extent, ADHD medications are associated with CVD is highly relevant from both clinical and public health perspectives, as an increasing number of individuals are receiving ADHD medications globally. Findings of any significant association would prompt research on underlying causal mechanisms (eg, dopaminergic dysfunction and alterations in cytochrome P450 2D6 metabolism).[8,21]

The current study aims to provide a comprehensive and updated systematic review and meta-analysis to assess the associations between ADHD medications and risks of a broad range of cardiovascular events. In addition, we aim to examine whether there is any difference in the associations by types of ADHD medication, types of cardiovascular events, sex, age, and preexisting CVD conditions.

Methods

This study was conducted and reported according to the Meta-analyses of Observational Studies in Epidemiology (MOOSE) checklist.[22] Our protocol is registered in the International Prospective Register of Systematic Reviews (CRD42021283702).[23]

Search Strategy and Selection of Studies

A systematic search for observational studies was conducted in MEDLINE via PubMed, Embase, PsycINFO, and Web of Science, up to May 1, 2022. We used various combinations of the following keywords: *cardiovascular disease*, *coronary heart disease*, *heart disease*, *sudden death*, *ischemic heart disease*, *hypertension*, *cerebrovascular disease*, *stroke*, *transient ischemic attack*, *attention-deficit hyperactivity disorder*, *central nervous system stimulants*, and *observational study*. No restrictions to language were applied. The search strategy was designed with the assistance of a university librarian at Karolinska Institute (eTable 1 in the Supplement). In addition, we performed manual searches through the reference lists of relevant original publications and reviews to identify further pertinent studies.

We included all types of observational studies investigating associations between ADHD medication use and the risk of any CVD. We excluded reports, review articles, animal research, RCTs, and conference abstracts; studies without a comparator group; and studies with abuse or misuse of ADHD medication as the exposure. Titles, abstracts, and full text of included studies were screened independently by 2 investigators (L.Z. and H.Y.). Discrepancies were resolved through discussion with a senior investigator (L.L.).

Data Extraction

The following information was extracted from each study for the qualitative and quantitative synthesis: first author, year of publication, sample size, data source, study country, age and sex distribution, study design, year of original data collection, follow-up time, type of ADHD medication, measure of medication use, definition of CVD, relative risk, and covariate adjustment. Two investigators conducted the data extraction separately (L.Z. and H.Y.), and any disagreements were resolved through discussion with a senior investigator (L.L.).

Good Research for Comparative Effectiveness (GRACE) checklist version 2 was used for quality assessment.[24] Unlike the commonly used Newcastle-Ottawa Scale,[25] the GRACE checklist is tailored for evaluating the quality of observational studies that examine the outcomes of medical treatment. It evaluates the quality of observational research based on the use of concurrent comparators, equivalent measurement of outcomes in different groups, collection of data on confounders and effect modifiers, risk of immortal time bias, and reporting of sensitivity analysis.[24] Eleven items in the GRACE Checklist are grouped into 2 groups reflecting the quality of data and methods (eTable 2 in the Supplement). The quality assessment was completed by two investigators independently (L.Z. and H.Y.), and any discrepancies were solved by discussing with a senior investigator (L.L.).

Statistical Analysis

The characteristics of all included studies were described. Hazard ratios (HRs) from Cox regression, incidence rate ratios (IRRs) from Poisson regression, and odds ratios (ORs) from logistic regression were combined as approximations to relative risks (RRs), because under rare event assumption, different effect measures would yield mathematically similar estimates.[26,27] We used random-effects models to account for heterogeneity between studies. The significance of heterogeneity across studies was examined using Cochran *Q* test, while the percentage of variation attributed to true heterogeneity was estimated using the inconsistency index (I^2).[28] The restricted maximum likelihood method was used to estimate between-study variability, with the Hartung-Knapp-Sidik-Jonkman confidence interval for the summary estimates.[29,30]

We meta-analyzed adjusted RRs across all studies and by age groups (children and adolescents, young and middle-aged adults, and older adults). To evaluate each study's influence on the pooled estimates, the leave-one-out analysis was conducted. Publication bias was first assessed through visual inspection of the funnel plot and then tested quantitatively with Egger test. Subgroup analyses were conducted to investigate the associations of (1) stimulant and nonstimulant medications with any CVD, (2) ADHD medications with specific CVD (ie, cardiac arrest or tachyarrhythmias, cerebrovascular disease, myocardial infarction), (3) stimulant ADHD medications with specific CVD, (4) ADHD medications with any CVD in individuals with and without a history of CVD, and (5) ADHD medications with any CVD by sex. All analyses were performed with Stata version 16.0 (StataCorp). Statistical significance was set at $P < .05$, and all tests were 2-tailed.

Results

Study Characteristics

The process of study selection is shown in **Figure 1**. Detailed information on excluded articles with reasons is shown in eTable 3 in the Supplement. Overall, we included 19 studies published during 2007 to 2021, and their main characteristics are presented in **Table 1**.[9-12,16-20,31-40] A total of 3 931 532 participants from 6 countries or regions (United States, South Korea, Canada, Denmark, Spain, and Hong Kong) were included. The study samples included children, adolescents, and adults, and 60.9% of participants were male. Average follow-up time ranged from 0.25 to 9.5 (median, 1.5) years. Most studies (14) were cohort studies,[9-12,18,20,32-37,39,40] followed by 3 nested case-control studies,[16,19,31] and 2 self-controlled case series.[17,38] The most common data source was insurance claims databases (15 studies).[9,10,12,16,17,20,31-33,35-39] More than half of the studies (10) used incident users,[17,20,31-33,35-39] while others included prevalent users.[9-12,16,18,19,34,40] Most studies used *International Classification of Diseases, Ninth Revision* or *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* to define CVD, except 1 study[34] that used self-reported CVD and another[40] without sufficient information on outcome measurement. Absolute

Figure 1. Flow Diagram for Inclusion of Studies

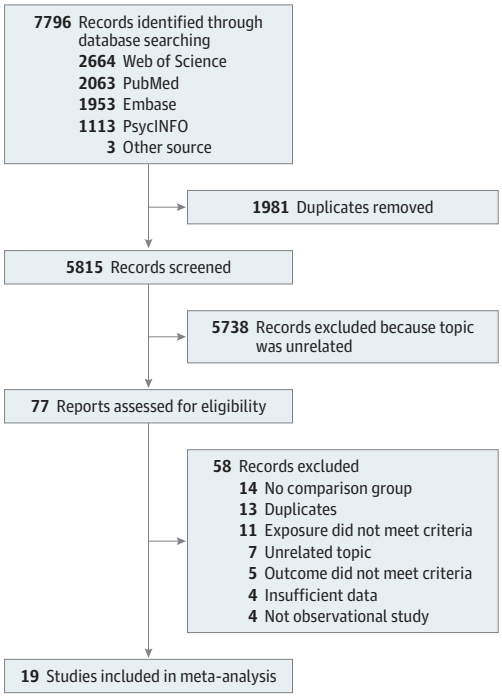


Table 1. Characteristics of Included Studies

Source (country)	Data source	Year of data collection	Study design	Median follow-up, y	Participants, No.	Male, %	Age, y	Exposure				Outcomes		Adjustment for covariates	GRACE score
								ADHD medication	New or prevalent user	Measure of use	Duration of use, y	Definition	Diseases		
Cooper et al,[9] 2011 (United States)	Claims	1986-2005	Cohort	2.1	1 200 438	71	Mean, 11; range, 2-24	AMP, MPH, DMPH, ATX, pemoline	Mixed[a]	Current	NA	*ICD-9*, *ICD-10*	MI, CA, stroke	Demographics, comorbidities, health care utilization	11
Dalsgaard et al,[11] 2014 (Denmark)	Register	1990-2008	Cohort	9.5	8300	81	Mean, 11	AMP, MPH	Mixed[a]	Current	2.5	*ICD-10*	CVD	Demographics, comorbidities, perinatal characteristics	8
Guertin et al,[31] 2014 (Canada)	Claims	2001-2010	NCC	NA	38 495	70	Mean, 9	AMP, MPH, ATX	New	Current	NA	*ICD-9*, *ICD-10*	CVD	Demographics	8
Habel et al,[10] 2011 (United States)	Claims	1986-2005	Cohort	1.3	443 198	46	Range, 25-64	AMP, MPH, ATX, pemoline	Mixed[a]	Current	0.33	*ICD-9*, *ICD-10*	MI, CA, stroke	Demographics, CV risk score	11
Holick et al,[32] 2009 (United States)	Claims	2003-2006	Cohort	1.5	86 205	52	≥18	AMP, MPH, ATX	New	Current	NA	*ICD-9*	Cerebrovascular disease, TIA	Demographics, comorbidities, comedications	9
Houghton et al,[16] 2020 (United States)	Claims	2000-2016	NCC	NA	2046	68	Mean, 14; range, 3-18	AMP, MPH, ATX	Mixed[a]	Current	NA	*ICD-9*, *ICD-10*	MI, arrhythmia, stroke	Demographics, CV risk, comorbidities, comedications	9
Jeong et al,[17] 2021 (South Korea)	Claims	2002-2018	SCCS	NA	2104	51	Mean, 58; ≥6	MPH	New	Current	2.8	*ICD-10*	MI	Age, comorbidities, comedications	10
Jeong et al,[17] 2021 (Taiwan)	Claims	2004-2015	SCCS	NA	484	64	Mean, 65; ≥6	MPH	New	Current	2.3	*ICD-9*	MI	Age, comorbidities, comedications	10
Jeong et al,[17] 2021 (Hong Kong)	Clinical data	2001-2016	SCCS	NA	30	50	Mean, 70; ≥48	MPH	New	Current	2.3	*ICD-9*	MI	Age, comorbidities, comedications	10
Latronica et al,[18] 2021 (United States)	EHR	2018-2020	Cohort	2	13 233	37	Mean, 70; ≥65	AMP	Mixed[a]	Current	NA	*ICD-10*	HF, stroke, MI, AF, IHD, arrhythmia	Demographics, BMI, comorbidities	7
Olfson et al,[33] 2012 (United States)	Claims	1997-2007	Cohort	1.8	171 126	67	Range, 6-21	AMP, MPH	New	Current	NA	*ICD-9*	Angina pectoris, arrhythmia, TIA	Demographics, comorbidities, comedications	9
Peyre et al,[34] 2014 (United States)	National representative survey	2004-2005	Cohort	1	807	59	Mean, 40	Not specified	Mixed[a]	Ever	NA	Self-report	MI, angina pectoris, stroke	CV risk factors	5
Saiz et al,[19] 2020 (Spain)	Primary care database	2002-2014	NCC	NA	2882	40	Mean, 14; range, 5-25	MPH	Mixed[a]	Current	0.65	ICPC, *ICD-9*	Valvular heart disease	Age, sex, smoking, comorbidities, comedications	9
Schelleman et al,[35] 2011 (United States)	Claims	1999-2006	Cohort	1.4	241 417	72	Range, 3-17	AMP, MPH, ATX	New	Current	0.37	*ICD-9*	Sudden death, ventricular arrhythmia	Data source	8
Schelleman et al,[36] 2012 (United States)	Claims	1999-2006	Cohort	1.2	219 954	45	≥18	MPH	New	Current	0.16	*ICD-9*	MI, stroke	Demographics, comorbidities, comedications	9
Schelleman et al,[37] 2013 (United States)	Claims	1999-2006	Cohort	1.2	192 905	46	≥18	AMP	New	Current	0.24	*ICD-9*	MI, stroke	Demographics, comorbidities, comedications	9

(continued)

Table 1. Characteristics of Included Studies (continued)

Source (country)	Data source	Year of data collection	Study design	Median follow-up, y	Participants, No.	Male, %	Age, y	Exposure				Outcomes		Adjustment for covariates	GRACE score
								ADHD medication	New or prevalent user	Measure of use	Duration of use, y	Definition	Diseases		
Shin et al,[38] 2016 (South Korea)	Claims	2008-2011	SCCS	NA	1224	78	Mean, 13; range, ≤17	MPH	New	Current	0.5	*ICD-10*	Arrythmias, HF, Hypertension, MI, stroke	Age, comorbidities, comedications	11
Tadrous et al,[20] 2021 (Canada)	Claims and health care database	2002-2016	Cohort	1	31 310	49	Mean, 74; range, ≥66	AMP, MPH	New	Current	NA	*ICD-9*, *ICD-10*	MI, ventricular arrhythmia, stroke, TIA	Demographics, CVD history, physician visits, comorbidities, comedications	11
Winterstein et al,[39] 2007 (United States)	Claims	1994-2004	Cohort	2.3	55 383	70	Range, 3-20	AMP, MPH, pemoline	New	Current	NA	*ICD-9*	MI, hypertensive diseases, aortic or thoracic aneurysm, arrhythmia, cardiac symptoms	Age, race, congenital anomalies, history of circulatory disease, comorbidities, comedications	9
Winterstein et al,[12] 2012 (United States)	Claims	1999-2006	Cohort	1.9	1 219 847	59	Range, 3-18	AMP, MPH	Mixed[a]	Current	NA	*ICD-9*	MI, CA, ventricular arrhythmia, stroke	Demographics, CV risk factors, comorbidities, and comedications	9
Zhang et al,[40] 2015 (United States)	Research sample	1979-2014	Cohort	7.9	144	62	Mean, 11	AMP, MPH, ATX, guanfacine	Mixed[a]	Current	NA	NA	Syncope, aborted CA	Age, gender, QTc-duration, prior cardiac event, comedications	6

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; AF, atrial fibrillation; AMP, amphetamines; ATX, atomoxetine; BMI, body mass index; CA, cardiac arrest; CV, cardiovascular; CVD, cardiovascular disease; DMPH, dexmethylphenidate; EHR, electronic health record; HF, heart failure; EHR, electronic health records; GRACE, The Good Research for Comparative Effectiveness Checklist; *ICD-9*, *International Classification of Diseases, Ninth Revision*; *ICD-10*, *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*; ICPC, international classification of primary care; IHD, ischemic heart disease; MI, myocardial infarction; MPH, methylphenidate; NA, not available; NCC, nested case-control; SCCS, self-controlled case series; TIA; transient ischemic attack.

[a] Mixed indicates mixture of incident and prevalent users.

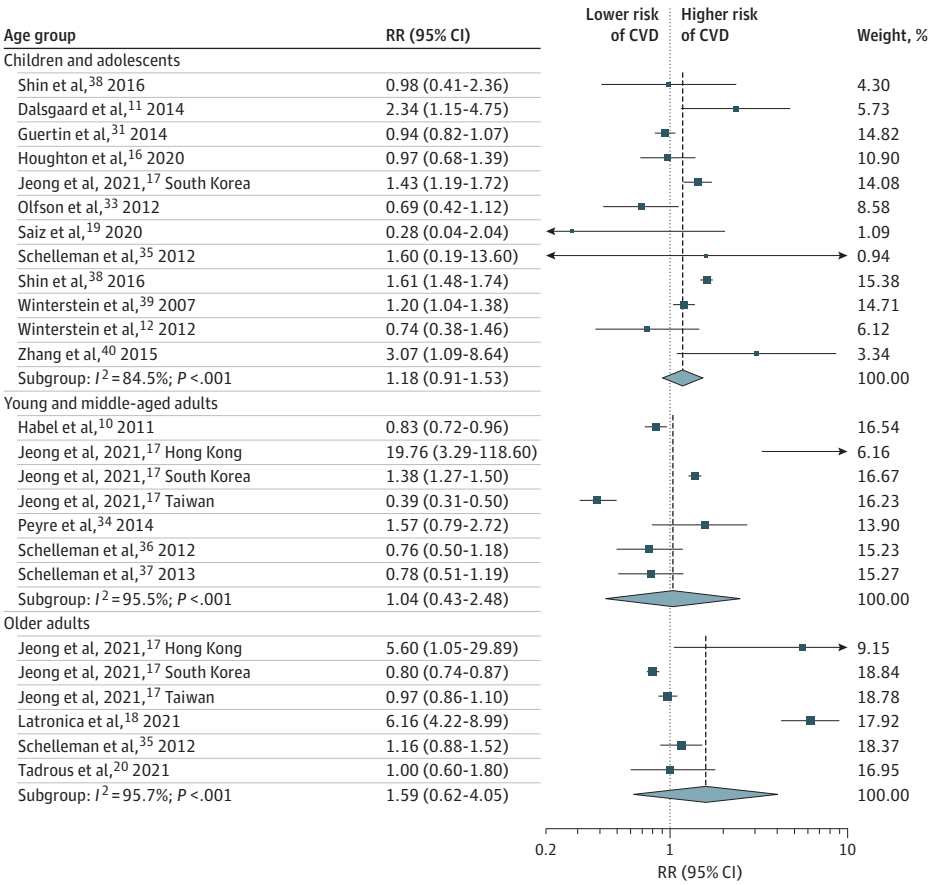
risks of CVD in the included studies are shown in eTable 4 in the Supplement. All studies adjusted for measured covariates as an attempt to control for confounding, but the included covariates varied substantially across studies. The 2 self-controlled case series studies[17,38] further accounted for unmeasured confounders that are time invariant. The GRACE quality scores ranged from 5 to 11 (median, 9). Immortal time bias and lack of meaningful sensitivity analyses were the most common limitations in studies with lower scores (eTable 5 in the Supplement).

Meta-analysis Results

We found that ADHD medication use was not statistically significantly associated with the risk of any CVD among children and adolescents (RR, 1.18; 95% CI, 0.91-1.53), young and middle-aged adults (RR, 1.04; 95% CI, 0.43-2.48), older adults (RR, 1.59; 95% CI, 0.62-4.05) (**Figure 2**), or overall (RR, 1.22; 95% CI, 0.88-1.68 (**Figure 3**). Analysis by effect measures also did not show significant estimates for HR (1.09; 95% CI, 0.84-1.42), OR (1.17; 95% CI, 0.51-2.66), or IRR (1.42; 95% CI, 0.43-4.68 (Figure 3). Heterogeneity between studies was high and significant (Cochran Q = 292.7; P < .001; I^2 = 93.2%). When restricting to specific effect measurements, heterogeneity was not significant for the analysis with HR as effect measures, yet it was still significant in other subgroups (Figure 3). As shown in the leave-one-out sensitivity analysis (eFigure 1 in the Supplement), the estimate was not driven by a single study. There was no evidence of publication bias, and a small study effect for the primary outcomes (eFigures 2 and 3 in the Supplement).

In subgroup analyses, we found no statistically significant associations of stimulant (RR, 1.24; 95% CI, 0.84-1.83) and nonstimulant medications (RR, 1.22; 95% CI, 0.25-5.97) with any CVD

Figure 2. Risk of Any Cardiovascular Event by Age Group Among Individuals Receiving Attention-Deficit/Hyperactivity Disorder Medication

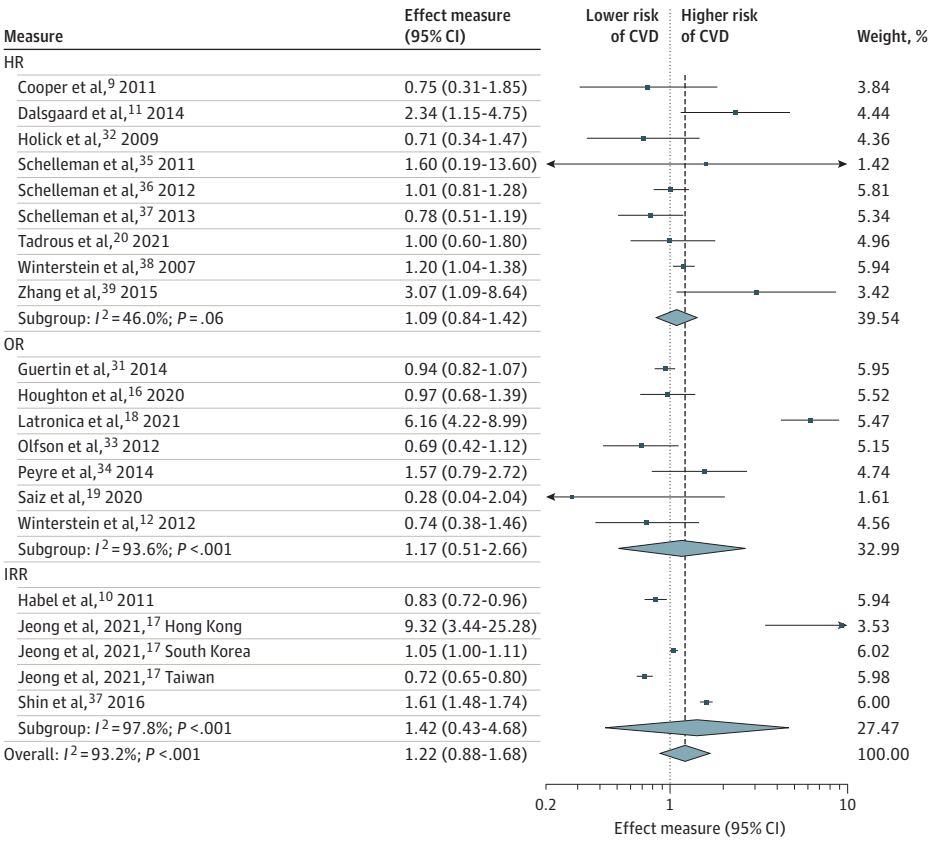


CVD indicates cardiovascular disease; RR, risk ratio.

(**Table 2**; eFigure 4 in the Supplement). When examining specific CVD outcomes (Table 2; eFigure 5 in the Supplement), no statistically significant associations were suggested for cardiac arrest or arrhythmias (RR, 1.60; 95% CI, 0.94-2.72), cerebrovascular diseases (RR, 0.91; 95% CI, 0.72-1.15), or myocardial infarction (RR, 1.06; 95% CI, 0.68-1.65). When examining stimulant medications, we found a similar pattern of results (eFigure 6 in the Supplement).

There was no association between ADHD medication use and any CVD for female (RR, 1.88; 95% CI, 0.43-8.24) and male (RR, 1.08; 95% CI, 0.32-3.67) patients. (Table 2; eFigure 7 in the

Figure 3. Risk of Any Cardiovascular Event by Measure of Association Among Individuals Receiving Attention-Deficit/Hyperactivity Disorder Medication



CVD indicates cardiovascular disease; HR, hazard ratio; IRR, incidence rate ratio; OR, odds ratio.

Table 2. Summary of Subgroup Analysis Results

Subgroup	Studies, No. (data sets, No.)	Pooled RRs	P[a]	I^2, %
Type of ADHD medication				
Stimulants	15 (17)	1.24 (0.84-1.83)	<.001	94.2
Nonstimulants	3 (3)	1.22 (0.25-5.97)	<.001	90.2
Specific CVD outcome				
Cardiac arrest or tachyarrhythmias	9 (9)	1.60 (0.94-2.72)	<.001	77.9
Cerebrovascular diseases	10 (10)	0.91 (0.72-1.15)	.14	34.0
Myocardial infarction	8 (10)	1.06 (0.68-1.65)	<.001	86.2
Sex groups				
Male	3 (5)	1.08 (0.32-3.67)	<.001	96.1
Female	3 (5)	1.88 (0.43-8.24)	<.001	85.6
Prior CVD history				
Without CVD history	10 (11)	0.99 (0.73-1.33)	<.001	98.7
With CVD history	7 (8)	1.31 (0.80-2.16)	<.001	99.0

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CVD, cardiovascular disease; RR, risk ratio.

[a] *P* value associated to the Cochran *Q* statistic of heterogeneity.

Supplement). We found no statistically significant associations in either individuals without a history of CVD (RR, 0.99; 95% CI, 0.73-1.33) or individuals with a history of CVD (RR, 1.31; 95% CI, 0.80-2.16) (Table 2). In particular, the only 2 studies[11,40] with long-term follow-up both showed elevated risk (RR, 2.01; 95% CI, 1.98-2.06 and RR, 3.07; 95% CI, 1.09-8.64) in those with a history of CVD (eFigure 8 in the Supplement).

Discussion

Main Findings

To our knowledge, this is the most comprehensive systematic review and meta-analysis of longitudinal observational studies on the association between ADHD medication use and the risk of CVD. By pooling results of 19 studies, we found no statistically significant association between ADHD medication use and CVD among children and adolescents, young and middle-aged adults, or older adults, although the pooled RR did not exclude a modest risk increase, especially for the risk of cardiac arrest or tachyarrhythmias. We did not detect any difference in the cardiovascular risk between stimulant and nonstimulant ADHD medication use. There was no association between ADHD medication and any CVD among female patients and those with preexisting CVD, although further study may be needed in these populations.

This updated meta-analysis enabled us to include 13 more studies than the previous meta-analyses.[14,15] Unlike the previous meta-analyses, we did not include all-cause mortality in our primary outcome (but sudden cardiac death), as previous studies have shown that most of the mortality in patients with ADHD was due to unnatural causes (eg, accidents and suicide).[41,42] We examined a broad range of cardiovascular outcomes including important cardiovascular outcomes (eg, hypertension and heart failure) in addition to those examined in previous meta-analyses (cardiac arrest, tachyarrhythmias, myocardial infarction, and stroke). We found no statistically significant association between ADHD medication use and CVD among children and adolescents, young and middle-aged adults, or older adults, although the confidence interval could not exclude an increased risk. It should be noted that as the absolute risk is relatively low, even a significant RR of 22% risk increase in general would possibly be offset by the benefits of medications, eg, alleviating ADHD symptoms and reducing risky behavior.[6,43] The trade-off between benefits and risks could be different in high-risk patients. Regarding specific cardiovascular outcomes, results from previous meta-analyses for specific cardiovascular outcomes (ie, cardiac arrest or tachyarrhythmias and stroke) are inconsistent.[14,15] We found that ADHD medication use seemed to be associated with an increased risk of cardiac arrest or tachyarrhythmias, but not with cerebrovascular disease and myocardial infarction.

We also reported several findings that were not explored in previous meta-analyses. In terms of types of ADHD medication, we found both stimulant and nonstimulant ADHD medications were not statistically significantly associated with any CVD, with similar pooled RRs. These would suggest similar null effects on CVD or similar degree of confounding in studies of both stimulants and nonstimulants. We were unable to compare stimulants vs nonstimulants for the risk of specific CVD due to the limited number of studies that examined nonstimulants. Of note, 1 previous open-label extension of an RCT study[44] compared the cardiovascular risks of a stimulant ADHD medication (dexmethylphenidate) vs a nonstimulant ADHD medication guanfacine. The study found that dexmethylphenidate was associated with increased systolic blood pressure, while guanfacine was associated with decreased heart rate, but both returned to baseline value during the 1-year open-label extension phase. It suggests that there might be differences in cardiovascular risks between stimulants and nonstimulants, but these differences may attenuate over time, thus not leading to a significant difference in clinically relevant outcomes. Nevertheless, head-to-head comparison studies based on observational data are warranted to compare stimulant vs nonstimulant ADHD medications regarding the risk of specific CVD.

We found that the risk of cardiovascular events associated with ADHD medications seemed to be higher among those with preexisting CVD compared with no prior CVD, although the findings did not reach the threshold for statistical significance. This coincides with raising concerns that individuals with congenital or acquired CVD are predisposed to additional risk.[45] Despite the lack of data supporting CVD history as a contraindication for ADHD medications, the FDA labeling includes a warning on the use of ADHD medications among individuals with structural cardiac abnormalities or other serious heart problems. Current treatment guidelines generally recommend carefully assessing patients with ADHD (eg, personal and family history of CVD, physical examination, electrocardiogram) and identifying individuals at risk before initiating ADHD medications.[45] Careful monitoring should also be performed after initiation.[46,47] Further studies focusing on the potential modifying risk of preexisting CVD, ideally separating risks for congenital or acquired CVD, are warranted. Clinical guidelines on prescribing ADHD medications among high-risk individuals should be updated once further evidence is available. We also found the point estimates for risk of CVD seemed to be higher among female compared with male patients, although only 3 studies have examined the sex-specific association along with high heterogeneity between studies. Previous research has shown that females with ADHD have somewhat different patterns of comorbidities[48,49] and response to stimulants[50] than males, and additional research is needed to examine this potential sex difference.

Methodology Consideration

The analysis of observational data provides an emerging opportunity to generate evidence to inform clinical decisions, but there are important issues to consider to avoid biases.[51] One key issue is that treatment is not randomly assigned, which could result in confounded estimates. The included studies mainly reflected practice in clinical settings rather than controlled settings, so the prescription of ADHD medications is influenced by the clinician's perception of CVD risk. Most studies adjusted for a range of measured confounders, but the included confounders varied across studies. Many studies adjusted for demographic characteristics, and several adjusted for baseline comorbid conditions (eg, psychosis, obesity, and diabetes) and comedications (eg, antiepileptics, antidepressants, and asthma medications), yet few studies accounted for time-varying confounding factors. Moreover, several studies used general population control (rather than individuals with ADHD) as the comparison group, but only 1 study[9] adjusted for ADHD status. Not accounting for ADHD status would lead to bias, as recent research found that ADHD itself is a risk factor for CVD independent from comorbid psychiatric and somatic conditions.[52]

In addition, other fundamental flaws, such as selection bias and immortal time bias, need to be considered carefully when interpreting results from observational studies.[51] Nine of the 19 included studies[9-12,16,18,19,34,40] used prevalent users instead of incident users, and 7 studies[16,18,19,34-37] were at risk of immortal time bias. Misclassification and exclusion of the so-called immortality period would necessarily bias the results toward favoring the treatment.[53] Unlike lack of randomization, these flaws can be easily prevented by study design, eg, explicitly emulating a pragmatic target trial.[54] Moreover, most of the included studies (17 of 19) had an average follow-up time of up to 2 years. Only 2 studies had sufficient follow-up time to examine the long-term cardiovascular risk associated with ADHD medication, but these studies were only moderate in their quality (GRACE score, 6 and 8 of 11). Thus, further studies with rigorous methods are needed to evaluate the long-term risk of CVD associated with ADHD medication use.

Clinical Implications

Overall, our meta-analysis provides reassuring data on the putative cardiovascular risk with ADHD medications, but the possible associations with cardiac arrest or tachyarrhythmias, among female patients, and among those with preexisting CVD warrants further investigation. Importantly, our findings are presented at the population level; in clinical practice, specific individuals with ADHD might be particularly prone to negative cardiovascular outcomes; therefore, clinicians should discuss

with their patients and families the possible cardiovascular risk of ADHD medication in light of the latest evidence, and they should rigorously follow clinical guidelines that suggest monitoring of blood pressure and heart rate at baseline and each medication review.

Limitations

There are several limitations to consider when interpreting the results. First, heterogeneity was high and significant for most analyses. Although this heterogeneity does not invalidate our results, it indicates that the pooled RR cannot appropriately summarize results from all individual studies and should therefore be interpreted with caution.[55] When restricting to specific cardiovascular outcomes, heterogeneity was not significant for the analysis on CVDs, yet it was still significant in the subgroup analyses by sex and preexisting CVD. Second, due to a lack of data, we were unable to compare the associations with specific ADHD medications. Third, as few studies have information on dosage and duration of medication use, investigation of the dose-response association was not possible. Fourth, although the GRACE checklist is validated for evaluating the quality of observational studies of medical treatment, a total score approach for risk of bias assessment needed to be validated. Additionally, most of the included studies were conducted in the United States and Europe, which means the results may not generalize to other settings.

Conclusions

The results of this meta-analysis suggested no statistically significant association between ADHD medication use and the risk of any cardiovascular events across age groups, although a modest risk increase could not be excluded, especially for the risk of cardiac arrest or tachyarrhythmias. Our study also warrants future studies with rigorous study designs to investigate the risk of cardiovascular events among female patients and among those with preexisting CVD, as well as the long-term risk of ADHD medication use.

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REFERENCES

1. Faraone SV, Asherson P, Banaschewski T, et al. Attention-deficit/hyperactivity disorder. *Nat Rev Dis Primers*. 2015;1:15020. doi:10.1038/nrdp.2015.20

2. Polanczyk GV, Willcutt EG, Salum GA, Kieling C, Rohde LA. ADHD prevalence estimates across three decades: an updated systematic review and meta-regression analysis. *Int J Epidemiol*. 2014;43(2):434-442. doi:10.1093/ije/dyt261

3. Simon V, Czobor P, Bálint S, Mészáros A, Bitter I. Prevalence and correlates of adult attention-deficit hyperactivity disorder: meta-analysis. *Br J Psychiatry*. 2009;194(3):204-211. doi:10.1192/bjp.bp.107.048827

4. Dobrosavljevic M, Solares C, Cortese S, Andershed H, Larsson H. Prevalence of attention-deficit/hyperactivity disorder in older adults: a systematic review and meta-analysis. *Neurosci Biobehav Rev*. 2020;118:282-289. doi:10.1016/j.neubiorev.2020.07.042

5. Raman SR, Man KKC, Bahmanyar S, et al. Trends in attention-deficit hyperactivity disorder medication use: a retrospective observational study using population-based databases. *Lancet Psychiatry*. 2018;5(10):824-835. doi:10.1016/S2215-0366(18)30293-1

6. Cortese S, Adamo N, Del Giovane C, et al. Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis. *Lancet Psychiatry*. 2018;5(9):727-738. doi:10.1016/S2215-0366(18)30269-4

7. Storebø OJ, Ramstad E, Krogh HB, et al. Methylphenidate for children and adolescents with attention deficit hyperactivity disorder (ADHD). *Cochrane Database Syst Rev*. 2015;2015(11):CD009885. doi:10.1002/14651858.CD009885.pub2

8. Torres-Acosta N, O'Keefe JH, O'Keefe CL, Lavie CJ. Cardiovascular effects of ADHD therapies: JACC review topic of the week. *J Am Coll Cardiol*. 2020;76(7):858-866. doi:10.1016/j.jacc.2020.05.081

9. Cooper WO, Habel LA, Sox CM, et al. ADHD drugs and serious cardiovascular events in children and young adults. *N Engl J Med*. 2011;365(20):1896-1904. doi:10.1056/NEJMoa1110212

10. Habel LA, Cooper WO, Sox CM, et al. ADHD medications and risk of serious cardiovascular events in young and middle-aged adults. *JAMA*. 2011;306(24):2673-2683. doi:10.1001/jama.2011.1830

11. Dalsgaard S, Kvist AP, Leckman JF, Nielsen HS, Simonsen M. Cardiovascular safety of stimulants in children with attention-deficit/hyperactivity disorder: a nationwide prospective cohort study. *J Child Adolesc Psychopharmacol*. 2014;24(6):302-310. doi:10.1089/cap.2014.0020

12. Winterstein AG, Gerhard T, Kubilis P, et al. Cardiovascular safety of central nervous system stimulants in children and adolescents: population based cohort study. *BMJ*. 2012;345:e4627. doi:10.1136/bmj.e4627

13. Winterstein AG. Cardiovascular safety of stimulants in children: findings from recent population-based cohort studies. *Curr Psychiatry Rep*. 2013;15(8):379. doi:10.1007/s11920-013-0379-y

14. Mazza M, D'Ascenzo F, Davico C, et al. Drugs for attention deficit-hyperactivity disorder do not increase the mid-term risk of sudden death in children: a meta-analysis of observational studies. *Int J Cardiol*. 2013;168(4):4320-4321. doi:10.1016/j.ijcard.2013.04.169

15. Liu H, Feng W, Zhang D. Association of ADHD medications with the risk of cardiovascular diseases: a meta-analysis. *Eur Child Adolesc Psychiatry*. 2019;28(10):1283-1293.

16. Houghton R, de Vries F, Loss G. Psychostimulants/atomoxetine and serious cardiovascular events in children with ADHD or autism spectrum disorder. *CNS Drugs*. 2020;34(1):93-101. doi:10.1007/s40263-019-00686-4

17. Jeong HE, Lee H, Lai EC-C, et al. Association between methylphenidate and risk of myocardial infarction: a multinational self-controlled case series study. *Pharmacoepidemiol Drug Saf*. 2021;30(10):1458-1467. doi:10.1002/pds.5322

18. Latronica JR, Clegg TJ, Tuan W-J, Bone C. Are amphetamines associated with adverse cardiovascular events among elderly individuals? *J Am Board Fam Med*. 2021;34(6):1074-1081. doi:10.3122/jabfm.2021.06.210228

19. Saiz LC, Gil M, Alonso A, Erviti J, Garjón J, Martínez M. Use of methylphenidate and risk for valvular heart disease: a case-control study nested in the BIFAP cohort. *Pharmacoepidemiol Drug Saf*. 2020;29(3):288-295. doi:10.1002/pds.4954

20. Tadrous M, Shakeri A, Chu C, et al. Assessment of stimulant use and cardiovascular event risks among older adults. *JAMA Netw Open*. 2021;4(10):e2130795-e2130795. doi:10.1001/jamanetworkopen.2021.30795

21. Michelson D, Read HA, Ruff DD, Witcher J, Zhang S, McCracken J. CYP2D6 and clinical response to atomoxetine in children and adolescents with ADHD. *J Am Acad Child Adolesc Psychiatry*. 2007;46(2):242-251. doi:10.1097/01.chi.0000246056.83791.b6

22. Stroup DF, Berlin JA, Morton SC, et al; Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology: a proposal for reporting. *JAMA*. 2000;283(15):2008-2012. doi:10.1001/jama.283.15.2008

23. Zhang L, Yao H, Li L, et al. Risk of adverse cardiovascular events associated with medications for attention-deficit hyperactivity disorder (ADHD): a systematic review and meta-analysis. November 8, 2021. Accessed October 19, 2022. https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021283702

24. Dreyer NABA, Bryant A, Velentgas P. The GRACE checklist: a validated assessment tool for high quality observational studies of comparative effectiveness. *J Manag Care Spec Pharm*. 2016;22(10):1107-1113. doi:10.18553/jmcp.2016.22.10.1107

25. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Accessed October 19, 2022. https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

26. Greenland S. Interpretation and choice of effect measures in epidemiologic analyses. *Am J Epidemiol*. 1987;125(5):761-768. doi:10.1093/oxfordjournals.aje.a114593

27. Cummings P. The relative merits of risk ratios and odds ratios. *Arch Pediatr Adolesc Med*. 2009;163(5):438-445. doi:10.1001/archpediatrics.2009.31

28. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21(11):1539-1558. doi:10.1002/sim.1186

29. Langan D, Higgins JPT, Jackson D, et al. A comparison of heterogeneity variance estimators in simulated random-effects meta-analyses. *Res Synth Methods*. 2019;10(1):83-98. doi:10.1002/jrsm.1316

30. IntHout J, Ioannidis JP, Borm GF. The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method. *BMC Med Res Methodol*. 2014;14(1):25. doi:10.1186/1471-2288-14-25

31. Guertin J, LeLorier J, Durand M, Gow R, Holbrook A, Levine M. Impact of a restrictive drug access program on the risk of cardiovascular encounters in children exposed to ADHD medications. *J Popul Ther Clin Pharmacol*. 2014;21(3):e357-e369.

32. Holick CN, Turnbull BR, Jones ME, Chaudhry S, Bangs ME, Seeger JD. Atomoxetine and cerebrovascular outcomes in adults. *J Clin Psychopharmacol*. 2009;29(5):453-460. doi:10.1097/JCP.0b013e3181b2b828

33. Olfson M, Huang C, Gerhard T, et al. Stimulants and cardiovascular events in youth with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 2012;51(2):147-156. doi:10.1016/j.jaac.2011.11.008

34. Peyre H, Hoertel N, Hatteea H, Limosin F, Dubuc C, Delorme R. Adulthood self-reported cardiovascular risk and ADHD medications: results from the 2004-2005 National Epidemiologic Survey on Alcohol and Related Conditions. *J Clin Psychiatry*. 2014;75(2):181-182. doi:10.4088/JCP.13l08736

35. Schelleman H, Bilker WB, Strom BL, et al. Cardiovascular events and death in children exposed and unexposed to ADHD agents. *Pediatrics*. 2011;127(6):1102-1110. doi:10.1542/peds.2010-3371

36. Schelleman H, Bilker WB, Kimmel SE, et al. Methylphenidate and risk of serious cardiovascular events in adults. *Am J Psychiatry*. 2012;169(2):178-185. doi:10.1176/appi.ajp.2011.11010125

37. Schelleman H, Bilker WB, Kimmel SE, et al. Amphetamines, atomoxetine and the risk of serious cardiovascular events in adults. *PLoS One*. 2013;8(1):e52991. doi:10.1371/journal.pone.0052991

38. Shin J-Y, Roughead EE, Park B-J, Pratt NL. Cardiovascular safety of methylphenidate among children and young people with attention-deficit/hyperactivity disorder (ADHD): nationwide self controlled case series study. *BMJ*. 2016;353:i2550. doi:10.1136/bmj.i2550

39. Winterstein AG, Gerhard T, Shuster J, Johnson M, Zito JM, Saidi A. Cardiac safety of central nervous system stimulants in children and adolescents with attention-deficit/hyperactivity disorder. *Pediatrics*. 2007;120(6):e1494-e1501. doi:10.1542/peds.2007-0675

40. Zhang C, Kutyifa V, Moss AJ, McNitt S, Zareba W, Kaufman ES. Long-QT syndrome and therapy for attention deficit/hyperactivity disorder. *J Cardiovasc Electrophysiol*. 2015;26(10):1039-1044. doi:10.1111/jce.12739

41. Dalsgaard S, Østergaard SD, Leckman JF, Mortensen PB, Pedersen MG. Mortality in children, adolescents, and adults with attention deficit hyperactivity disorder: a nationwide cohort study. *Lancet*. 2015;385(9983):2190-2196. doi:10.1016/S0140-6736(14)61684-6

42. Sun S, Kuja-Halkola R, Faraone SV, et al. Association of psychiatric comorbidity with the risk of premature death among children and adults with attention-deficit/hyperactivity disorder. *JAMA Psychiatry*. 2019;76(11):1141-1149. doi:10.1001/jamapsychiatry.2019.1944

43. Chang Z, D'Onofrio BM, Quinn PD, Lichtenstein P, Larsson H. Medication for attention-deficit/hyperactivity disorder and risk for depression: a nationwide longitudinal cohort study. *Biol Psychiatry*. 2016;80(12):916-922. doi:10.1016/j.biopsych.2016.02.018

44. Sayer GR, McGough JJ, Levitt J, et al. Acute and long-term cardiovascular effects of stimulant, guanfacine, and combination therapy for attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol*. 2016;26(10):882-888. doi:10.1089/cap.2015.0264

45. Vetter VL, Elia J, Erickson C, et al; American Heart Association Council on Cardiovascular Disease in the Young Congenital Cardiac Defects Committee; American Heart Association Council on Cardiovascular Nursing. Cardiovascular monitoring of children and adolescents with heart disease receiving medications for attention deficit/hyperactivity disorder [corrected]: a scientific statement from the American Heart Association Council on Cardiovascular Disease in the Young Congenital Cardiac Defects Committee and the Council on Cardiovascular Nursing. *Circulation*. 2008;117(18):2407-2423. doi:10.1161/CIRCULATIONAHA.107.189473

46. Graham J, Banaschewski T, Buitelaar J, et al; European Guidelines Group. European guidelines on managing adverse effects of medication for ADHD. *Eur Child Adolesc Psychiatry*. 2011;20(1):17-37. doi:10.1007/s00787-010-0140-6

47. Kooij JJS, Bijlenga D, Salerno L, et al. Updated European consensus statement on diagnosis and treatment of adult ADHD. *Eur Psychiatry*. 2019;56(1):14-34. doi:10.1016/j.eurpsy.2018.11.001

48. Solberg BS, Halmøy A, Engeland A, Igland J, Haavik J, Klungsøyr K. Gender differences in psychiatric comorbidity: a population-based study of 40 000 adults with attention deficit hyperactivity disorder. *Acta Psychiatr Scand*. 2018;137(3):176-186. doi:10.1111/acps.12845

49. Du Rietz E, Brikell I, Butwicka A, et al. Mapping phenotypic and aetiological associations between ADHD and physical conditions in adulthood in Sweden: a genetically informed register study. *Lancet Psychiatry*. 2021;8(9):774-783. doi:10.1016/S2215-0366(21)00171-1

50. Franconi F, Brunelleschi S, Steardo L, Cuomo V. Gender differences in drug responses. *Pharmacol Res*. 2007;55(2):81-95. doi:10.1016/j.phrs.2006.11.001

51. Dickerman BA, García-Albéniz X, Logan RW, Denaxas S, Hernán MA. Avoidable flaws in observational analyses: an application to statins and cancer. *Nat Med*. 2019;25(10):1601-1606. doi:10.1038/s41591-019-0597-x

52. Li L, Chang Z, Sun J, et al. Attention-deficit/hyperactivity disorder as a risk factor for cardiovascular diseases: a nationwide population-based cohort study. *World Psychiatry*. 2022;21(3):452-459. doi:10.1002/wps.21020

53. Lévesque LE, Hanley JA, Kezouh A, Suissa S. Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. *BMJ*. 2010;340:b5087. doi:10.1136/bmj.b5087

54. Hernán MA, Robins JM. Using big data to emulate a target trial when a randomized trial is not available. *Am J Epidemiol*. 2016;183(8):758-764. doi:10.1093/aje/kwv254

55. Cortese S, Sun S, Zhang J, et al. Association between attention deficit hyperactivity disorder and asthma: a systematic review and meta-analysis and a Swedish population-based study. *Lancet Psychiatry*. 2018;5(9):717-726. doi:10.1016/S2215-0366(18)30224-4

SUPPLEMENT.

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The association between type 2 diabetes and attention- deficit/ hyperactivity disorder: A systematic review, meta-analysis, and population-based sibling study

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ABSTRACT

We conducted a systematic review and a meta-analysis to quantitatively summarize evidence on the association between attention-deficit/hyperactivity disorder (ADHD) and type 2 diabetes (T2D). Moreover, a register-based sibling study was conducted to simultaneously control for confounding factors. A systematic search identified four eligible observational studies (N = 5738,287). The meta-analysis showed that individuals with ADHD have a more than doubled risk of T2D when considering adjusted estimates (OR=2.29 [1.48–3.55], *d*=0.46). Results from the register-based Swedish data showed a significant association between ADHD and T2D (HR=2.35 [2.14–2.58]), with substance use disorder, depression, and anxiety being the main drivers of the association, and cardiovascular and familiar risk playing a smaller role. While results from the meta-analysis provide evidence for an increased risk of T2D in individuals with ADHD, the register-based analyses show that the association between ADHD and T2D is largely explained by psychiatric comorbidities. Pending further evidence of causal association, our findings suggest that early identification and treatment of ADHD comorbidities might greatly reduce the risk of developing T2D in individuals with ADHD.

1. Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is a prevalent neuropsychiatric condition characterized by age-inappropriate and impairing inattention and/or hyperactivity/impulsivity. Although once conceived as a childhood limited disorder, ADHD has been estimated to affect 5–10 % of school-age children worldwide and 2–5 % of adults (Polanczyk et al., 2014), and its impairing symptoms persist into adulthood in up to 65 % of those diagnosed with ADHD in childhood (Faraone et al., 2006). Previous research has provided evidence of significant psychiatric comorbidity in ADHD (Faraone et al., 2021), which has informed clinical guidelines to support the diagnosis and treatment

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of ADHD patients with co-occurring psychiatric disorders. Results from genome-wide association studies (Demontis et al., 2019), cohort studies (Galéra et al., 2022), and an umbrella review of meta-analyses of observational studies (Arrondo et al., 2022) suggests that ADHD is also associated with physical conditions. More specifically, there is meta-analytic evidence of a significant association between ADHD and obesity (Cortese et al., 2016), and ADHD and asthma (Cortese et al., 2018; Sun et al., 2021). However, evidence on the association between ADHD and a physical condition associated with obesity, namely type 2 diabetes mellitus (T2D), is sparse and has not been meta-analysed yet.

T2D is a metabolic disorder characterized by chronic hyperglycemia and insulin resistance with a worldwide rising prevalence that more than doubled over the past decades translating into a global economic burden and a serious public concern (Zhang and Gregg, 2017). T2D used to be considered as solely occurring in adults, while research has now demonstrated an increasing incidence in young adults, adolescents, and children (Pinhas-Hamiel and Zeitler, 2005). T2D affects individuals' quality of life and is associated with medical comorbidities and increased mortality (Pantalone et al., 2015). Risk factors for T2D include modifiable factors such as overweight and obesity, sedentary behaviors, poor dietary habits, smoking, hypertension, sleeping disorders, depression, antipsychotics use and non-modifiable factors such as age, family history of T2D, and history of gestational diabetes (Chen et al., 2012; Grajales et al., 2019).

Therefore, both ADHD and T2D share several risk factors and comorbidities that require careful consideration to advance the understanding of why ADHD and T2D co-occurs. Whilst the association of ADHD with T2D-related cardiometabolic comorbidities such as obesity, hypertension, and maternal diabetes is established (Cortese et al., 2016; Fuemmeler et al., 2011; Garcia-Argibay et al., 2022; Zhao et al., 2019), less is known on the association between ADHD and T2D. Although an association between ADHD and T2D has been documented in individual studies (Chen et al., 2013; Chen et al., 2018a, 2018b; Du Rietz et al., 2021; Xu et al., 2021), the magnitude of the association is not consistent across studies. Furthermore, no study has controlled simultaneously for a number of potential mediating factors including psychiatric comorbidities (e.g., anxiety disorders, depression, schizophrenia, substance use disorder) and unmeasured familial confounding (i.e., genetic and environmental risk factors shared by family members).

Therefore, the aim of this study was to 1) critically review all observational studies on the association between ADHD and T2D, 2) meta-analyze the available studies to establish the association between ADHD and T2D, and 3) address limitations of the current studies such as poor confounder/mediator control by conducting a large nationwide sibling study using national register data from Sweden that allowed us to simultaneously control for a large number of confounding factors. We hypothesize that psychiatric comorbidity in ADHD may explain part of the ADHD-T2D association. In particular, we expected that internalizing disorders such as anxiety and depression might increase the risk of developing T2D among people with ADHD.

2. Methods

2.1. Systematic review and meta-analysis

The study protocol was preregistered on the International Prospective Register of Systematic Reviews (PROSPERO; Number: CRD42022322364). We followed guidelines from the Meta-Analysis of Observational Studies in Epidemiology group (MOOSE; Stroup, 2000) and Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) (Page et al., 2021).

2.1.1. Search strategy and selection of studies

A systematic literature search was performed in EMBASE, MEDLINE via PubMed and Web of Science, and databases were searched from their inception date until August 2nd, 2021. The search terms and syntax are provided in the supplement. From the search results, we selected articles using the following criteria: 1) Studies assessing the relationship between ADHD and T2D in individuals of any age and sex; 2) peer reviewed papers; 3) observational studies (case-control or cohort studies), 4) diagnosis of ADHD defined as a) presence of a register-based diagnosis according to DSM (III, III-R, IV, IV-TR or 5) or hyperkinetic disorder according to ICD-9 or ICD-10 codes 314/F90; or ADHD medication prescriptions as a proxy to diagnosis or b) sum score of ADHD symptoms above an established cut-off based on validated rating scales such as Child Behavior Checklist (CBCL) and Strengths and Difficulties Questionnaire (SDQ), assessed by parents, teachers, or self-ratings, or c) a positive answer from the individual to a question similar to "have you ever been diagnosed with ADHD?" or by parents to the question: "Has the child ever been told having ADHD by a doctor?". When there were multiple studies from the same population, only the one with the largest sample size was included in the meta-analysis to avoid over-representation bias. Two authors (MG and LL) independently screened the articles for relevance and eligibility, and, in case of disagreement, discrepancies between authors were adjudicated by a third, senior reviewer (HL). Fig. 1 displays the PRISMA flowchart of the search, with respective reasons for study exclusion.

2.1.2. Data extraction

Data extracted included: surname of the first author, year of publication, country, source of the data, age range, total sample size, number of cases and controls with ADHD, number of cases and controls with T2D, mean age of the sample, percentage of men, covariates adjusted for, and maximally adjusted odds ratio (OR), risk ratio (RR), or hazard ratio (HR).

2.1.3. Assessment of study quality

Before performing the meta-analysis, a quality assessment was performed of all eligible studies. Study quality was evaluated using the Newcastle–Ottawa Scale (NOS; Stang, 2010), and study quality was scored from zero to nine on the basis of study group selection, comparability, and outcome and follow-up. NOS scores lower than 7 deemed low quality. Disagreements were resolved by consensus.

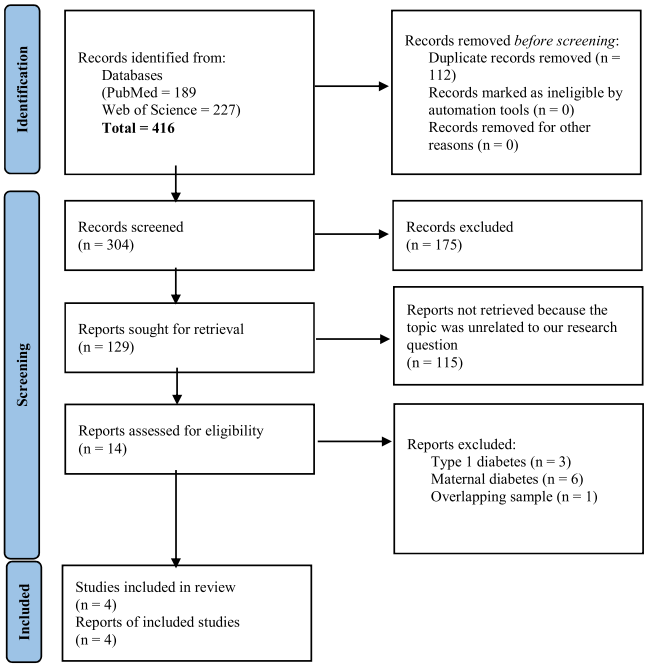

Fig. 1. PRISMA 2020 flowchart of the systematic review.

2.1.4. Statistical analysis

Given the expected variability across studies, a random-effects model with a restricted maximum likelihood (REML) estimator and the Knapp–Hartung (IntHout et al., 2014; Knapp and Hartung, 2003) small-sample adjustment was fitted to calculate the pooled OR with 95 % confidence interval (CI). The RR and HR were considered as OR for the pooled analysis given the low prevalence of ADHD in adults and older adults (Zhang and Yu, 1998). Heterogeneity between studies was assessed using the Cochrane *Q*-test and the I^2 statistic, with significant heterogeneity indicated when $p_q < 0.1$ or ≥ 50 %, respectively (Higgins, 2003). Profiled restricted log-likelihood plots with respect to τ^2 were examined to ensure that a global maximum was found. In order to detect potential outliers/influential studies, studentized residuals and Cook's distances were used. Studies were considered outliers when studentized residuals were larger than $100 \times (1 - 0.05/(2 \times k))th$ percentile of a standard normal distribution, and influential studies when a Cook's distance was larger than the median$+ 6 \times$IQR. Methods to test for publication bias such as a funnel plot, Egger regression asymmetry test, or the adjusted rank correlation were not carried out given the small number of studies. We used a method that is not based on funnel plot asymmetry, namely a one-parameter selection model (Vevea and Woods, 2005) using a half-normal selection function. This method attempts to detect publication bias by modelling the underlying selection process by which the included studies in a meta-analysis might have been influenced and corrects the estimates (Sterne et al., 2001). The trim-and-fill method was used to assess the stability of the pooled results. Leave-one-out sensitivity analysis was performed in order to identify individual studies with a substantial influence on the between-study heterogeneity or overall risk estimate. In order to detect possible biases, effect sizes were regressed on NOS score, total sample size, and year of publication. A Bayesian linear regression with the inverse of the variance as weights was fitted using Jeffreys-Zellner-Siow (JZS) priors (Wetzels and Wagenmakers, 2012). The null model and the models including NOS score, total sample size, and year of publication were compared using Bayes Factor (BF) (Schönbrodt and Wagenmakers, 2018). Lastly, to ensure adequate statistical power ($>$0.80) for the pooled effect size and test of homogeneity, post hoc power analyses were carried out. All data analyses were performed in R 4.1.0 (R Development Core Team, 2020) with the r-package *metafor* version 3.1.46 (Viechtbauer, 2010).

2.2. Nationwide population-based cohort study

The study population was based on the linkage of several population-based national registers in Sweden linked by unique personal numbers (Ludvigsson et al., 2009), namely The Total Population Register (TPR), Cause of Death Register, Prescribed Drug Register (PDR), National Patient Register (NPR), the Multi-generation Register (MGR), and Longitudinal Integration Database for Health Insurance and Labor Market Studies (LISA).

The cohort included all individuals born between 1941 and 1983 who were alive and living in Sweden in 2001 with information on their biological parents (N = 4,257,955). Individuals with a previous history of T2D before the start of follow-up were excluded from the analyses (n = 40,795). We identified full siblings through the MGR (1,306,841 clusters with at least 2 full siblings). The study had ethical approval from the Regional Ethical Review Board in Stockholm, Sweden (Dnr 2013/862–31/5). The requirement for informed consent was waived because the study was register-based and data on the included individuals were deidentified. The investigation conforms to the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

2.2.1. Exposure

Individuals with ADHD were identified as those who had either an ADHD diagnosis (inpatient or outpatient specialist care services) after age 3 years in the NPR using the International Classification of Diseases (ICD) version 9 (1987–1996; ICD-code 314) or ICD version 10 (1997-present; ICD-code F90) or a prescription of any medication approved for the treatment of ADHD in Sweden during the follow-up period (methylphenidate: N06BA04, amphetamine: N06BA01, dexamphetamine: N06BA02, atomoxetine: N06BA09, lisdexamfetamine: N06BA12) from the PDR. Guanfacine (C02AC02) was not included as, in Sweden, it was not approved for the treatment of ADHD until 2016 (Huss et al., 2016).

2.2.2. Outcome

T2D was defined as the presence of a registered diagnosis in the NPR of ICD version 10, ICD-code E11, ICD version 8 and 9, ICD-code 250.

2.2.3. Covariates

Demographics such as year of birth, sex, and highest achieved education (elementary, high school, and postgraduate) were collected from the TPR and LISA. Diagnoses of psychiatric conditions including anxiety, depression, schizophrenia, bipolar disorder, and substance use disorder, as well as cardiovascular risk factors including hyperlipidemia, obesity, and sleep disorders were identified from the NPR using ICD codes (inpatient or outpatient specialist care services). Individuals prescribed antipsychotic drugs were identified as a registered prescription of any medication with Anatomical Therapeutic Chemical (ATC) codes N05A, excluding lithium (N05AN01). Antipsychotics were included given that they may be used in individuals with ADHD, especially for aggressiveness (Zhang et al., 2021), and its relationship with T2D (Galling et al., 2016). Each disorder/medication was defined as 0 or 1 based on whether the person has ever been diagnosed/prescribed with each disorder or drug before or during that person-time interval. To facilitate open science and transparent reporting (Larsson, 2022) all ICD and ATC codes used to define each covariate are presented in Supplementary Table S1. Missing data on education was dealt with by creating a new factor level for those with missing values to avoid listwise deletion from our models.

2.2.4. Statistical analysis

All individuals were followed up from January 1st, 2001 —when outpatient data was introduced— until death, emigration, date of the first T2D diagnosis, or December 31st, 2013, whichever occurred first. Individuals with T2D before the start of follow-up were excluded. A time-dependent Cox regression model with age as the underlying time scale was fitted to assess the relationship between ADHD and T2D. Each psychiatric disorder (including ADHD) and physical condition was allowed to vary over time from unexposed to exposed (0/1), i.e., the hazard at time t depends only on the value of each covariate at that given timepoint.

The concordance index (C-index) and Bayesian Information Criterion (BIC) were used to measure the goodness-of-fit for each model and to compare fit to the unadjusted models. First, we performed a series of sequential adjustments: 1) a crude model (henceforth referred to as baseline) adjusted for birth year and sex, 2) we further adjusted for psychiatric conditions (i.e., anxiety, depression, schizophrenia, bipolar disorders, substance use disorder) and cardiometabolic risk factors (i.e., hyperlipidemia, obesity, sleep disorders) that could mediate this relationship, and 3) we adjusted for all aforementioned variables together with use of antipsychotic medications. Second, we stratified by sex in order to assess potential sex differences. Third, in separate models, we adjusted the baseline model for 1) education, 2) psychiatric comorbidities, 3) psychiatric comorbidities plus antipsychotic use, and 4) cardiometabolic risk factors and compared estimates to the baseline model to determine which mediator attenuates the association the most. Finally, to explore the extent to which this relationship is influenced by unmeasured familial confounders shared within sibling pairs, a Cox model adjusted for birth year and sex with a separated stratum for each cluster of full siblings was fitted. This method adjusts for shared familial confounders including genetic factors and shared unmeasured confounders (Allison, 2009). Benjamini–Hochberg correction was

performed to control false discovery rate due to multiple resting. Data management and statistical analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC) and R version 4.1.0 (R Development Core Team, 2020).

2.2.5. Sensitivity analyses

A series of sensitivity analyses were carried out to assess the robustness of our results. First, analyses were rerun assuming that individuals who received an ADHD diagnosis at any point during follow up had ADHD since the start of follow up in 2001, in order to test the robustness of the results. Second, to explore the possibility of different magnitude of associations at different ages, we reran all baseline analyses stratified by age at the start of follow up divided into four categories (less than 31, 31–40, 41–50, and 51–72 years). Adjusted analyses were not performed when stratifying by age categories due to low count of individuals with both ADHD and T2D.

3. Results

3.1. Systematic review and meta-analysis

3.1.1. Study characteristics

We identified four individual studies with non-overlapping samples that met our inclusion criteria for the meta-analysis. The total number of individuals was 5,738,287 (103,022 individuals with ADHD and 5,635,265 without ADHD). The mean age of the overall population was 26.88 years (SD = 18.82; range 5–79) and 64.53% were men. Among the four studies, three used register-based data (Chen et al., 2013; Chen et al., 2018a, 2018b), and one used questionnaire data. For the diagnosis of ADHD and T2D, one study relied on retrospective recollection from a clinician (Xu et al., 2021), two studies used version ICD-9 codes (Chen et al., 2013; Chen et al., 2018a), and one used version ICD-9 and version ICD-10 codes (Chen et al., 2018b). A summary of the selected studies is shown in Table 1. The NOS rated all four studies as high quality, with an average NOS score of 8.75/9 (see Supplementary Table S2).

One register-based study from Taiwan (Chen et al., 2013), including 4,302 newly diagnosed ADHD patients and 21,510 randomly selected controls, displayed a significant association between ADHD and T2D (OR = 2.83) after adjustments. Individuals with ADHD had a higher prevalence than controls (0.8 vs 0.3%). Similarly, using the Taiwan National Health Insurance Research Database in a matched-control cohort design, 107,847 adolescents and young adults (35,949 individuals with ADHD and 71,898 age- and sex-matched controls), with mean age of 12.89 years and predominantly men (78.8%), were followed for up to 9 years (Chen et al., 2018a). The results showed an increased risk of developing T2D later in life in both adolescents and young adults (HR = 2.83 and HR = 3.28, respectively) after adjustments for demographic characteristics, ADHD medications, atypical antipsychotics, and comorbidities. With the linkage of multiple Swedish national registers, Chen et al. (2018b) explored the association between ADHD and T2D in a total sample of 5,551,807 adults (50.8% males) with a mean age of 40.55 years. In those with ADHD, the prevalence ratio (PR) was more than twice as large compared to those without ADHD (PR = 2.41) after adjustments for sex and age, with a higher prevalence in males (4.32% vs 3.58%). Lastly, Xu et al. (2021) using data from the National Health Interview Survey (NHIS; 2007 and 2012 cycles) in a study of 52,821 adults (48.6 % men) with a mean age of 45.5 years (range 20–79). They found an increased likelihood of having T2D among those with ADHD compared with those without ADHD after adjustments (OR = 1.54).

3.1.2. Meta-analysis

A total of $k = 4$ studies were included in the analysis. The profiled restricted log-likelihood plot displayed a unimodal distribution and that a global maximum was reached. The estimated average adjusted OR based on the random-effects model was $\hat{\mu} = 2.29$, 95 % CI [1.48–3.55],

Table 1
Study characteristics of the included studies.

Study	Year	N_{total}	N_{adhd}	N_{noadhd}	Mean age	% Men	Adjustments	Data type	Country	Age range	Diagnoses	IR ADHD	IR no ADHD	Raw IRR	aOR	NOS
Chen HJ. et al.	2013	25,812	4302	21,510	8.6	80	Age, sex, index year, geographic location, and obesity	Register-based	TW	5–15	ICD-9	8.37 (5.87–11.57)	2.98 (2.29–3.80)	2.81 (1.87–4.23)	2.75	9
Chen MH. et al.	2018	107,847	35,949	71,898	12.9	78.8	Age, sex, level urbanization, income, ADHD medication, antipsychotic medication, hypertension, dyslipidemia, and obesity	Register-based	TW	10–29	ICD9	4.40 (3.74–5.13)	1.10 (0.87–1.37)	4.01 (3.05–5.24)	2.84	9
Chen Q. et al.	2018	5551,807	61,129	5490,678	40.5	50.8	Sex and age	Register-based	SWE	18–64	ICD-9 ICD-10	17.08 (16.07–18.14)	16.31 (16.21–16.42)	1.05 (0.99–1.11)	2.41	9
Xu et al.	2020	52,821	1642	51,179	45.5	48.6	Age, sex, race/ethnicity, education, family income level, alcohol drinking, smoking, and physical activity, and BMI	Questionnaire	US	20–79	Retrospective diagnosis	70.04 (58.17–83.47)	88.24 (85.8–90.73)	0.78 (0.66–0.95)	1.54	8

Note. Incidence risk calculated per 1000 population units. US = United States, TW = Taiwan, SWE = Sweden, IRR = incidence rate ratio, aOR = Adjusted odds ratio.

indicating a significant, medium pooled association between ADHD and T2D (Cohen's d = 0.46, Common Language Effect Size [CLES] = 62.74%), $t(3) = 6.03$, $p = 0.009$. Fig. 2 displays the results of the meta-analysis. According to the Q-test, there was a significant heterogeneity, i.e., the variance in the ORs was larger than what can be attributed to sampling error (χ^2 (3) = 10.84, $p = 0.013$, $\hat{\tau} = 0.23$, 95 % CI [0.05–1.04]; $I^2 = 77.69\%$, 95% CI [15.99–98.61]). After examining the studentized residuals, one study (Xu et al., 2021) showed values greater than ± 2.49, suggesting that it may be deemed as a potential outlier in the context of this model. Based on the Cook's distances, none of the studies seemed to be overly influential. Sensitivity analysis using the leave-one-out method showed that the pooled effect remained largely unchanged (OR range 2.16–2.43), however, after removing Xu et al. (2021) study, between-study variation substantially decreased ($\chi^2(2) = 1.24$, $p = 0.54$; $I^2 = 0\%$) and the pooled effect size increased (OR=2.43). Power analyses showed excellent statistical power (0.99) for both the summary of the effect sizes and heterogeneity tests. Results from the meta-regression did not provide evidence for presence of any influence from NOS scores, total sample size, or year of publication on the effect sizes (BF_{10} = 0.676, BF_{10} = 0.845, and BF_{10} = 0.623, respectively). The trim-and-fill method suggested one potential missing study, however, including this possible missing study did not significantly change the association or its significance (OR = 2.16, 95 % CI [1.69–2.75]). Moreover, the selection model using a half-normal function showed a nonsignificant publication bias, likelihood ratio test $\chi^2 = 0.09$, $p = 0.756$.

3.2. Population-based study

The cohort comprised 4,216,216 individuals (3,226,030 individuals nested within 1,306,841 families with at least 2 full-siblings, [Median = 2, range = 2–16]) of whom 2,158,775 (51%) were men and 34,715 (0.82%) had an ADHD diagnosis (see Table 2). We followed individuals for a total of 52,873,533 person-years (Md = 13, SD = 1.85) with a median age at start of follow-up of 38.13 years (IQR = 28–50). The age- and sex-adjusted incidence rate of T2D in individuals with ADHD was 51.1, 95% CI (47.9–54.5) cases per 10,000 person-years and 23.0, 95% CI (22.8–23.1) in individuals without ADHD. Supplementary Fig. S1 displays cumulative hazard functions for the overall cohort and each age category.

In the baseline model, individuals with ADHD were at increased risk of developing T2D, HR = 2.35, 95% CI (2.14–2.58). The association between T2D and ADHD attenuated after further adjusting for education and psychiatric comorbidity, HR = 1.21 (1.10–1.33). The HR associated with ADHD further decreased when also adjusting for use of antipsychotic drugs, HR = 1.13, 95% CI (1.03–1.25), with a similar risk between males and females (HR = 1.14, 95% CI [1.01–1.29], HR = 1.14, 95% CI [0.98–1.33], respectively). BIC indicated that the fully adjusted model provided the best model fit to the data and the concordance index showed a strong discrimination power. Baseline sibling comparisons showed a similar magnitude of associations to the general population (i.e., between-individuals analyses) for developing T2D in individuals with ADHD compared to their undiagnosed full siblings, HR = 2.22 (1.78–2.76).

When separately adjusting each set of factors (education, psychiatric comorbidities, psychiatric comorbidities and antipsychotic use, and cardiometabolic risk factors), we observed that among those risk factors, psychiatric comorbidities attenuated the most the relationship between ADHD and T2D from 2.08 to 1.21 (see Table 3). Given that psychiatric comorbidities showed a substantial impact on the observed association, we explored which specific psychiatric comorbidities contributed the most by adjusting the baseline model for each psychiatric comorbidity in separate models. Amongst the psychiatric comorbidities, substance use disorder (SUD) seemed to be the main driver of the association between ADHD and T2D, followed by anxiety and depression with a similar magnitude (Table 3). Neither bipolar disorder or schizophrenia seemed to have a strong influence on the association between ADHD and T2D.

Sensitivity analyses showed that when analyzing ADHD as a time-fixed variable (i.e., individuals who were diagnosed with ADHD during follow up were assumed to have ADHD since the start of follow up), result remained unchanged in terms of both estimates and significance (Supplementary Table S3). Moreover, when assessing the relationship between ADHD and T2D at different ages, the magnitude of the association seemed to decrease with age and was no longer significant in the oldest individuals (51–73 years), range of HR = 1.24–3.84. For the complete estimates see Supplementary Table S4.

4. Discussion

In this study, we systematically reviewed and meta-analyzed all studies that met our inclusion criteria assessing the relationship between ADHD and T2D. In addition, we performed a nationwide population-based register-linkage study and sibling comparisons to further clarify the role of potential mediators and unmeasured familial factors. The results from the meta-analysis of 5,738,287 individuals (103,022 with ADHD) from 4 studies showed that individuals with ADHD had more than a two-fold increased risk of developing T2D compared to those without ADHD, thus showing a medium-sized association between ADHD and T2D (Cohen's d = 0.46, CLES = 62.68 %).

Similarly, results from the population-based study revealed a more than 2-fold increased risk of T2D (HR = 2.35, 95 % CI [2.14–2.58]), with a similar risk found in males and females. Adjustments for measured and

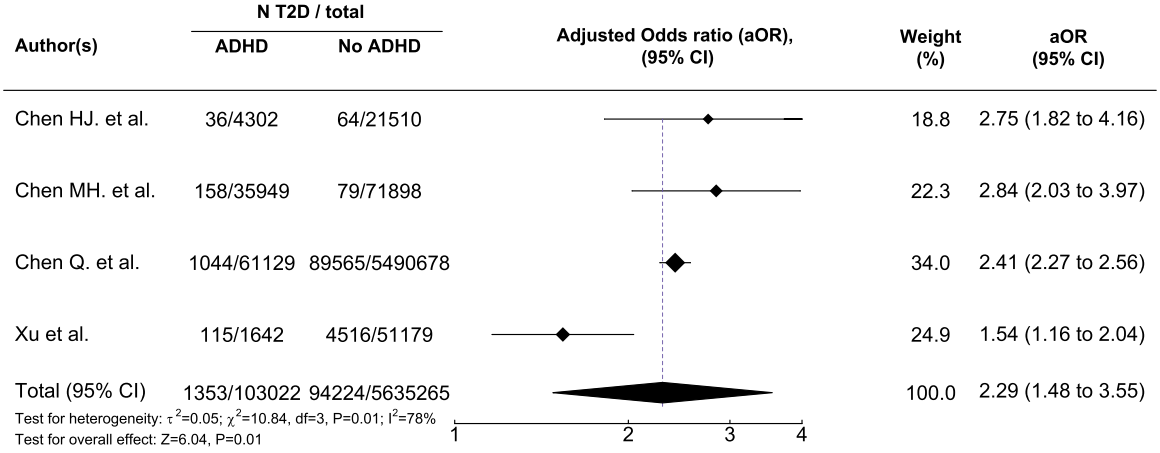

Fig. 2. Forest plot of the observed adjusted odds ratios (OR) and the estimate of the random-effects model for the association of ADHD with T2D with 95 % confidence interval, weight, heterogeneity, and overall effect. *Note.* T2D=Type 2 diabetes, CI=confidence interval, aOR=adjusted odds ratio.

Table 2
Descriptive statistics of the study population stratified by individuals with and without an ADHD diagnosis.

Variable	Overall, N = 4216,216[a]	Without ADHD, N = 4181,501[a]	With ADHD, N = 34,715[a]	p-value[b]
Demographics				
Sex				< 0.001
Male	2158,775 (51%)	2139,484 (51%)	19,291 (56%)	
Female	2057,441 (49%)	2042,017 (49%)	15,424 (44%)	
Education				< 0.001
Primary and lower secondary	592,902 (14%)	583,916 (14%)	8986 (26%)	
Upper secondary	1909,431 (45%)	1892,599 (45%)	16,832 (48%)	
Postsecondary	1471,391 (35%)	1463,982 (35%)	7409 (21%)	
Postgraduate	46,269 (1.1%)	46,136 (1.1%)	133 (0.4%)	
N/A	196,223 (4.7%)	194,868 (4.7%)	1355 (3.9%)	
Age at follow up	38 (12)	38 (12)	38 (10)	0.6
Person-years	52,873,533	52,421,995	451,538	
Median Person-years	13.00 (2.01)	13.00 (1.85)	13.0 (1.50)	< 0.001
Physical conditions				
T2D	119,055 (2.8%)	118,625 (2.8%)	430 (1.2%)	< 0.001
Anxiety	182,466 (4.3%)	167,494 (4.0%)	14,972 (43%)	< 0.001
Autism	12,896 (0.3%)	8887 (0.2%)	4009 (12%)	< 0.001
Bipolar disorder	41,275 (1.0%)	36,218 (0.9%)	5057 (15%)	< 0.001
Conduct disorder	1695 (<0.1%)	1276 (<0.1%)	419 (1.2%)	< 0.001
Depression	227,537 (5.4%)	212,111 (5.1%)	15,426 (44%)	< 0.001
Eating disorders	10,859 (0.3%)	9857 (0.2%)	1002 (2.9%)	< 0.001
Hyperlipidemia	141,748 (3.4%)	141,214 (3.4%)	534 (1.5%)	< 0.001
Intellectual disability	18,361 (0.4%)	17,255 (0.4%)	1106 (3.2%)	< 0.001
Obesity	112,832 (2.7%)	110,590 (2.6%)	2242 (6.5%)	< 0.001
Personality disorders	57,251 (1.4%)	49,678 (1.2%)	7573 (22%)	< 0.001
Schizophrenia	24,239 (0.6%)	23,402 (0.6%)	837 (2.4%)	< 0.001
Sleep disorders	141,161 (3.3%)	136,974 (3.3%)	4187 (12%)	< 0.001
Substance use disorder	195,326 (4.6%)	181,740 (4.3%)	13,586 (39%)	< 0.001
Antipsychotic medications	131,493 (3.1%)	119,367 (2.8%)	12,126 (34%)	< 0.001

N/A=Not available
[a] n (%); Median (SD)
[b] Pearson's Chi-squared test; Wilcoxon rank sum test

Table 3
Results from the Cox regression model displaying the association between ADHD and T2D.

Model	T2D	Concordance	BIC
Sequential adjustment			
Baseline (sex and birth year)[1]	**2.35 (2.14–2.58)**	0.571	3278437.83
Psychiatric disorders and cardiometabolic risk factors[2]	**1.21 (1.10–1.33)**	0.678	3232592.64
Psychiatric disorders and cardiometabolic risk factors antipsychotics[3]	**1.13 (1.03–1.25)**	0.679	3232135.95
Fully adjusted by sex			
Males	**1.14 (1.01–1.29)**	0.643	1966939.52
Females	1.14 (0.98–1.33)	0.673	1108204.72
Individual adjustment[4]			
Education	**2.08 (1.89–2.29)**	0.631	3258690.00
Psychiatric disorders	**1.32 (1.20–1.45)**	0.597	3271714.88
Psychiatric disorders/ antipsychotics	**1.21 (1.09–1.33)**	0.600	3270961.37
Cardiometabolic risk factors	**1.91 (1.74–2.11)**	0.627	3253948.07
Psychiatric disorder[4]			
Anxiety	**1.78 (1.62–1.96)**	0.581	3276279.81
Depression	**1.78 (1.61–1.96)**	0.584	3275674.76
SUD	**1.73 (1.57–1.91)**	0.585	3274990.69
Bipolar	**2.05 (1.86–2.26)**	0.575	3277631.86
Schizophrenia	**2.26 (2.05–2.48)**	0.576	3276909.77
Sibling analyses			
Baseline (sex and birth year)[1]	**2.22 (1.78–2.76)**	0.579	99694.10

Note. [1]Model adjusted for birth year and sex. [2]Model adjusted for birth year, sex, education, anxiety, hyperlipidemia, obesity, sleep disorders, depression, schizophrenia, bipolar disorder, and substance use. [3]Model adjusted for birth year, sex, education, anxiety, hyperlipidemia, obesity, sleep disorders, depression, schizophrenia, bipolar disorder, substance use, and antipsychotic use. [4]Model adjusted for birth year and sex. Bolded estimates display FDR-adjusted *p*-values < 0.05.

unmeasured familial factors suggested a statistically significant association between ADHD and T2D, and that the observed association, while remaining significant, was largely explained by psychiatric comorbidities, in particular SUD, depression, and anxiety. Further, unmeasured familial factors (i.e., genetic and environmental) shared between siblings appeared to be of limited importance, as evidenced by a recent Swedish co-aggregation study (Du Rietz et al., 2021). Our findings contribute to the available literature in three important ways. First, the increased risk for development of T2D observed in individual studies may largely be explained by psychiatric comorbidities that may mediate this relationship (e.g., ADHD increases the risk of SUD, which in turn increases the risk of T2D). This is a novel finding given that previous studies included in the meta-analyses did not include psychiatric comorbidities as covariates in their analyses. Second, cardiovascular risk factors and antipsychotic medications also had an impact on the relationship between ADHD and T2D, but with a smaller effect size compared to psychiatric comorbidities. An extensive body of literature highlighted an association between ADHD and obesity (Cortese et al., 2016; Leppert et al., 2020), however, our results showed a small effect and that the ADHD-T2D relationship remained significant after adjustments for obesity and other well-established cardiovascular risk factors (Garcia-Argibay et al., 2022). Third, our results indicated that unmeasured familial factors seem to have minimal impact on this relationship. This finding is not necessarily inconsistent with evidence from a recent large-scale genome-wide association study (GWAS) on ADHD suggesting a significant genetic correlation between ADHD and T2D ($r_g = 0.18$; Demontis et al., 2019). It is important to highlight that the observed genetic correlation between ADHD and T2D was weak and that the sibling comparison design, used in the current study, only accounts for genetic factors shared by full siblings, which is on average 50 % of their segregating genes. One plausible explanation for the findings of the current study is that ADHD is an important risk factor for T2D and that psychiatric problems (e.g., SUD) that typically emerge after ADHD may mediate this association.

There are several possible explanations for the mediating effect of SUD, depression, and anxiety with T2D. These include behavioral factors, such as unhealthy behaviors (i.e., alcohol consumption and smoking) and dietary habits (i.e., skipping meals/overeating and skipping physical activity) and neurobiological abnormalities. For instance, SUD could potentially worsen the symptoms of ADHD (Perugi et al., 2019), engaging in behaviors that increase the risk of developing T2D, such as poor diet and lack of exercise. Individuals with anxiety disorders (e.g., generalized anxiety disorder) may experiment physical symptoms, such as increased heart rate and rapid breathing (Stein and Sareen, 2015), which could make it more difficult for a person to engage in healthy behaviors that can prevent the development of T2D or engage in

unhealthy eating patterns that increase the likelihood of T2D. A similar pattern could arise in depressed individuals, by which symptoms of depression (e.g., anhedonia, tiredness, and lack of energy (American Psychiatric Association, 2013)) may also lead to unhealthy behaviors including eating disorders or lack of physical exercise. In terms of neurobiological abnormalities, one hypothesis could be a dysregulated hypothalamic–pituitary–adrenal (HPA) axis. Both T2D and anxiety are associated with increased activity in the hypothalamic–pituitary–adrenal (HPA) axis and, therefore, increased secretion of cortisol (Joseph and Golden, 2017). For example, it has been shown that cortisol levels are elevated in individuals with T2D (Hackett et al., 2014; Joseph and Golden, 2017; Liu et al., 2005) and people with a history of anxiety disorders (Chaudieu et al., 2008; Mantella et al., 2008). A similar HPA dysregulation can also be seen in SUD (Huizink et al., 2006; Thayer et al., 2006). Further, it is possible that in people with ADHD, depression may contribute to the development of T2D by causing changes in the body that increase the risk of developing the condition. For example, depression has been shown to affect the way the body processes insulin, which is a hormone that plays a key role in regulating blood sugar levels (Kan et al., 2013; Leonard and Wegener, 2020). If the body is not able to process insulin effectively, this can lead to high blood sugar levels and an increased risk of developing T2D. Additionally, depression may also cause changes in other hormones and chemicals in the body that can affect blood sugar levels and increase the risk of developing T2D, such as pro-inflammatory cytokines and glucocorticoids (Kan et al., 2013). However, more research is needed to fully understand the exact mechanisms by which these conditions may mediate the relationship between ADHD and T2D.

An alternative explanation that cannot be ruled out is that a general disease liability may increase the risk of both multiple mental as well as physical diseases (Cortese et al., 2021). Future research is needed to address these potential explanations. Additional research is also needed to explore the potential impact of ADHD medications on the association between ADHD and T2D (Chen et al., 2018a), of particular interest would be guanfacine, a drug that is approved for the treatment of ADHD by the FDA and that has been linked to weight gain and obesity (Galling et al., 2016).

We found that the association between ADHD and T2D varied as function of age, with stronger associations in young adulthood compared to older age groups. This pattern of results might be caused by ADHD misclassification among the older participants, as ADHD is underdiagnosed and undertreated in the oldest individuals in our cohort (Dobrosavljevic et al., 2020). Alternatively, it could suggest that those who are diagnosed at an early age, and thus, potentially more severe cases, may be at higher risk for T2D than less severe cases. However, due to power constraints caused by a low number of ADHD cases with T2D, we were unable to further adjust estimates for age-stratified analyses. Although ADHD and T2D prevalence is higher in men compared to women (Nordström et al., 2016; Willcutt, 2012), the relationship between ADHD and T2D did not vary as a function of sex.

Our results should be interpreted in the context of a number of limitations. First, only four studies investigated the relationship between ADHD and T2D. Although meta-analyses are statistically appropriate even in cases with a small number of studies, results may be unstable and may vary with the inclusions of new studies. This limitation was addressed by fitting a random effects model and performing a leave-one-out sensitivity analysis, which showed that the association was not driven by one particular study. Second, variability between studies in effect sizes in the meta-analysis reflects methodological differences and limitations related to confounder/mediator control, number of factors adjusted for, and small sample sizes. Several studies lacked an in-depth mediator control, and no study performed a sibling design to account for unmeasured confounding. Lastly, a major limitation of the current literature is that most studies (3/4) were registry-based and, thus, ADHD diagnoses might capture only the most severe cases of the ADHD spectrum who sought specialized medical care. This limitation is also evident in our register-based study. Furthermore, the directionality of the ADHD-T2D association remains unclear, as two of the included studies used a cross-sectional design (Chen et al., 2018b; Xu et al., 2021), and the available longitudinal studies focused on how T2D associates with ADHD (Chen et al., 2013; Chen et al., 2018a). However, results from our register-based study, together with epidemiological data about age of onset for ADHD and T2D (Koopman, 2005; Polanczyk et al., 2010) suggest that individuals with ADHD are more likely to develop T2D. Nevertheless, further studies attempting to determine the directional and causal nature of the relationship between ADHD and T2D should employ other methodology such as Mendelian randomization. Moreover, misclassification of ADHD in older ages is likely given that ADHD is underdiagnosed in adults (Dobrosavljevic et al., 2020). In contrast, one study used ADHD diagnoses from self-reports (Xu et al., 2021), which might capture less severe and subclinical ADHD symptoms. In addition, relying on individual reports to determine the presence of ADHD and T2D may introduce the possibility of faulty recollection affecting the study results. However, results from the leave-one-out sensitivity analysis did not show a change in the significance, and the pooled effect increased when removing that study. Lastly, diagnoses of hyperlipidemia, obesity, and sleep disorders were identified from the NPR and therefore, are imperfect measures for cardiovascular risk factors, possibly underestimating effect on T2D. These diagnoses mainly apply to individuals who were referred for treatment due to other reasons or the most severe cases that developed related complications. Due to this low reliability on those diagnoses, we were not able to explore the role of metabolic syndrome in the ADHD-T2D association. We cannot rule out that ADHD influences SUD, that in turn increases the likelihood of metabolic syndrome and ultimately T2D. Future research is needed to further explore the possible effect that ADHD pharmacological treatment has on this association. Another factor that warrants further attention and has not been explored is the severity of ADHD, given that it is plausible that the relationship between ADHD and T2D varies at different levels of severity.

5. Conclusions

This study revealed a significant association between ADHD and T2D that was largely due to psychiatric comorbidities, in particular SUD, depression, and anxiety. Our findings suggest that clinicians need to be aware of the increased risk of developing T2D in individuals with ADHD and that psychiatric comorbidities may be the main driver of this association. Appropriate identification and treatment of these psychiatric comorbidities may reduce the risk for developing T2D in ADHD, together with efforts to intervene on other modifiable T2D risk factors (e.g., unhealthy lifestyle habits and use of antipsychotics, which are common in ADHD), and to devise individual programs to increase physical activity (Quesada et al., 2018). Considering the significant economic burden of ADHD (Garcia-Argibay et al., 2021) and T2D (Zhang and Gregg, 2017), a better understanding of this relationship is essential for targeted interventions or prevention programs with the potential for a positive impact on both public health and the lives of persons living with ADHD.

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Role of the Funding source

The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Contributors

Dr Garcia-Argibay had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis, Concept and design: Garcia-Argibay, Larsson, Statistical analysis: Garcia-Argibay, Acquisition, analysis, or interpretation of data: All authors, Drafting of the manuscript: Garcia-Argibay, Critical revision of the manuscript for important intellectual content: All authors, Supervision: Larsson.

Ethical approval

The study had ethical approval from the Regional Ethical Review Board in Stockholm, Sweden (Dnr 2013/862–31/5). The requirement for informed consent was waived because the study was register-based and data on the included individuals were deidentified. The investigation conforms to the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Declaration of Competing Interest

Henrik Larsson reported receiving grants from Shire/Takeda Pharmaceuticals during the conduct of the study; personal fees from and serving as a speaker for Shire/Takeda Pharmaceuticals and Evolan Pharma AB outside the submitted work; and sponsorship for a conference on attention-deficit/hyperactivity disorder from Shire Pharmaceuticals outside the submitted work. Johan Jendle reported receiving grants from Novo Nordisk during the conduct of the study; fees from and serving as a speaker for Abbott, Boehringer Ingelheim, Eli Lilly, Medtronic, Nordic Infucare, Novo Nordisk, Sanofi, outside the submitted work. Ebba Du Rietz has served as a speaker for Shire Sweden AB outside the submitted work.

J.A.R.Q was on the speakers' bureau and/or acted as consultant for Janssen-Cilag, Novartis, Shire, Takeda, Bial, Shionogi, Sincrolab, Novartis, BMS, Medice, Rubió, Uriach, Technofarma and Raffo in the last 3 years. He also received travel awards (air tickets + hotel) for taking part in psychiatric meetings from Janssen-Cilag, Rubió, Shire, Takeda, Shionogi, Bial and Medice. The Department of Psychiatry chaired by him received unrestricted educational and research support from the following companies in the last 3 years: Janssen- Cilag, Shire, Oryzon, Roche, Psious, and Rubió.

The remaining authors declare having no conflict of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2023.105076.

References

Allison, P., 2009. Fixed Effects Regression Models. SAGE Publications, Inc., 2455 Teller Road, Thousand Oaks California 91320 United States of America https://doi.org/10.4135/9781412993869.

American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. American Psychiatric Association. https://doi.org/10.1176/appi.books.9780890425596.

Arrondo, G., Solmi, M., Dragioti, E., Eudave, L., Ruiz-Goikoetxea, M., Ciaurriz-Larraz, A. M., Magallon, S., Carvalho, A.F., Cipriani, A., Fusar-Poli, P., Larsson, H., Correll, C. U., Cortese, S., 2022. Associations between mental and physical conditions in children and adolescents: an umbrella review. Neurosci. Biobehav. Rev. 137, 104662 https://doi.org/10.1016/j.neubiorev.2022.104662.

Chaudieu, I., Beluche, I., Norton, J., Boulenger, J.-P., Ritchie, K., Ancelin, M.L., 2008. Abnormal reactions to environmental stress in elderly persons with anxiety disorders: evidence from a population study of diurnal cortisol changes. J. Affect. Disord. 106, 307–313. https://doi.org/10.1016/j.jad.2007.07.025.

Chen, H.-J., Lee, Y.-J., Yeh, G.C., Lin, H.-C., 2013. Association of attention-deficit/hyperactivity disorder with diabetes: a population-based study. Pediatr. Res. 73, 492–496. https://doi.org/10.1038/pr.2013.5.

Chen, L., Magliano, D.J., Zimmet, P.Z., 2012. The worldwide epidemiology of type 2 diabetes mellitus—present and future perspectives. Nat. Rev. Endocrinol. 8, 228–236. https://doi.org/10.1038/nrendo.2011.183.

Chen, M.-H., Pan, T.-L., Hsu, J.-W., Huang, K.-L., Su, T.-P., Li, C.-T., Lin, W.-C., Tsai, S.-J., Chang, W.-H., Chen, T.-J., Bai, Y.-M., 2018a. Risk of type 2 diabetes in adolescents and young adults with attention-deficit/hyperactivity disorder: a nationwide longitudinal study. J. Clin. Psychiatry 79. https://doi.org/10.4088/JCP.17m11607.

Chen, Q., Hartman, C.A., Haavik, J., Harro, J., Klungsøyr, K., Hegvik, T.-A., Wanders, R., Ottosen, C., Dalsgaard, S., Faraone, S.V., Larsson, H., 2018b. Common psychiatric and metabolic comorbidity of adult attention-deficit/hyperactivity disorder: a population-based cross-sectional study. PLOS ONE 13, e0204516. https://doi.org/10.1371/journal.pone.0204516.

Cortese, S., Moreira-Maia St., C.R., Fleur, D., Morcillo-Peñalver, C., Rohde, L.A., Faraone, S.V., 2016. Association between ADHD and obesity: a systematic review and meta-analysis. Am. J. Psychiatry 173, 34–43. https://doi.org/10.1176/appi.ajp.2015.15020266.

Cortese, S., Sun, S., Zhang, J., Sharma, E., Chang, Z., Kuja-Halkola, R., Almqvist, C., Larsson, H., Faraone, S.V., 2018. Association between attention deficit hyperactivity disorder and asthma: a systematic review and meta-analysis and a Swedish population-based study. Lancet Psychiatry 5, 717–726. https://doi.org/10.1016/S2215-0366(18)30224-4.

Cortese, S., Arrondo, G., Correll, C.U., Solmi, M., 2021. Beyond the p factor: Is there a d factor? JCPP Adv. 1. https://doi.org/10.1002/jcv2.12051.

Demontis, D., Walters, R.K., Martin, J., Mattheisen, M., Als, T.D., Agerbo, E., Baldursson, G., Belliveau, R., Bybjerg-Grauholm, J., Bækvad-Hansen, M., Cerrato, F., Chambert, K., Churchhouse, C., Dumont, A., Eriksson, N., Gandal, M., Goldstein, J.I., Grasby, K.L., Grove, J., Gudmundsson, O.O., Hansen, C.S., Hauberg, M.E., Hollegaard, M.V., Howrigan, D.P., Huang, H., Maller, J.B., Martin, A.R., Martin, N. G., Moran, J., Pallesen, J., Palmer, D.S., Pedersen, C.B., Pedersen, M.G., Poterba, T., Poulsen, J.B., Ripke, S., Robinson, E.B., Satterstrom, F.K., Stefansson, H., Stevens, C., Turley, P., Walters, G.B., Won, H., Wright, M.J., , ADHD Working Group of the Psychiatric Genomics Consortium (PGC), Early Lifecourse & Genetic Epidemiology (EAGLE) Consortium, 23andMe Research Team, Andreassen, O.A., Asherson, P., Burton, C.L., Boomsma, D.I., Cormand, B., Dalsgaard, S., Franke, B., Gelernter, J., Geschwind, D., Hakonarson, H., Haavik, J., Kranzler, H.R., Kuntsi, J., Langley, K., Lesch, K.-P., Middeldorp, C., Reif, A., Rohde, L.A., Roussos, P., Schachar, R., Sklar, P., Sonuga-Barke, E.J.S., Sullivan, P.F., Thapar, A., Tung, J.Y., Waldman, I.D., Medland, S.E., Stefansson, K., Nordentoft, M., Hougaard, D.M., Werge, T., Mors, O., Mortensen, P.B., Daly, M.J., Faraone, S.V., Børglum, A.D., Neale, B.M., 2019. Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. Nat. Genet 51, 63–75. https://doi.org/10.1038/s41588-018-0269-7.

Dobrosavljevic, M., Solares, C., Cortese, S., Andershed, H., Larsson, H., 2020. Prevalence of attention-deficit/hyperactivity disorder in older adults: a systematic review and meta-analysis. Neurosci. Biobehav. Rev. 118, 282–289. https://doi.org/10.1016/j.neubiorev.2020.07.042.

Du Rietz, E., Brikell, I., Butwicka, A., Leone, M., Chang, Z., Cortese, S., D'Onofrio, B.M., Hartman, C.A., Lichtenstein, P., Faraone, S.V., Kuja-Halkola, R., Larsson, H., 2021. Mapping phenotypic and aetiological associations between ADHD and physical conditions in adulthood in Sweden: a genetically informed register study. Lancet Psychiatry 8, 774–783. https://doi.org/10.1016/s2215-0366(21)00171-1.

Faraone, S.V., Biederman, J., Mick, E., 2006. The age-dependent decline of attention deficit hyperactivity disorder: a meta-analysis of follow-up studies. Psychol. Med. 36, 159–165. https://doi.org/10.1017/S003329170500471X.

Faraone, S.V., Banaschewski, T., Coghill, D., Zheng, Y., Biederman, J., Bellgrove, M.A., Newcorn, J.H., Gignac, M., Al Saud, N.M., Manor, I., Rohde, L.A., Yang, L., Cortese, S., Almagor, D., Stein, M.A., Albatti, T.H., Aljoudi, H.F., Alqahtani, M.M.J., Asherson, P., Atwoli, L., Bölte, S., Buitelaar, J.K., Crunelle, C.L., Daley, D., Dalsgaard, S., Döpfner, M., Espinet (on behalf of CADDRA), S., Fitzgerald, M., Franke, B., Gerlach, M., Haavik, J., Hartman, C.A., Hartung, C.M., Hinshaw, S.P., Hoekstra, P.J., Hollis, C., Kollins, S.H., Sandra Kooij, J.J., Kuntsi, J., Larsson, H., Li, T., Liu, J., Merzon, E., Mattingly, G., Mattos, P., McCarthy, S., Mikami, A.Y., Molina, B.S.G., Nigg, J.T., Purper-Ouakil, D., Omigbodun, O.O., Polanczyk, G.V., Pollak, Y., Poulton, A.S., Rajkumar, R.P., Reding, A., Reif, A., Rubia, K., Rucklidge, J., Romanos, M., Ramos-Quiroga, J.A., Schellekens, A., Scheres, A., Schoeman, R., Schweitzer, J.B., Shah, H., Solanto, M.V., Sonuga-Barke, E., Soutullo, C., Steinhausen, H.-C., Swanson, J.M., Thapar, A., Tripp, G., van de Glind, G., van den Brink, W., Van der Oord, S., Venter, A., Vitiello, B., Walitza, S., Wang, Y., 2021. The World Federation of ADHD International Consensus Statement: 208 evidence-based conclusions about the disorder. Neurosci. Biobehav. Rev. 128, 789–818. https://doi.org/10.1016/j.neubiorev.2021.01.022.

Fuemmeler, B.F., Østbye, T., Yang, C., McClernon, F.J., Kollins, S.H., 2011. Association between attention-deficit/hyperactivity disorder symptoms and obesity and

hypertension in early adulthood: a population-based study. Int. J. Obes. 35, 852–862. https://doi.org/10.1038/ijo.2010.214.
Galéra, C., Cortese, S., Orri, M., Collet, O., van der Waerden, J., Melchior, M., Boivin, M., Tremblay, R.E., Côté, S.M., 2022. Medical conditions and Attention-Deficit/Hyperactivity Disorder symptoms from early childhood to adolescence. Mol. Psychiatry 27, 976–984. https://doi.org/10.1038/s41380-021-01357-x.
Galling, B., Roldán, A., Nielsen, R.E., Nielsen, J., Gerhard, T., Carbon, M., Stubbs, B., Vancampfort, D., De Hert, M., Olfson, M., Kahl, K.G., Martin, A., Guo, J.J., Lane, H.-Y., Sung, F.-C., Liao, C.-H., Arango, C., Correll, C.U., 2016. Type 2 diabetes mellitus in youth exposed to antipsychotics: a systematic review and meta-analysis. JAMA Psychiatry 73, 247. https://doi.org/10.1001/jamapsychiatry.2015.2923.
Garcia-Argibay, M., du Rietz, E., Lu, Y., Martin, J., Haan, E., Lehto, K., Bergen, S.E., Lichtenstein, P., Larsson, H., Brikell, I., 2022. The role of ADHD genetic risk in mid-to-late life somatic health conditions. Transl. Psychiatry 12, 152. https://doi.org/10.1038/s41398-022-01919-9.
Garcia-Argibay, M., Pandya, E., Ahnemark, E., Werner-Kiechle, T., Andersson, L.M., Larsson, H., Du Rietz, E., 2021. Healthcare utilization and costs of psychiatric and somatic comorbidities associated with newly diagnosed adult ADHD. Acta Psychiatr. Scand. acps 13297. https://doi.org/10.1111/acps.13297.
Garcia-Argibay, M., Du Rietz, E., Hartman, C.A., Lichtenstein, P., Chang, Z., Fava, C., Cortese, S., Larsson, H., 2022. Cardiovascular risk factors in attention-deficit/hyperactivity disorder: a family design study of Swedish conscripts. Int. J. Methods Psychiatr. Res. https://doi.org/10.1002/mpr.1930.
Grajales, D., Ferreira, V., Valverde, Á.M., 2019. Second-generation antipsychotics and dysregulation of glucose metabolism: beyond weight gain. Cells 8, 1336. https://doi.org/10.3390/cells8111336.
Hackett, R.A., Steptoe, A., Kumari, M., 2014. Association of Diurnal patterns in salivary cortisol with type 2 diabetes in the whitehall II study. J. Clin. Endocrinol. Metab. 99, 4625–4631. https://doi.org/10.1210/jc.2014-2459.
Higgins, J.P.T., 2003. Measuring inconsistency in meta-analyses. BMJ 327, 557–560. https://doi.org/10.1136/bmj.327.7414.557.
Huizink, A.C., Ferdinand, R.F., Ormel, J., Verhulst, F.C., 2006. Hypothalamic-pituitary-adrenal axis activity and early onset of cannabis use. Addiction 101, 1581–1588. https://doi.org/10.1111/j.1360-0443.2006.01570.x.
Huss, M., Chen, W., Ludolph, A.G., 2016. Guanfacine extended release: a new pharmacological treatment option in Europe. Clin. Drug Investig. 36, 1–25. https://doi.org/10.1007/s40261-015-0336-0.
IntHout, J., Ioannidis, J.P., Borm, G.F., 2014. The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method. BMC Med. Res. Methodol. 14, 25. https://doi.org/10.1186/1471-2288-14-25.
Joseph, J.J., Golden, S.H., 2017. Cortisol dysregulation: the bidirectional link between stress, depression, and type 2 diabetes mellitus: Role of cortisol in stress, depression, and diabetes. Ann. N. Y. Acad. Sci. 1391, 20–34. https://doi.org/10.1111/nyas.13217.
Kan, C., Silva, N., Golden, S.H., Rajala, U., Timonen, M., Stahl, D., Ismail, K., 2013. A systematic review and meta-analysis of the association between depression and insulin resistance. Diabetes Care 36, 480–489. https://doi.org/10.2337/dc12-1442.
Knapp, G., Hartung, J., 2003. Improved tests for a random effects meta-regression with a single covariate. Stat. Med. 22, 2693–2710. https://doi.org/10.1002/sim.1482.
Koopman, R.J., 2005. Changes in age at diagnosis of type 2 diabetes mellitus in the United States, 1988 to 2000. Ann. Fam. Med. 3, 60–63. https://doi.org/10.1370/afm.214.
Larsson, H., 2022. Transparent and complete reporting of confounding in observational research. JCPP Adv. 2. https://doi.org/10.1002/jcv2.12086.
Leonard, B.E., Wegener, G., 2020. Inflammation, insulin resistance and neuroprogression in depression. Acta Neuropsychiatr. 32, 1–9. https://doi.org/10.1017/neu.2019.17.
Leppert, B., Millard, L.A.C., Riglin, L., Davey Smith, G., Thapar, A., Tilling, K., Walton, E., Stergiakouli, E., 2020. A cross-disorder PRS-pheWAS of 5 major psychiatric disorders in UK Biobank. PLoS Genet 16, e1008185. https://doi.org/10.1371/journal.pgen.1008185.
Liu, H., Bravata, D.M., Cabaccan, J., Raff, H., Ryzen, E., 2005. Elevated late-night salivary cortisol levels in elderly male type 2 diabetic veterans. Clin. Endocrinol. (Oxf.) 63, 642–649. https://doi.org/10.1111/j.1365-2265.2005.02395.x.
Ludvigsson, J.F., Otterblad-Olausson, P., Pettersson, B.U., Ekbom, A., 2009. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. Eur. J. Epidemiol. 24, 659–667. https://doi.org/10.1007/s10654-009-9350-y.
Mantella, R.C., Butters, M.A., Amico, J.A., Mazumdar, S., Rollman, B.L., Begley, A.E., Reynolds, C.F., Lenze, E.J., 2008. Salivary cortisol is associated with diagnosis and severity of late-life generalized anxiety disorder. Psychoneuroendocrinology 33, 773–781. https://doi.org/10.1016/j.psyneuen.2008.03.002.
Nordström, A., Hadrévi, J., Olsson, T., Franks, P.W., Nordström, P., 2016. Higher prevalence of Type 2 diabetes in men than in women is associated with differences in visceral fat mass. J. Clin. Endocrinol. Metab. 101, 3740–3746. https://doi.org/10.1210/jc.2016-1915.
Page, M.J., McKenzie, J.E., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D., Shamseer, L., Tetzlaff, J.M., Akl, E.A., Brennan, S.E., Chou, R., Glanville, J., Grimshaw, J.M., Hróbjartsson, A., Lalu, M.M., Li, T., Loder, E.W., Mayo-Wilson, E., McDonald, S., McGuinness, L.A., Stewart, L.A., Thomas, J., Tricco, A.C., Welch, V.A., Whiting, P., Moher, D., 2021. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ n71. https://doi.org/10.1136/bmj.n71.
Pantalone, K.M., Hobbs, T.M., Wells, B.J., Kong, S.X., Kattan, M.W., Bouchard, J., Yu, C., Sakurada, B., Milinovich, A., Weng, W., Bauman, J.M., Zimmerman, R.S., 2015. Clinical characteristics, complications, comorbidities and treatment patterns among patients with type 2 diabetes mellitus in a large integrated health system. BMJ Open Diabetes Res. Care 3, e000093. https://doi.org/10.1136/bmjdrc-2015-000093.
Perugi, G., Pallucchini, A., Rizzato, S., De Rossi, P., Sani, G., Maremmani, A.G., Pinzone, V., Maremmani, I., 2019. Pharmacotherapeutic strategies for the treatment of attention-deficit hyperactivity (ADHD) disorder with comorbid substance-use disorder (SUD). Expert Opin. Pharmacother. 20, 343–355. https://doi.org/10.1080/14656566.2018.1551878.
Pinhas-Hamiel, O., Zeitler, P., 2005. The global spread of type 2 diabetes mellitus in children and adolescents. J. Pedia 146, 693–700. https://doi.org/10.1016/j.jpeds.2004.12.042.
Polanczyk, G., Caspi, A., Houts, R., Kollins, S.H., Rohde, L.A., Moffitt, T.E., 2010. Implications of extending the ADHD age-of-onset criterion to age 12: results from a prospectively studied birth cohort. J. Am. Acad. Child Adolesc. Psychiatry 49, 210–216. https://doi.org/10.1016/j.jaac.2009.12.014.
Polanczyk, G.V., Willcutt, E.G., Salum, G.A., Kieling, C., Rohde, L.A., 2014. ADHD prevalence estimates across three decades: an updated systematic review and meta-regression analysis. Int. J. Epidemiol. 43, 434–442. https://doi.org/10.1093/ije/dyt261.
Quesada, D., Ahmed, N.U., Fennie, K.P., Gollub, E.L., Ibrahimou, B., 2018. A review: associations between attention-deficit/hyperactivity disorder, physical activity, medication use, eating behaviors and obesity in children and adolescents. Arch. Psychiatr. Nurs. 32, 495–504. https://doi.org/10.1016/j.apnu.2018.01.006.
R Development Core Team, 2020. R: A language and environment for statistical computing.
Schönbrodt, F.D., Wagenmakers, E.-J., 2018. Bayes factor design analysis: Planning for compelling evidence. Psychon. Bull. Rev. 25, 128–142. https://doi.org/10.3758/s13423-017-1230-y.
Stang, A., 2010. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur. J. Epidemiol. 25, 603–605. https://doi.org/10.1007/s10654-010-9491-z.
Stein, M.B., Sareen, J., 2015. Generalized anxiety disorder. N. Engl. J. Med 373, 2059–2068. https://doi.org/10.1056/NEJMcp1502514.
Sterne, J.A.C., Egger, M., Smith, G.D., 2001. Systematic reviews in health care: investigating and dealing with publication and other biases in meta-analysis. BMJ 323, 101–105. https://doi.org/10.1136/bmj.323.7304.101.
Stroup, D.F., 2000. Meta-analysis of observational studies in epidemiology a proposal for reporting. JAMA 283, 2008. https://doi.org/10.1001/jama.283.15.2008.
Sun, S., Kuja-Halkola, R., Chang, Z., Cortese, S., Almqvist, C., Larsson, H., 2021. Familial liability to asthma and ADHD: a Swedish national register-based study. JCPP Adv. 1. https://doi.org/10.1002/jcv2.12044.
Thayer, J.F., Hall, M., Sollers, J.J., Fischer, J.E., 2006. Alcohol use, urinary cortisol, and heart rate variability in apparently healthy men: Evidence for impaired inhibitory control of the HPA axis in heavy drinkers. Int. J. Psychophysiol. 59, 244–250. https://doi.org/10.1016/j.ijpsycho.2005.10.013.
Vevea, J.L., Woods, C.M., 2005. Publication bias in research synthesis: sensitivity analysis using a priori weight functions. Psychol. Methods 10, 428–443. https://doi.org/10.1037/1082-989X.10.4.428.
Viechtbauer, W., 2010. Conducting meta-analyses in R with the metafor package. J. Stat. Softw. 36. https://doi.org/10.18637/jss.v036.i03.
Wetzels, R., Wagenmakers, E.-J., 2012. A default Bayesian hypothesis test for correlations and partial correlations. Psychon. Bull. Rev. 19, 1057–1064. https://doi.org/10.3758/s13423-012-0295-x.
Willcutt, E.G., 2012. The prevalence of DSM-IV attention-deficit/hyperactivity disorder: a meta-analytic review. Neurotherapeutics 9, 490–499. https://doi.org/10.1007/s13311-012-0135-8.
Xu, G., Liu, B., Yang, W., Snetselaar, L.G., Jing, J., 2021. Association of attention-deficit/hyperactivity disorder with diabetes mellitus in US adults. J. Diabetes 13, 299–306. https://doi.org/10.1111/1753-0407.13107.
Zhang, J., Yu, K.F., 1998. What's the relative risk?: A method of correcting the odds ratio in cohort studies of common outcomes. JAMA 280, 1690. https://doi.org/10.1001/jama.280.19.1690.
Zhang, L., Reif, A., Du Rietz, E., Lagerberg, T., Butwicka, A., D'Onofrio, B.M., Johnell, K., Pedersen, N.L., Larsson, H., Chang, Z., 2021. Comedication and polypharmacy with ADHD medications in adults: a Swedish nationwide study. J. Atten. Disord. 25, 1519–1528. https://doi.org/10.1177/1087054720923725.
Zhang, P., Gregg, E., 2017. Global economic burden of diabetes and its implications. Lancet Diabetes Endocrinol. 5, 404–405. https://doi.org/10.1016/S2213-8587(17)30100-6.
Zhao, L., Li, X., Liu, G., Han, B., Wang, J., Jiang, X., 2019. The association of maternal diabetes with attention deficit and hyperactivity disorder in offspring: a meta-analysis. Neuropsychiatr. Dis. Treat. Volume 15, 675–684. https://doi.org/10.2147/NDT.S189200.