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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.

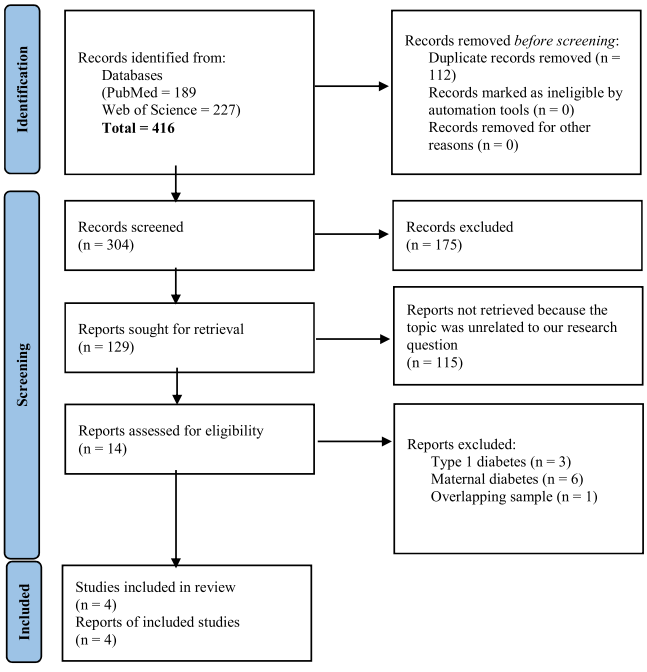

Fig. 1. PRISMA 2020 flowchart of the systematic review.

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

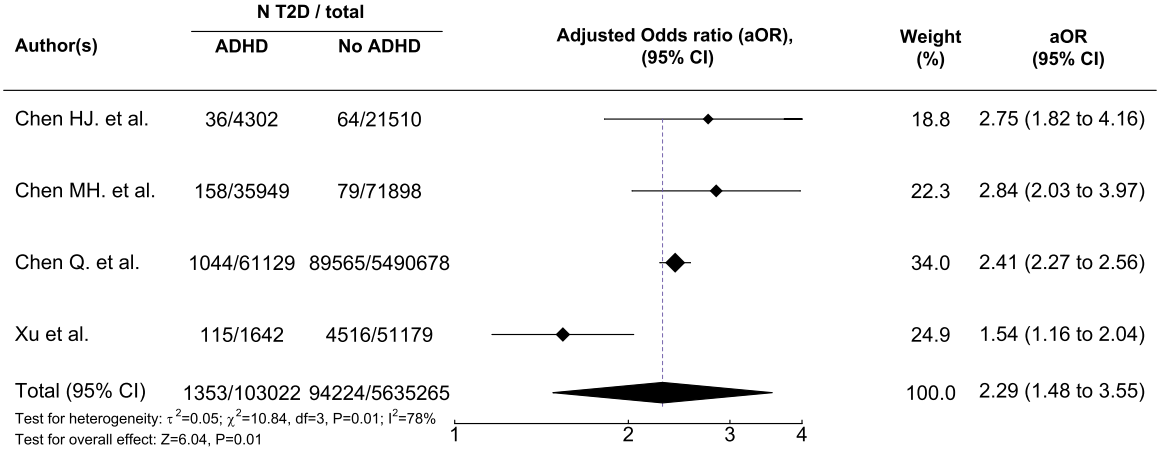

Fig. 2. Forest plot of the observed adjusted odds ratios (OR) and the estimate of the random-effects model for the association of ADHD with T2D with 95 % confidence interval, weight, heterogeneity, and overall effect. *Note.* T2D=Type 2 diabetes, CI=confidence interval, aOR=adjusted odds ratio.

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.

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