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Review article

Association between autism spectrum disorder and diabetes: systematic review and meta-analysis

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ABSTRACT

There is mixed evidence on the link between autism spectrum disorder (ASD) and diabetes. We conducted the first systematic review/meta-analysis on their association. Based on a pre-registered protocol (PROSPERO: CRD42021261114), we searched Pubmed, Ovid, and Web of Science databases up to 6 December 2021, with no language/type of document restrictions. We assessed study quality using the Newcastle-Ottawa Scale (NOS). We included 24 studies (total: 3427,773 individuals; 237,529 with ASD and 92,832 with diabetes) in the systematic review and 20 in the meta-analysis (mean stars number on the NOS: 5.89/10). There was a significant association, albeit characterized by significant heterogeneity, when pooling unadjusted OR (1.535, 95% CI = 1.109–2.126), which remained significant when restricting the analysis to children and type 2 diabetes, but became non-significant when considering adjusted ORs (OR: 1.528, 95% CI = 0.954–2.448). No significant prospective association was found (n = 2) on diabetes predicting ASD (HR: 1.232, 0.826–11.837). Therefore, the association between ASD and diabetes is likely confounded by demographic and clinical factors that should be systematically investigated in future studies.

1. Introduction

There is increasing evidence that conditions classically thought as disorders of the central nervous system are actually characterized by abnormalities in other physiological systems (Qureshi and Mehler, 2013). This has prompted a growing line of research on the association between neuropsychiatric and physical conditions (Cortese et al., 2020). Among other neuropsychiatric conditions, autism spectrum disorder (ASD) has been the focus of research in this area due to the increasing awareness of its impact on the life of affected individuals and their families. Indeed, beyond its defining core symptoms, i.e., qualitative differences in social interaction/communication and repetitive, restrictive, or unusual sensori-motor behaviors/interest (Lord et al., 2018), ASD is often characterized by a range of comorbidities. In addition to

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neuropsychiatric conditions such as anxiety, ADHD, and depressive disorders (Lai et al., 2019), meta-analytic evidence shows a significant association between autism and important physical conditions including obesity (Kahathuduwa et al., 2019), dermatitis (Tsai et al., 2020), and food allergy (Li et al., 2021). Some studies have explored a possible cross-sectional or prospective association with diabetes. These studies were prompted by evidence of a significant association between gestational diabetes and ASD (Rowland and Wilson, 2021), possibly accounted for by the impact of hyperglycemia on neurodevelopment via oxidative stress (Wells et al., 2009).

The association of ASD to diabetes might be plausible from a neurobiological standpoint. In relation to the association with diabetes type 1, shared inflammatory factors might be considered from a theoretical perspective at least. Indeed, it is well established that diabetes type 1 is related to the destruction of insulin-producing beta cells via autoimmune-mediated mechanisms (DiMeglio et al., 2018). Interestingly, some studies have reported evidence of immunological dysfunctions (neuroinflammation, increased autoantibodies, cytokines and immunoglobulins or abnormalities in immune cells,) in individuals with ASD (Bjørklund et al., 2016; Masi et al., 2017). Therefore, it has been proposed that individuals with ASD are at increased risk of disorders mediated by immunological dysfunctions such as diabetes type 1, asthma, inflammatory bowel disease and atopic dermatitis (Zerbo et al., 2015). As for the association with diabetes type 2, which is related to insulin resistance and relative insulin deficiency (Chatterjee et al., 2017), it has been postulated that the link may be mediated by the significant association of ASD to obesity and dyslipidemia, as well as by the metabolic side effects of antipsychotic medications that are quite commonly prescribed in individuals with ASD (Tromans et al., 2021).

However, whilst a significantly association with diabetes (both type 1 (e.g., Freeman et al., 2005),and 2 (e.g., Chen et al., 2016)) has been found in some studies, other studies, e.g. (Bethin et al., 2019), have failed to replicate these positive findings. Given this mixed evidence, there is a need to quantitatively synthesize available evidence. Therefore, the aim of this study was to conduct the first systematic review with meta-analyses of studies (cross-sectional of prospective) providing data on the link between ASD and diabetes.

2. Methods

We followed the 2020 PRISMA guidelines (Page et al., 2021), and pre-registered the protocol in PROSPERO (CRD42021261114). As per the original, pre-registered protocol, we aimed to address two questions: 1) Is there a significant association between autism spectrum disorder (ASD) and diabetes in children, adolescents, or adults? 2) Is there a significant association between diabetes in mothers during pregnancy and ASD in their children? As we deemed that reporting the results related to both objectives would have been unpractical in a single paper, the current paper is related to question #1. Of note, recent meta-analytic evidence has been published in relation to question #2 (Rowland and Wilson, 2021). We will update this evidence and report the results of question #2 in a separate, subsequent paper.

2.1. Search

We searched PubMed (MEDLINE), Ovid databases (PsycINFO, EMBASE + EMBASE Classic, Ovid MEDLINE), and Web of Knowledge [Web of Science (Science Citation Index Expanded), Biological Abstracts, BIOSIS, Food Science and Technology Abstracts] from inception to 6 December 2021 with no restrictions in terms of type of document or language. The syntax for Pubmed, adapted for the other databases, was as follows: (autis* [tiab] or asperger [tiab] or "pervasive developmental disorder" [tiab]) AND diabet* . References of relevant systematic reviews were hand searched to retrieve any additional eligible study.

2.2. Inclusion criteria

We included observational (cross-sectional or prospective) studies providing data on the strength of the association between ASD and diabetes in children, adolescents or adults. Eligible definitions of ASD were as follows: 1) a categorical diagnosis of ASD according to the DSM III, DSM-III-R, DSM-IV, DSM-IV-TR, and DSM-5 or ICD 9 and ICD-10; 2) diagnosis based on the ADOS (Autism Diagnostic Observation Schedule) or similar validated tools; 3) a positive answer to the question: "Did your doctor ever tell you that you have ASD?" or similar; 4) a diagnosis of ASD recorded in medical files/registries. We planned a sensitivity analysis restricted to formal diagnosis of ASD, confirmed by (semi) structured interviews as per DSM/ICD criteria. Studies including individuals of any age and of both genders were eligible. Studies were included regardless of the past or current treatment of the participants with psychotropics for symptoms of ASD or related impairments (e.g., sleep or ADHD symptoms). However, we planned to assess the feasibility of conducting a sensitivity analysis including only studies with ASD medication naïve participants. Control groups recruited due to having other disorders potentially related to a differential risk of diabetes or ASD were not accepted (e.g., groups of individuals with another psychiatric disorder). Siblings of ASD participants were accepted as controls. Studies including participants recruited in clinical settings or in the general population were included.

2.3. Outcomes

The main outcome was the unadjusted ratio (odds ratio-OR-, risk ratio-RR-, hazard ratio -HR- or equivalent, prioritizing the OR) expressing the association between ASD and diabetes. Secondary outcome was the maximally adjusted ratio, when available. The choice of the primary and secondary outcome was made based on the estimated number of eligible studies, expected to be higher for studies reported unadjusted estimates, and, hence, more suitable for secondary/sensitivity analyses, but arguably the adjusted ORs are more informative, as potentially less prone to biased derived from the selection of the groups.

2.4. Screening and data extraction

In order to minimize the possibility of missing relevant studies, four researchers (Alessandra Gabellone; Lucia Marzulli; Iciar Iturmendi-Sabater; Diego de La Chica-Duarte) carried out the screening stage independently and any study considered of interest by any of them was moved to the full-text evaluation phase. Full texts from retrieved references were independently and blindly coded for eligibility by two study authors. Any disagreement was resolved by the first and last author. Two authors independently extracted data from the retained studies. Per protocol, we planned to extract the following information/data: 1) Publication detail: year and language of publication, country where the study was conducted; 2) Design: type of study (including cross-sectional, case-control, cohort.); 3) Study temporality (cross-sectional, prospective, retrospective); 4) Patient enrolment (consecutive, non-consecutive); 5) Setting (clinical vs. population-based study); 6) Study participants details: number, mean age (SD), gender distribution, SES and ethnicity of participants with and without ASD and diabetes; 6) Psychiatric comorbidities of individuals with and without ASD (type and prevalence); 7) Method to establish the diagnosis of ASD (self-reported diagnosis, diagnosis recorded in medical files/registry, structured or semi-structured interview); 8) Medication status of individuals with and without ASD (type of medication and percentage of treated participants, during and prior to the study); 9) Outcome (OR, RR, HR or equivalent)- we extracted both adjusted and unadjusted ratios if available and we used the most adjusted (= maximally adjusted) ratios in the analyses, 10) Number of outcomes within the exposed and unexposed participants- this was used to obtain the unadjusted odds ratio whenever it was not provided.

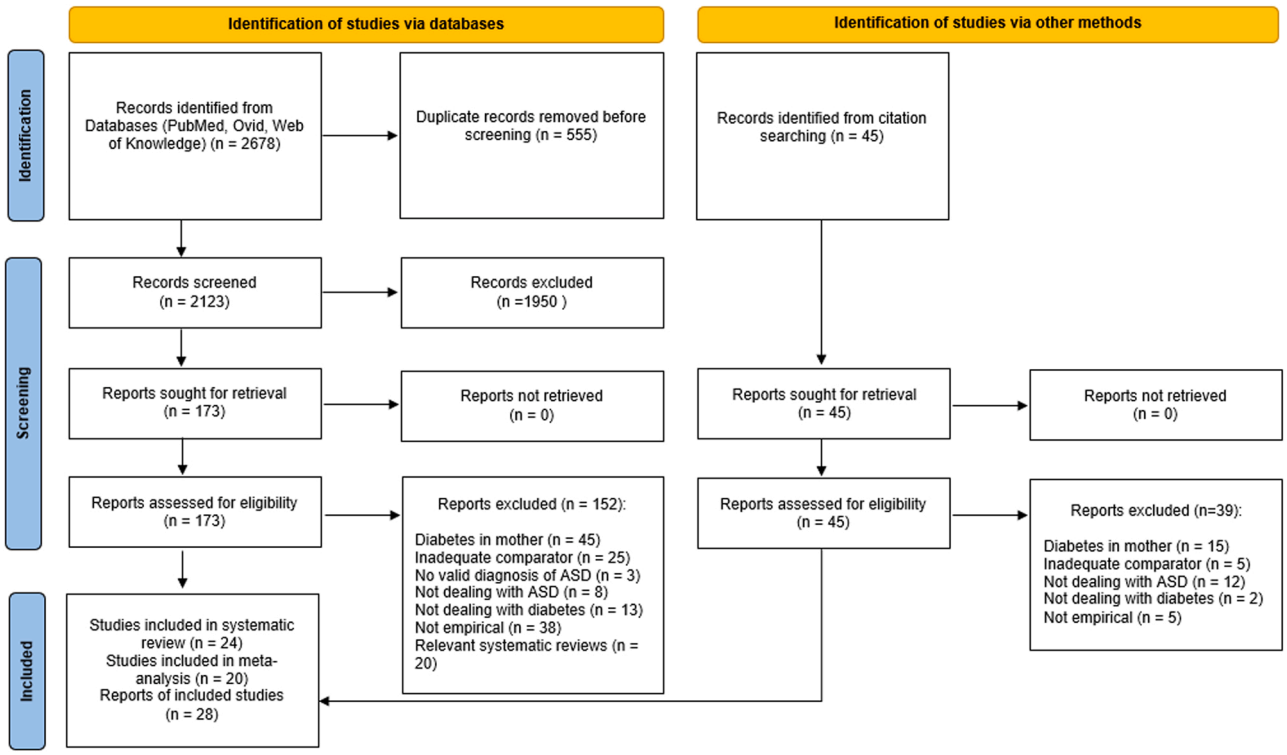

Fig. 1. PRISMA 2020 flow chart- selection of studies.

2.5. Risk of bias/quality assessment

Two authors independently performed the assessment of risk of bias in the included studies using the Newcastle–Ottawa Scale, NOS (Wells et al., 2000). Any discrepancies in the rating of study quality/risk of bias was resolved by consensus between the two authors. If this was not possible, the first and last authors made a judgement on rating and acted as arbitrators.

2.6. Data synthesis

Odds ratios expressing the association between ASD and diabetes were extracted when available or calculated from available data. We conducted two analyses: one focused on non-adjusted odds ratios, and another one on ratios adjusted (by study authors of individual studies) for possible confounders, that inevitably varied form study to study. Meta-analyses used random-effects models (with the DerSimonian and Laird procedure) because it allows the true population effect size to differ among studies. In the adjusted analysis we pooled HRs together to ORs as both diabetes and ASD occur unfrequently. Nevertheless, studies reporting HRs were later removed in a sensitivity analysis.

Per protocol, we planned to assess the feasibility of conducting the following subgroup meta-analyses: 1) analyzing children/adolescents and adults separately; 2) analyzing clinical and population-based studies separately; 3) including only studies with current (as opposed to lifetime) prevalence of ASD and diabetes; 4) including only studies with a diagnosis of ASD confirmed by structured/semi-structured interviews; 5) including only studies with ASD medications naive participants; 6) excluding studies that used siblings as controls; 7) including only longitudinal studies separately. We also planned to perform a meta-regression analysis including unadjusted ratios as outcome and year of study publication, gender, and the rating on the Newcastle-Ottawa Scale as regressors. The meta-analyses and meta-regressions were weighted by the reciprocal of the variance of the effect size, which gives greater weight to larger studies. We used the Q (indicating the presence, but not the degree, of heterogeneity) and the I^2 index (percentage of variance due to true heterogeneity) to estimated indices of heterogeneity of effect sizes. We used Egger's test to assess publication bias and Duval and Tweedie's trim and fill procedure to adjust for it. Analyses were performed using Comprehensive Meta-Analysis v3 (Biostat Inc, 2021).

3. Results

3.1. Overview of included studies

The search in the electronic databases yielded 2678 references. Fleiss' Kappa, a measure of the agreement between more than two raters where agreement due to chance is factored out, was 0.52, indicating a moderate agreement (Zaiontz, 2021a). Cohen's Kappa when judging inclusion versus exclusion in the full text screening phase was 0.60, which is also considered a moderate rate of agreement (Zaiontz, 2021b). After the screening process, 24 studies (reported in 27 publications) were included in the qualitative review (Alabaf et al., 2019; Barrett et al., 2021; Bilder et al., 2017; Butwicka et al., 2015; Chen et al., 2009, 2016, 2013; Croen et al., 2015; Dybdal et al., 2018; Flygare Wallén et al., 2018; Gurney et al., 2006; Kohane et al., 2012; Liu et al., 2021; McDermott et al., 2007; McManus et al., 2009; Schott et al., 2021; Shedlock et al., 2016; Spann et al., 2019; Supekar et al., 2017; Tyler et al., 2011; Vohra et al., 2017; Weir et al., 2021; Weiss et al., 2018; Zerbo et al., 2015). Fig. 1 shows the screening process. Table S1 reports the list of studies excluded after checking the full text, with reason for exclusion. Table S2 details the included studies reported in multiple records (papers).

The total sample size of the studies included in the systematic review was 3427,773 individuals, out of which 237,529 had ASD and 92,832 diabetes. The main study characteristics are reported in Table 1. Table S3 provides additional information on the cases and controls in each study.

Retained studies were all published in English, between 2006 and 2021, and were carried out in North America (n = 12), Northern Europe (Sweden n = 4, Denmark n = 1, Finland n = 1, United Kingdom n = 1) and Taiwan (n = 3), with an additional study being an internet-based transnational survey. Most studies were based on administrative

Table 1
Characteristics of the included studies. NOS: Total number of stars in the Newcastle-Ottawa scale.

Author year	Country	Database	Design	Diagnosis of ASD	Diagnosis of diabetes	Diabetes subtype	Age	Gender (% M)	Total N	ASD N	Diabetes N	NOS
Alabaf et al., 2019	Sweden	Child and Adolescent Twin Study 1992–2006	Cross-sectional	Clinical (A-TAC)	Self-report	Not specified	9–12 years	50.92%	22329	301	93	7
Barrett et al., 2021	USA	National Survey of Children's Health 2006–2019	Cross-sectional	Self-report	Self-report	Not specified	Children and adolescents 3–17 years	Not specified	131774	3601	593	4
Bilder et al., 2017	USA	MarketScan® Research Databases	Cross-sectional	Registers	Registers	T1&T2	Adults ≥ 18	39.32%	29786	37	7060	7
Butwicka et al., 2015	Sweden	Multiple national registries	Longitudinal	Registers	Registers	T1	< 18 years	Not specified	1713733	7038	17122	9
Chen et al., 2009	Taiwan	National Health Insurance Research Databases, 1997–2004	Cross-sectional	Registers	Registers	T1&T2	Children < 19 years	Not specified	37831	3440	102	7
Chen et al., 2013	Taiwan	National Health Insurance Research Databases, 1996–2010	Cross-sectional	Registers	Registers	T1	Any age	Not specified	7994	1598	8	7
Chen et al., 2016	Taiwan	National Health Insurance Research Databases, 2002–2009	Longitudinal	Registers	Registers	T2	Adolescents (10–17 years) and young adults (18–29 years)	Not specified	30610	6122	187	9
Croen et al., 2015	USA	Kaiser Permanente in Northern California, 2008–2012	Cross-sectional	Registers	Registers	Not specified	Adults ≥ 18	Not specified	16577	1507	767	7
Dybdal et al., 2018	Denmark	Multiple national registries 1996–2013	Longitudinal	Registers	Registers	T1	Children. Girls M = 9.6, SD = 4.4; Boys M = 10.2, SD = 4.6	52%	40672	520	5084	9
Gurney et al., 2006	USA	National Survey of Children's Health 2003–2004	Cross-sectional	Self-report	Self-report	Not specified	Children and adolescents 3–17 years	Not specified	85272	483	256	4
Liu et al., 2021	Sweden	Multiple national registries 1973–2013	Longitudinal	Registers	Registers	T1	Children and adolescents	Not specified	92730	738	8430	9
Schott et al., 2021	USA	Medicaid Analytic eXtract	, 2008–2012	Cross-sectional	Registers	Registers	Not specified	Adults 18–65 years	74,1	667808	155617	57283
Shedlock et al., 2016	USA	Military Health System 2000–2013	Cross-sectional	Registers	Registers	T2	Children. M = 8.83, SD = 3.44	80%	292572	48762	1485	7
Spann et al., 2019	Finland	Finnish Prenatal Study of Autism 1987–2007	Cross-sectional	Registers	Registers	T1	Any age	Not specified	22658	4600	180	7
Tyler et al., 2011	USA	Individuals With Intellectual and Other Developmental Disabilities Electronic Health Record Analysis 2005–2008	Cross-sectional	Registers	Registers	Not specified	Adults ≥ 18	71.65%	314	108	23	7
Vohra et al., 2017	USA	Medicaid Analytic eXtract 2000–2008	Cross-sectional	Registers	Registers	Not specified	Adults 22–64 years	Not specified	7092	1772	313	7
Flygare Wallén et al., 2018	Sweden	Central Administrative Database of Stockholm County, 1998–2015	Cross-sectional	Registers	Registers	Not specified	Any age	Not specified	2010061	13921	117547	5
Weir et al., 2021	Multiple	Online physical health survey, 2018–2019	Cross-sectional	Self-report	Self-report	T2	Adults ≥ 18	Not specified	2368	1156	172	4
Weiss et al., 2018	Canada	Health Care Access Research and Developmental Disabilities	Cross-sectional	Registers	Registers	Not specified	Adults 18–24 years	Not specified	398358	5095	2641	6
Zerbo et al., 2015	USA	Kaiser Permanente in Northern California, 1995–2006	Cross-sectional	Registers	Registers	T1	M = 12.15, SD = 5.2	82%	33390	5565	64	7
Kohane et al., 2012	USA	Shared Health Research Informatics Network	Cross-sectional	Registers	Registers	T1	0–34 y	NR	1246494	9105	4238	5
Supekar et al., 2017	USA	Stanford Translational Research Integrated Database Environment	Cross-sectional	Registers	Registers	T1	Any	44	1847365	4790	10891	5
McDermott et al., 2007	USA	Two local practices in Columbia	Cross-sectional	Clinical notes and diagnostic codes	Clinical notes and diagnostic codes	Not specified	Not reported	Not reported	1873	45	272	4
McManus et al., 2009[a]	United Kingdmom	Adult psychiatric morbidity in England Household Survey	Cross-sectional	Clinical (ADOS)	Not reported	Not specified	Adults	Not reported	618	19	38	Not reported

[a] Data obtained from Tromans et al. (2021), which in turn obtained it directly from raw data of the survey.

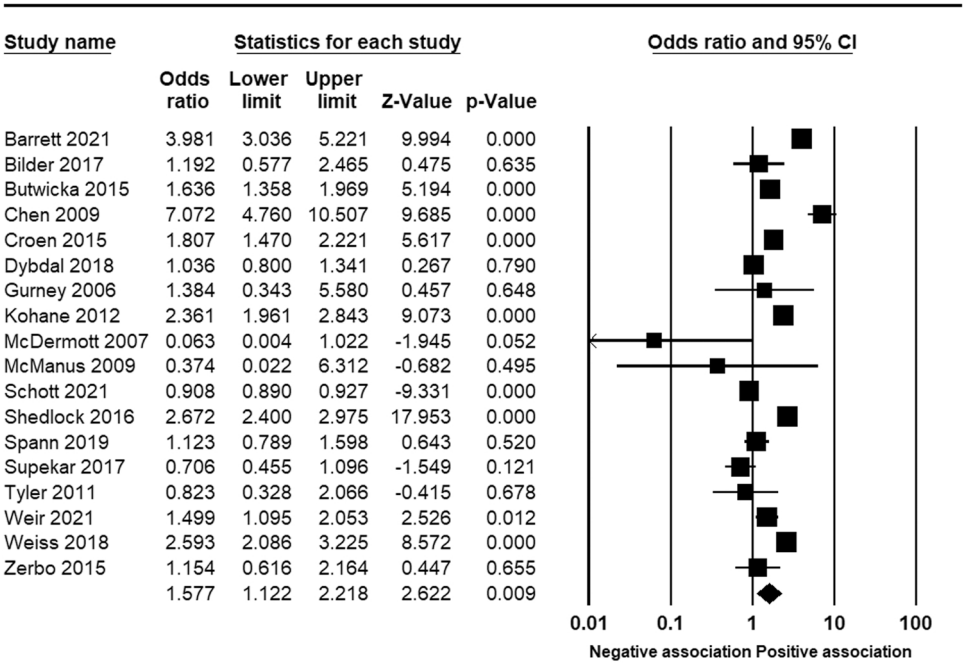

Fig. 2. Forest plot. Meta-analysis of unadjusted ORs. Negative association means a decreased risk of ASD with diabetes while a positive association means an increased risk of ASD with diabetes.

registers, whereas four relied on self-reported surveys (Barrett et al., 2021; Gurney et al., 2006; McManus et al., 2009; Weir et al., 2021), and one on a twin database and clinical diagnoses (Alabaf et al., 2019). Four studies aimed to assess prospective associations (Butwicka et al., 2015; Chen et al., 2016; Dybdal et al., 2018; Liu et al., 2021) and were considered cohort studies for the purpose of risk of bias assessment, while the remaining studied cross-sectional associations and the case-control version of the NOS was used to evaluate their risk of bias. Regarding diabetes, eight studies dealt with the association between ASD and type 1 diabetes, three with type 2 diabetes, and the remaining with both types. Four studies included likely overlapping samples from Sweden (Alabaf et al., 2019; Butwicka et al., 2015; Flygare Wallén et al., 2018; Liu et al., 2021), and two from the USA (Schott et al., 2021; Vohra et al., 2017) so only the largest sample obtained at the country level was included in the meta-analysis (Butwicka et al., 2015; Schott et al., 2021). Similarly, there were three studies with likely overlapping samples from Taiwan (Chen et al., 2009, 2016, 2013). They were not combined into the same analysis, but instead, contributed to specific sensitivity analyses. Hence, 20 studies were finally meta-analyzed.

Table S4 and S5 report the summary of the risk of bias/quality assessment for case-control and cohort study, respectively. The mean number of stars in the Newcastle-Ottawa scale for case-control studies was 5.89 (Standard deviation-SD- = 1.52) and of 9 (SD = 0) for cohort studies.

Table S6 provides data on the outcome matrix, i.e., the number of individuals with and without ASD and with and without diabetes (2 × 2 matrix).

3.2. Results of the meta-analyses

When pooling unadjusted ORs (k = 18), the summary effect indicated a significant association (OR: 1.58, 95% CI = 1.12–2.22), albeit

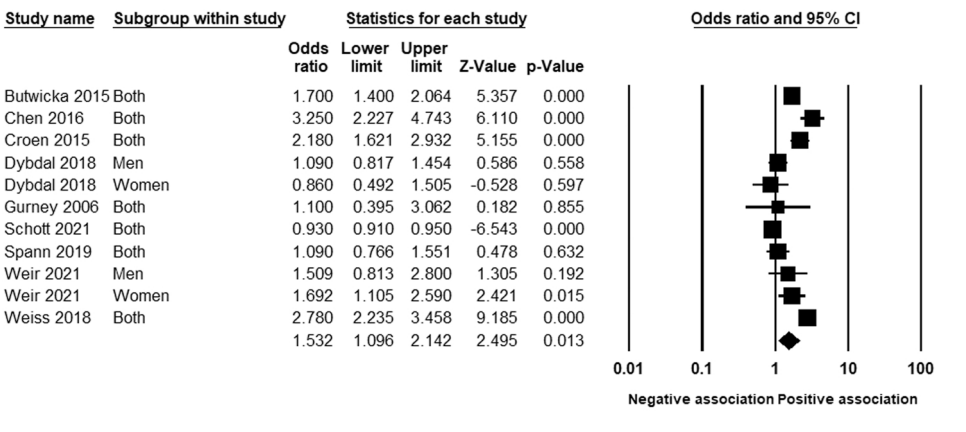

Fig. 3. Forest plot. Meta-analysis of maximally adjusted effect sizes. Negative association means a decreased risk of ASD with diabetes while a positive association means an increased risk of ASD with diabetes.

Table 2
Covariates adjusted for in relation to maximally adjusted outcomes retained in the analyses.

Author_year	Type	ES (95%CI)	Covariates adjusted for statistically	Direction
Butwicka et al., 2015	HR	1.70 (1.40,2.00)	Socioeconomic factors (maternal/paternal age at childbirth, maternal/paternal psychiatric history, maternal/paternal country of birth, level of education of higher educated parent), perinatal variables (gestational age, birth weight, being born small for gestational age, being born large for gestational age, Apgar score), and history of psychiatric disorders prior to the recruitment.	Diabetes > > ASD
Chen et al., 2016	HR	3.25 (2.23,4.75)	Demographic data, use of atypical antipsychotics, and medical comorbidities	ASD > > Diabetes
Croen et al., 2015	OR	2.18 (1.62,2.93)	Age, sex, and race/ethnicity	NA
Dybdal et al., 2018 (men)	HR	1.09 (0.82,1.46)	Age at inclusion	Diabetes > > ASD
Dybdal 2018 (women)	HR	0.86 (0.49,1.50)	Age at inclusion	Diabete s > > ASD
Gurney et al., 2006	OR	1.10 (0.40,3.10)	Age, sex, primary language, insurance, and household educational attainment	NA
Schott et al., 2021	OR	0.93 (0.91,0.96)	Age, race/ ethnicity, months enrolled, Medicaid eligibility category, state and whether the individual had an Intellectual Disability diagnosis.,	NA
Spann et al., 2019	OR	1.09 (0.77,1.56)	Maternal socioeconomic status, gestational age, and maternal and familial psychiatric diagnosis	NA
Vohra et al., 2017	OR	0.74 (0.56,0.99)	Age, sex, and race/ethnicity	NA
Weir et al., 2021 (men)	OR	1.51 (0.82,2.83)	Age, ethnicity, country of residence, education-level BMI, alcohol use, and smoking	NA
Weir et al., 2021 (women)	OR	1.69 (1.11,2.60)	Age, ethnicity, country of residence, education-level BMI, alcohol use, and smoking	NA
Weiss et al., 2018	OR	2.78 (2.23,3.45)	Age, sex, rurality, and neighborhood income quintile	NA

Table 3
Summary of results of sensitivity analyses. K: number of effect sizes. ES: pooled effect size. LBCI and UBCI: Lower and upper bound of the 95% confidence interval, pQ: p-value associated to the Q statistic of heterogeneity, PB: Evidence of publication bias (when $p < 0.1$ for Egger test).

Analysis	K	ES (95%CI)	Q	pQ	I^2	PB
Children	7	1.49 (0.97,2.29)	109.38	93.6%	No	109.38
Adults	9	1.7 (1.13,2.57)	157.17	95.55%	Yes	157.17
T1 diabetes	8	2.39 (2.21,2.58)	47.54	87.38%	No	47.54
T2 diabetes	8	1.44 (0.93,2.22)	22.24	91.01%	No	22.24
Registry diagnosis	7	1.35 (0.96,1.9)	718.84	98.19%	Yes	718.84
Self-reported diagnosis	3	2.57 (1.65,4.03)	22.07	90.94%	No	22.07
Epidemiological studies	14	1.51 (1.05,2.19)	828.69	98.19%	Yes	828.69
Case-controlled studies	3	2.2 (0.96,5.04)	799.87	98.25%	Yes	799.87

characterized by significant heterogeneity ($Q = 829,29$, $p < 0.05$, I^2: 97.95%) (Fig. 2) and evidence of publication bias (Fig. S1). When the trim and filled procedure was implemented, the association was no longer significant (OR: 0.99, 95% CI = 0.71–1.38). A very similar result was obtained when all adjusted effect sizes ($k = 9$) were combined (OR: 1.532, 95% CI = 1.096–2.141, $Q = 212.32$, $I^2 = 95.29\%$), which also showed evidence of publication bias (Fig. 3 and S2, and Table 2 for a list of covariates adjusted for in each study). When aHRs were excluded, the summary effect size derived from pooling adjusted ORs ($k = 7$) was lower and statistically not significant (OR: 1.528, 95% CI = 0.954–2.448), with significant heterogeneity ($Q = 136.68$ $p < 0.05$, I^2: 95.610) and publication bias (Fig. 4 and S3). Results were substantially replicated in the subgroup analysis focusing on children but not in adults, where the summary effect became not significant (Figs. S4 to S7).

Although the number of pooled studies was small, the association was significant for type 2 diabetes (OR:2.57, 95% CI = 1.65–4.03) but not for type 1 (OR: 1.35, 95% CI = 0.96–1.90) as shown in Figs. S8 to S11. Since all studies involved diagnoses over the whole life or long time periods, we could not evaluate the effect of using only current diagnoses. Conversely, no study reported the number of medication-naïve individuals with ASD and the only study using siblings as controls was not included in the quantitative synthesis.

Furthermore, results held in the analyses focusing on population-based studies (only one study was in a clinical population), using diagnoses derived from administrative registries, or limiting the analysis to case-controlled studies (Figs. S12 to S19).

The meta-analysis of the studies reporting a prospective association (diabetes predicting ASD) showed a non-significant summary effect, with significant heterogeneity ($Q = 9.617$, $p < 0.008$, $I^2 = 79.20$) (Fig. S20). There was only one study assessing the opposite temporal direction (ASD preceding diabetes) and it was significant (HR = 3.25, 95% CI = 2.23–4.75). Paucity of information/data prevented the conduct of the other planned analyses.

Based on the availability of data, we could only test, via meta-regression, the moderating effect of two variables: study quality rating, and year of publication, both of which were not significant ($p > 0.05$).

4. Discussion

To the best of our knowledge, this is the first meta-analysis of studies providing data on the association between ASD and diabetes. Whilst previous meta-analytic evidence established a significant association

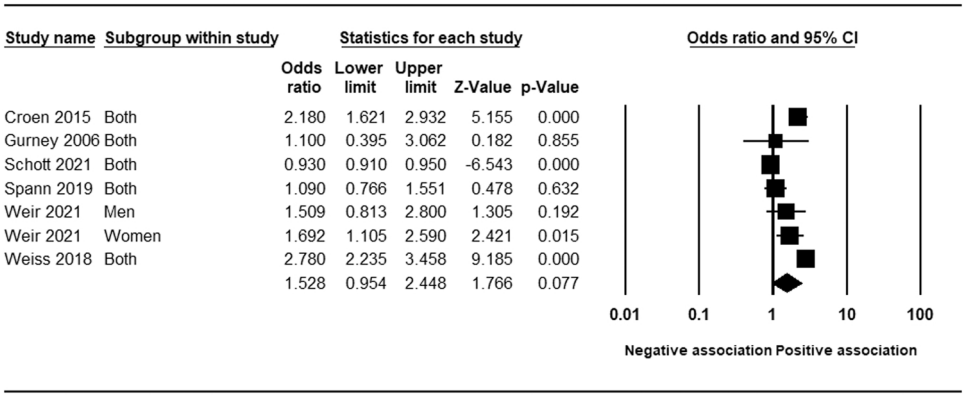

Fig. 4. Forest plot. Meta-analysis of maximally adjusted effect sizes, excluding studies presenting hazard ratios. Negative association means a decreased risk of ASD with diabetes while a positive association means an increased risk of ASD with diabetes.

between gestational diabetes and ASD in offspring, studies assessing the association of ASD to diabetes type I or 2 in the same individual had not been meta-analyzed so far.

While our systematic review/meta-analysis points towards a statistically significant association between ASD and diabetes, robust evidence is currently lacking. Even though the primary analysis pooling all eligible studies showed a significant effect size, it was characterized by statistically significant heterogeneity, indicating the inappropriateness of considering the summary effect as representative of the true effect, and the need to gain insight into the sources of heterogeneity. While the analysis combining all adjusted effect sizes obtained similar results to our main analysis, the pooled effect size was reduced and was not statistically significant when only adjusted ORs (i.e., excluding aHRs) were combined. Of note, the covariates adjusted for inevitably varied form study to study. Furthermore, while the subgroup meta-analysis in children provided a significant effect this was not the case in the analysis in adults.

We also found no meta-analytic evidence that diabetes increases the risk of later ASD or viceversa, with just two studies showing no significant predictive role of diabetes on later ASD and a single study for the other direction.

High heterogeneity was a hallmark in all the analyses in our systematic review/meta-analysis, and we could not establish its sources in our subgroup our meta-regression analyses. Data also pointed towards publication bias in the main analysis, as well as many of the other analyses, which we tried to adjust for with the trim and fill procedure. However, it must be noted that procedures for evaluation and adjusting for such bias are less reliable with a reduced number of studies, especially when effect sizes are heterogeneous, as was our case. The risk of bias of included studies, as estimated by the Newcastle-Ottawa scale, was also variable, but consistently lower in cohort studies. However, risk of bias was not shown to be related to the direction of the effect sizes in the meta-regression analysis. Importantly, several studies failed to select an unbiased control group. Relatedly, the study by Schott et al.- the largest among the included ones- controlled for intellectual disability when selecting the control group for its ASD sample, as opposed to all other studies. Hence, these differences in design could be related to some of the discrepancies among effect sizes.

The results of the present systematic review/meta-analysis need to be considered in the light of a number of limitations. First, we overall included a relatively limited number of (heterogeneous) studies. Second, due limitations in the reporting of individual studies we were only able to pool a very low number of studies in the analyses differentiating between type 1 and 2 diabetes, as we intended to do in a post hoc analysis. Third, due to lack of data, we could not assess a number of moderating factors (i.e., current- as opposed to lifetime- diagnosis of ASD and diabetes; effects of psychotropic medications) in the planned subgroup analyses as well as regressors in the planned meta-regression. Fourth, whilst we could have categorized the confounding variables and using such categories in a meta-regression, given the inconsistency in the type and definition of confounding variables across studies (Table 2), we deemed that this would have been potentially misleading. Future studies should control for common and more consistently defined confounders to allow such meta-regression.

Therefore, despite representing the most comprehensive evidence synthesis to date, our systematic-review/meta-analysis points to the need of conducting large population-based studies controlling simultaneously, for a broad number of confounders, identified via directed acyclic graph, as done in previous work. For instance, following a systematic review and meta-analysis identifying confounding factors controlled in each study included in the systematic review on the association between asthma and ADHD, Cortese et al. performed a study in the Swedish registries controlling simultaneously for all the confounders identified via the systematic review (Cortese et al., 2018).

5. Conclusions

Despite its limitations, our work suggests that claims on a significant association between ASD and diabetes are currently not supported by robust evidence. Future research should focus on moderators that may explain significant associations in subgroups of individuals. Meanwhile, stakeholders and policy makers should be aware that any suggestion of systematically screening diabetes in individuals with ASD and vice versa is not grounded on solid evidence.

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CRediT authorship contribution statement

Samuele Cortese: Conceptualization, Methodology, Formal analysis, Investigation, Resources, Writing – original draft, Writing – review & editing, Supervision, Project administration, Funding acquisition. **Alessandra Gabellone:** Investigation, Writing – review and editing. **Lucia Marzulli:** Conceptualization, Methodology, Investigation, Writing – review & editing, Funding acquisition. **Iciar Iturmendi-Sabater:** Investigation, Writing – review & editing. **Diego de La Chica-Duarte:** Investigation, Writing – review & editing. **Isabella M. Piqué:** Investigation, Writing – review & editing. **Marco Solmi:** Conceptualization, Methodology, Writing – review & editing. **Jae Il Shin:** Conceptualization, Methodology, Writing – review & editing. **Lucia Margari:** Conceptualization, Methodology, Investigation, Writing – review & editing, Funding acquisition. **Gonzalo Arrondo:** Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Supervision, Project administration.

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Conflicts of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data presented in this study are available in the Supplementary material.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2022.104592.

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