Neurocognitive and behavioural outcomes in offspring exposed to maternal pre-existing diabetes: a systematic review and meta-analysis

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Abstract

Aims/hypothesis We performed a systematic review and meta-analysis to determine whether exposure to maternal pre-existing diabetes in pregnancy is associated with neurocognitive or behavioural outcomes in offspring.

Methods We searched MEDLINE, EMBASE, PsychINFO, the Cochrane Database of Systematic Reviews and Scopus for studies that examined any neurocognitive or behavioural outcomes in offspring of mothers with pre-existing diabetes in pregnancy in accordance with a published protocol (PROSPERO CRD42018109038). Title and abstract review, full-text review and data extraction were performed independently and in duplicate. Risk of bias was assessed using the Newcastle–Ottawa scale. Meta-analyses of summary measures were performed using random-effects models.

Results Nineteen articles including at least 18,681 exposed and 2,856,688 control participants were identified for inclusion. Exposure to maternal pre-existing diabetes in pregnancy was associated with a lower pooled intelligence quotient in the offspring (pooled weighted mean difference -3.07 [95% CI $-4.59, -1.55$]; $I^2 = 0\%$) and an increased risk of autism spectrum disorders (effect estimate 1.98 [95% CI $1.46, 2.68$]; $I^2 = 0\%$). There was also an increased risk of attention deficit/hyperactivity disorder (pooled HR 1.36 [95% CI $1.19, 1.55$]; $I^2 = 0\%$), though this was based on only two studies. Although most studies were found to be high quality in terms of participant selection, in many studies, comparability of cohorts and adequacy of follow-up were sources of bias.

Conclusions/interpretation There is evidence to suggest that in utero exposure to maternal pre-existing diabetes is associated with some adverse neurocognitive and behavioural outcomes. It remains unclear what the role of perinatal factors is and the degree to which other environmental factors contribute to these findings.

Jennifer M. Yamamoto and Jamie L. Benham contributed equally to this study.

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Research in context

What is already known about this subject?

- Pre-existing diabetes in pregnancy is associated with increased risk of poor obstetric/neonatal outcomes
- The adverse effect of in utero exposure to maternal pre-existing diabetes may extend beyond the neonatal period to include an increased risk of poor neurocognitive and behavioural outcomes, although the evidence is inconsistent

What is the key question?

- Is exposure to maternal pre-existing diabetes in utero associated with neurocognitive or behavioural problems in the offspring?

What are the new findings?

- Exposure to maternal pre-existing diabetes in pregnancy was associated with a lower pooled intelligence quotient and an increased risk of autism spectrum disorder
- While we found an increased risk of attention deficit/hyperactivity disorder in offspring of mothers with maternal pre-existing diabetes, this analysis was based on only two studies and should be interpreted with caution
- The relationship between maternal glycaemic control and offspring neurocognitive and behavioural outcomes is unclear

How might this impact on clinical practice in the foreseeable future?

- Heightened awareness of the association of exposure to pre-existing diabetes in utero with intelligence and autism spectrum disorder should contribute to a low threshold for investigating parental concerns in these children

Keywords ADHD · ASD · Autism · Behaviour · Childhood · Diabetes · IQ · Meta-analysis · Neurocognitive · Offspring · Pregnancy · Systematic review

Abbreviations

ADHD	Attention deficit/hyperactivity disorder
ASD	Autism spectrum disorder
GCSE	General Certificate of Secondary Education
IQ	Intelligence quotient
RR	Risk ratio

Introduction

Diabetes in pregnancy is associated with an increased risk of obstetric and neonatal complications [1, 2]. Maternal pre-existing diabetes is becoming increasingly prevalent in pregnancy. In type 1 diabetes, as many as one in two pregnancies will have a complication such as preterm delivery, offspring being large for gestational age, neonatal hypoglycaemia or neonatal intensive care unit admission [2, 3]. There is also an increased risk of less common but serious adverse outcomes such as congenital anomalies, stillbirth and neonatal death [4–6]. While the risk of short-term complications following diabetes in pregnancy is well established, the risk of longer-term adverse outcomes is not well defined.

It is hypothesised that in utero exposure to maternal diabetes, during this critical period of brain development,

may lead to neurocognitive and behavioural difficulties persisting into child- and adulthood. Studies have evaluated exposure to maternal diabetes (all types) in relation to a wide range of neurocognitive and behavioural outcomes including intelligence quotient (IQ), school achievement, memory difficulties, attention deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) [7–10]. However, the results are inconsistent, with some but not all studies showing an association between exposure to maternal diabetes (all types) and various neurocognitive and behavioural outcomes [7–10].

Systematic reviews have been performed to assess the association between maternal diabetes (all types) and childhood cognitive function and behaviour, but these reviews do not address the wide range of possible neurocognitive and behavioural outcomes evaluated in the literature and/or address the association between maternal diabetes and outcomes beyond childhood [11, 12]. In addition, these reviews included gestational diabetes where the degree of hyperglycaemia is less severe and of shorter duration.

To address this knowledge gap, we performed a systematic review and meta-analysis to determine whether exposure to pre-existing diabetes (type 1, type 2 and other forms of pre-existing diabetes such as monogenic diabetes) in pregnancy is

associated with neurocognitive or behavioural outcomes in offspring at any age of assessment.

Methods

We performed a systematic review and meta-analysis in accordance with a published protocol (PROSPERO CRD42018109038). The Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines were used to report the findings [13].

Study question and eligibility This review aimed to address the following question: ‘Is exposure to hyperglycaemia in utero associated with poor neurocognitive or behavioural outcomes in the offspring of mothers with pre-existing diabetes?’

Studies needed to address the following Population Exposure Comparison Outcome Design (PECOD) research question and meet all inclusion criteria to be eligible for inclusion in this review:

- 1) population: offspring of mothers with pre-existing diabetes in pregnancy;
- 2) exposure: maternal pre-existing diabetes in pregnancy (type 1, type 2 and other forms such as monogenic diabetes);
- 3) comparison: no maternal diabetes (all types) or population-based standards;
- 4) outcomes: any neurocognitive or behavioural outcomes (e.g. IQ, Child Behaviour Checklist scores, Bayley Scale of Infant Development, Conners’ Rating Scales for ADHD, etc.) beyond the neonatal period;
- 5) study design and methodology: we included only published randomised controlled trials or cohort studies that reported on original data. Only articles reported in English or French were included because these are the languages of the authors.

Search strategy and study selection The search was performed in duplicate using the search strategy outlined in the electronic supplementary material ([ESM Methods](#)). The search was performed on 12 September 2018. The search strategy was developed in collaboration with a medical librarian. The search was created using key words and Medical Subject Heading (MeSH) terms which were adjusted for each database. MEDLINE, EMBASE, PsychINFO, the Cochrane Database of Systematic Reviews and Scopus were searched using the identified search strategy for all available time periods. References of included studies and relevant reviews were hand-searched in duplicate to identify additional articles for inclusion. We conferred with experts in the field for the potential inclusion of additional articles.

Title and abstract review of all citations identified was performed to assess eligibility. Full-text review was completed

for all citations identified at title and abstract review as eligible. Reasons for exclusion at full-text review were recorded. All stages of study selection were performed in duplicate by two independent reviewers. If multiple articles reported on the same cohort, they were only included if they reported different outcomes or the assessment was performed at different ages. If two articles reported data on the same outcome for the same cohort, the study that reported the measures most comprehensively was included. Agreement between reviewers was recorded and reported as a κ statistic. Any disagreement between reviewers was resolved through consensus and/or in consultation with a third reviewer when necessary.

Data extraction Data were extracted independently and in duplicate using standardised forms. Extracted information included elements such as study design and other study characteristics, study population, number of participants, type of diabetes, neurocognitive and behavioural outcomes and their definitions, measures of association of maternal pre-existing diabetes with neurocognitive and behavioural outcomes, age at assessment, effect of maternal glycaemic control, adjustment for confounders, etc. Each reviewer independently assessed study quality. The Newcastle–Ottawa scale was used to assess the quality of nonrandomised studies [14]. Data management was performed using Covidence (Veritas Health Information Limited, Melbourne, Victoria, Australia, 2018) and Microsoft Excel (Microsoft Corporation, Redmond, WA, USA, version 15.30, 2017).

Data synthesis and analysis Meta-analyses were performed using random-effects models using the DerSimonian and Laird method. Summary measures of the effect size for standardised testing (i.e., IQ) and other neurocognitive and behavioural outcomes were expressed as mean differences, ORs, HRs or risk ratios (RRs) with 95% CIs where appropriate. ORs were substituted for RRs. All extracted ORs met the following criteria: (1) the incidence of the outcome was less than 10%; and (2) the OR was between 0.5 and 2.5 [15]. Statistical heterogeneity was quantified using I^2 statistics. Pre-specified stratified analyses were performed by type of diabetes to explore reasons for heterogeneity; however, not all analyses pre-specified in our protocol could be performed given the lack of available data. Publication bias was assessed using graphical aids as appropriate. Statistical analyses were performed using STATA (StataCorp LP, College Station, TX, USA, version 14.1).

Results

A total of 4301 records were identified and their titles and abstracts reviewed (Fig. 1). Of these, 66 articles were chosen for full-text review. A total of 19 articles including more than

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram

18,681 participants with pre-existing diabetes and 2,856,688 control participants were included in the qualitative analysis [7–10, 16–30] and 12 articles including more than 13,000 participants (two studies did not report an *n* for offspring with exposure to maternal pre-existing diabetes [21, 25]) in the quantitative synthesis [7, 9, 10, 16, 17, 19–21, 23, 25–27, 29, 30]. The literature search did not identify any randomised controlled trials with eligible follow-up data or data collected for secondary analysis that met inclusion criteria. Three of the included studies used the same cohort but reported on different outcomes; therefore, all were included in the review [17, 18, 22]. No studies knowingly included women with monogenic diabetes. The κ statistic for inter-rater agreement was 0.70 (95% CI 0.63, 0.77) for the title and abstract review and 0.79 (95% CI 0.62, 0.95) for the full-text review.

Study characteristics The characteristics of included studies are summarised in Table 1. Twelve studies were performed in Europe [7–9, 17, 18, 20–24, 27, 28] and seven in North America [10, 16, 19, 25, 26, 29, 30]. Sample sizes ranged from 40 to over 1,380,000, with retrospective administrative database studies being largest. Age of assessment varied from 0.5 years to 27 years. Outcomes assessed included intelligence, behaviour, psychomotor development, developmental disorders such as ADHD and ASD, and psychiatric disorders.

Study quality assessment An assessment of study quality using the Newcastle–Ottawa scale for cohort studies is presented in Table 2 [14]. Most studies had high-quality participant selection [7, 9, 10, 16–19, 21–23, 25–30]. Due to the nature of the outcome assessed, none of the studies had low risk of bias for ‘demonstration that outcome not present at study onset’; therefore, this category was not included in the table. Studies were mixed in terms of comparability. In some studies, the exposed and unexposed cohorts were thought to be well matched and highly adjusted for potential confounders [7, 9, 10, 17, 18, 21–23, 25, 26], other studies had matching or adjusted analyses alone [20, 24, 27, 29] and some had no matching or adjustment at all [8, 16, 19, 28, 30]. Adequacy of follow-up was frequently unreported or thought to be a source of bias.

Exposure to maternal pre-existing diabetes and measures of intelligence We identified ten studies that examined the association of maternal pre-existing diabetes with measures of intelligence or intellectual disability [7–9, 17, 25–30]. Six were pooled in a meta-analysis for IQ [7, 9, 17, 27, 29, 30] (Table 3).

Two studies reported data that could not be pooled because they did not have a comparator group [8, 28]. Persson et al assessed children of mothers with diabetes using the Terman–

Table 1 Characteristics of included studies

Study (year)	Country	Type of diabetes	<i>n</i> ^a	Comparator group	<i>n</i> ^a	Study design	Age at assessment in years	Neurocognitive or behavioural outcome
Burstyn et al (2010) [16]	Canada	Pre-pregnancy	1645	No pre-pregnancy diabetes	213,575	Retrospective cohort	Not reported	ASD
Byrøft et al (2016) [17]	Denmark	Type 1	278	Matched for sex, age and postal code	303	Prospective cohort	13–19	Intellectual assessment
Byrøft et al (2017) [18]	Denmark	Type 1	269	Matched for sex, age and postal code	293	Prospective cohort	13–19	Attention
Clausen et al (2011) [7]	Denmark	Type 1	158	Women referred for antenatal care and delivery at the same department and time	118	Retrospective cohort	18–27	Cognitive function
Dodds et al (2011) [19]	Canada	Pre-existing	533	No pre-existing diabetes	129,200	Retrospective cohort	Follow-up up to 17	ASD
Fraser et al (2012) [9]	UK	Pre-existing	26	No evidence of glucosuria or diabetes	8192	Prospective cohort	4, 8 and 16	Cognitive measures
Hod et al (1999) [20]	Israel	Type 1 and 2	21 and 10, respectively	Matched for age, education, religious belief, ethnic origin	41	Prospective cohort	1	Development
Ji et al (2018) [21]	Sweden	Type 1	Not reported	No diagnosis of diabetes in either parent. Matched for sex and date of birth	1,380,829	Retrospective cohort	Median follow-up 25	ADHD
Knoor et al (2015) [22]	Denmark	Type 1	707	Matched for maternal birth year, gave birth within ±90 days of index mother, sex of index child	60,341	Prospective cohort	15–16	Academic achievement
Kong et al (2018) [23]	Finland	Treated with insulin pre-pregnancy	4000	No pre-gestational or gestational diabetes	543,347	Retrospective cohort	Up to 11	Psychiatric disorders
Kowalczyk et al (2002) [24]	Poland	Type 1	19	Age- and sex-matched control participants from healthy mothers	20	Prospective cohort	1–3	Psychomotor development
Li et al (2016) [25]	USA	Pre-existing	Not reported	No gestational or pre-gestational diabetes in same cohort	Not reported	Retrospective cohort	Median follow-up 6.0 (IQR 3.6–9.0)	Developmental disorders (ASD, ID, ADHD, other)
Mann et al (2013) [26]	USA	Type 1 and 2	582	No diabetes	147,323	Retrospective cohort	Minimum of 3	ID
Omoy et al (1998) [27]	Israel	Type 1 and 2	57	Matched by age, parental education and occupation, gestational age, birth order, family size	57	Retrospective cohort	7–13	Neurobehaviour
Persson et al (1984) [28]	Sweden	Type 1	64	Not applicable	Not applicable	Retrospective cohort	5	Intelligence, behavioural/conduct disorders
Rizzo et al (1991) [29]	USA	Type 1 and 2	89	Normal glucose metabolism during pregnancy	35	Prospective cohort	2 and 3–5	Intelligence
Sells et al (1994) [30]	USA	Insulin dependent	109	Mothers without diabetes recruited from the university	90	Prospective cohort	0.5, 1, 2 and 3	Developmental outcomes
Temple et al (2011) [8]	UK	Type 1	40	None—compared with UK normative data	Not applicable	Retrospective cohort	6–12	Cognitive function
Xiang et al (2018) [10]	USA	Type 1 and 2	621 and 9453, respectively	No diabetes	372,924	Retrospective cohort	Median follow-up 6.9 (IQR 3.4–11.9)	ASD

^aThe numbers of cases and control participants (*n*) are presented as reported in each study—some authors reported total participants while others reported total number of participants assessed ID, intellectual disability; IQR, interquartile range

Table 2 Study quality assessment

Study (year)	Selection			Comparability of cohorts based on design or analysis ^a	Outcome		
	Exposed cohort represented	Selection of non-exposed cohort	Ascertainment of exposure		Assessment of outcome	Follow-up long enough for valid use of assessment tool	Adequacy of follow-up
Burstyn et al (2010) [16]	★	★	★	—	★	?	★
Bytoft et al (2016) [17]	★	★	★	★★	★	★	—
Bytoft et al (2017) [18]	★	★	★	★★	★	★	—
Clausen et al (2011) [7]	★	★	★	★★	★	★	—
Dodds et al (2011) [19]	★	★	★	—	★	★	?
Fraser et al (2012) [9]	★	★	★	★★	★	★	?
Hod et al (1999) [20]	?	?	★	★	?	★	?
Ji et al (2018) [21]	★	★	★	★★	★	★	?
Knorr et al (2015) [22]	★	★	★	★★	★	★	?
Kong et al (2018) [23]	★	★	★	★★	★	★	★
Kowalczyk et al (2002) [24]	?	?	★	★	?	★	?
Li et al (2016) [25]	★	★	★	★★	★	—	?
Mann et al (2013) [26]	★	★	★	★★	★	—	—
Omoy et al (1998) [27]	★	★	★	★	★	★	★
Persson et al (1984) [28]	★	Not applicable	★	Not applicable	?	★	—
Rizzo et al (1991) [29]	★	★	★	★	★	★	?
Sells et al (1994) [30]	★	★	★	—	★	★	—
Temple et al (2011) [8]	?	Not applicable	★	—	?	★	?
Xiang et al (2018) [10]	★	★	★	★★	★	★	?

★, low risk of bias; —, high risk of bias; ?, unclear risk of bias

^a Two stars awarded if studies matched cases and control participants and reported adjusted estimates; one star awarded if they performed one or the other

Merril method to assess intelligence and reported that children of mothers with ‘insulin-dependent diabetes’ had an average IQ of 119 [28]. However, they did not provide a measure of error or have a comparison group. Temple et al assessed children of mothers with type 1 diabetes using the Wechsler Intelligence Scale for Children, version 4, and found that when compared with UK normative data there was no difference in overall IQ [8]. However, working memory scores were significantly lower in offspring exposed to maternal type 1 diabetes compared with UK normative data (Table 3).

A meta-analysis was performed for offspring IQ using data from six studies (Fig. 2). Because one study performed a stratified analysis by ‘early entry’ and ‘late entry’ cohorts (the exact definition of these cohorts was unclear), two main meta-analyses were performed: one with the early cohort and one with the late cohort [30]. In the main meta-analyses including the Sells ‘early cohort’, the pooled weighted mean difference was -3.07 (95% CI -4.59 , -1.55 ; $I^2 = 0\%$), suggesting that offspring exposed to maternal pre-existing diabetes have a significantly lower IQ compared with control groups. The second main pooled analysis including the Sells ‘late cohort’ similarly found a lower IQ in offspring exposed to maternal pre-existing diabetes (mean difference -3.92

[95% CI -5.55 , -2.28]; $I^2 = 0\%$). A sensitivity analysis including only offspring of women with type 1 diabetes was performed and found a mean difference of -4.62 (95% CI -6.75 , -2.50 ; $I^2 = 0\%$) compared with control participants. Both studies in women with type 1 diabetes only were in Denmark [7, 17]. It should be noted that Bytoft et al found a significantly lower IQ in offspring exposed to maternal type 1 diabetes after adjustment for confounders [17]. In contrast, Clausen et al reported that the significant difference between the groups was lost after adjustment [7]. The confounders and mediators adjusted for were similar between the two studies (ESM Table 1).

Exposure to maternal pre-existing diabetes and academic achievement Two studies assessed academic achievement; however, these data could not be pooled [9, 22]. Fraser et al studied a cohort from the UK and examined for differences in School Entry Assessment (age 4) and General Certificate of Secondary Education (GCSE) results (age 16) (Table 3) [9]. There was no significant difference in School Entry Assessment in offspring of mothers with pre-existing diabetes ($n = 21$) compared with offspring of mothers without diabetes or glycosuria ($n = 5804$). However, offspring exposed to

Table 3 Summary of results of included studies

Study (year)	Measurement	Summary of main result	Adjusted analysis ^a	Assessment of role of glycaemic control	In meta-analysis
Burshtyn et al (2010) [16]	ICD codes for ASD	RR of ASD if maternal pre-pregnancy DM 1.65 (95% CI 1.01, 2.71)	No	Not reported	Yes
Byroft et al (2016) [17]	Reynolds Intellectual Assessment Scales and parental questionnaires	Offspring of mothers with T1D had lower scores on all cognitive measures as well as an increase in mathematics difficulties (adjusted OR 2.68 [95% CI 1.09, 6.61]; $p = 0.032$)	Yes	No association between HbA _{1c} and Reynolds Intellectual Assessment Scale	Yes
Byroft et al (2017) [18]	Conners' Continuous Performance Test-II	Higher self-reported ADHD medication use (2.2% vs 0%; $p = 0.01$). No significant difference in regression analyses of Conners' Continuous Performance Test-II	Yes	Not reported	No
Clausen et al (2011) [7]	Raven's Progressive Matrices and Weschler Adult Intelligence Scale	Difference in crude test results but no difference after adjustment for confounders	Yes	Mean glucose in 1st or 3rd trimester not associated with global cognitive scores	Yes
Dodds et al (2011) [19]	ICD codes for ASD	RR of ASD if maternal pre-pregnancy DM 1.98 (95% CI 0.94, 4.16)	No	Not reported	Yes
Fraser et al (2012) [9]	School Entry Assessment (age 4); WISC-III (age 8); GCSE (age 16)	Pre-existing DM associated with increased odds of low achievement on GCSE (fully adjusted OR 5.06 [95% CI 1.42, 18.10]). No significant difference in School Entry Assessment or WISC-III	Yes	Not reported	Yes
Hod et al (1999) [20]	BSID, 2nd Edition, and observed infant behaviour	Offspring of mothers with DM had lower scores in three areas of development (mental, psychomotor and orientation)	No	Not reported	Yes
Ji et al (2018) [21]	ICD codes for ADHD	ADHD in T1D offspring higher than control participants after adjustment (HR 1.35 [95% CI 1.18, 1.55]; $p < 0.0001$)	Yes	Not reported	Yes
Knorr et al (2015) [22]	School grades	No significant association between maternal T1D and school grades (adjusted $\beta = -0.13$ [95% CI $-0.30, 0.03$]; $p = 0.12$)	Yes	Lower HbA _{1c} associated with higher average school grades	No
Kong et al (2018) [23]	ICD codes for psychiatric disorders	Joint effect of maternal obesity and pre-pregnancy DM on development of most psychiatric and neurodevelopmental disorders	Yes	Not reported	Yes
Kowalczyk et al (2002) [24]	Brunet–Lezine Psychomotor Development Scale	Developmental quotient of T1D children 90.1 vs control 99.2; $p = 0.002$	No	1st trimester HbA _{1c} >64 mmol/mol (8%) associated with increased developmental concerns	No
Li et al (2016) [25]	Billings codes on electronic medical records for ASD and other developmental disabilities	HR (95% CI) of maternal DM for ASD 2.25 (1.14, 4.42), ID 2.26 (1.25, 4.09), ADHD 1.56 (0.86, 2.84), other DD 1.31 (0.96, 1.77). Association stronger when mother also obese	Yes	Not reported	Yes
Mann et al (2013) [26]	ICD codes on at least five occasions for ID	No significant increased risk of ID if maternal 'chronic DM' (adjusted OR 1.31 [95% CI 0.83, 2.06])	Yes	Not reported	Yes
Ornoy et al (1998) [27]	Touwen–Prechtl; Pollack tapper; WISC-R; Bender Visual Gestalt; Bruininks–Oseretsky Motor Development; Southern California Integration; Conners' Abbreviated Parent–Teacher Questionnaire	No significant difference in WISC-R (IQ control 118.5 [1.3] vs DM 117.7 [1.7]; $p = 0.60$). Bender (control 48.6% [3.7] vs 48.0% [4.0]; $p = 0.90$, or Conners' (control 7.7 [0.5] vs 9.1 [0.8]; $p = 0.24$); different motor development (Bruininks total control 138.2 [3.7] vs 129.2 [3.9]; $p = 0.008$). Touwen–Prechtl score (control 4.00 vs 8.45; $p = 0.01$), and Pollack test (control 28.9 [0.7] vs 24.3 [1.6]; $p = 0.008$)	No	Positive correlation between glucose concentrations and the results of the Bender test ($r = 0.32$; $p < 0.05$) and WISC-R ($r = 0.27$; $p < 0.05$)	Yes
Persson et al (1984) [28]	Termin–Merril method; detailed interview	Children of mothers with T1D 'average' IQ 119 (no control group)	No	Not reported	No

Table 3 (continued)

Study (year)	Measurement	Summary of main result	Adjusted analysis ^a	Assessment of role of glycaemic control	In meta-analysis
Rizzo et al (1991) [29]	BSID, 1st Edition (2 years), and Stanford–Binet Intelligence Test (3–5 years)	No significant difference in mental development index for offspring of mothers with DM 89 ± 18 vs control 89 ± 13, or Stanford–Binet score for offspring of mothers with DM 89 ± 14 vs control 92 ± 10	Yes	No significant correlation between intelligence scores and fasting glucose, HbA _{1c} or hypoglycaemia	Yes
Sells et al (1994) [30]	BSID, 1st Edition (age 6 months, 1 and 2 years), and Stanford–Binet Intelligence Test (age 3)	No significant difference in BSID between control vs ‘early entry’ vs ‘late entry’ infants at 6, 12 or 24 months. No significant difference in composite IQ or subcategories	Yes	Not reported	Yes
Temple et al (2011) [8]	WISC, version 4	Normal overall cognitive function (97.54 in T1D offspring vs 100.22 in UK normative data); difference in digit span (T1D 8.4 ± 2.2 vs UK 10.1 ± 3.2; $p < 0.01$); T1D offspring had a lower score for working memory vs perceptual reasoning or processing speed (working memory 95.0 ± 11.1 vs perceptual reasoning 99.2 ± 13.0; $p = 0.04$; and processing 99.1 ± 13.0; $p = 0.04$)	No	No correlation between digit span and HbA _{1c} at any stage of pregnancy ($r = -0.225$ to 0.0002)	No
Xiang et al (2018) [10]	ICD codes for ASD	Adjusted HR for ASD if maternal T1D 2.33 (95% CI 1.29, 4.21; $p = 0.005$); T2D 1.39 (95% CI 1.18, 1.62; $p < 0.001$)	Yes	Not reported	Yes

^a For details see ESM Table 2; except where otherwise stated, data are reported as mean ± SD and IQ data, Conners’, Stanford–Binet score, Developmental quotient, Bruininks, Touwen–Prechtl, Pollack test and digit span are reported in points

BSID, Bayley Scales of Infant Development; DD, developmental disorder; DM, diabetes mellitus; ICD, International Classification of Diseases; ID, intellectual disability; T1D, type 1 diabetes; T2D, type 2 diabetes; WISC, Wechsler Intelligence Scale for Children; WISC-R, Wechsler Intelligence Scale for Children-Revised

Fig. 2 Forest plots of IQ in offspring exposed to maternal pre-existing diabetes compared with control participants. **(a)** Main analysis including the early cohort from Sells et al. **(b)** Main analysis including the late cohort from Sells et al. **(c)** Sensitivity analysis restricted to exposure to maternal type 1 diabetes. **(a)** and **(b)** include all types of pre-existing diabetes; **(c)** is limited to studies including women with type 1 diabetes only. Weights are from random-effects analysis. WMD, weighted mean difference of IQ points

diabetes had greater odds of having low achievement on their GCSEs (adjusted OR 5.06 [95% CI 1.42, 18.10]). Conversely, Knorr et al did not find a significant difference in academic achievement in primary school performance in Denmark between offspring of mothers with type 1 diabetes and matched control participants [22].

Exposure to maternal pre-existing diabetes and child development Four studies looked at developmental measures in childhood [20, 24, 29, 30], three of which could be pooled in a meta-analysis [20, 29, 30] (Table 3). Kowalczyk et al used the Brunet–Lezine Psychomotor Development Scale, which could not be pooled with the Bayley Scales of Infant

Development (1st and 2nd Editions) used in the other three studies [24]. Kowalczyk et al found that children of mothers with type 1 diabetes had lower scores, with a developmental quotient of 90.1 in offspring of mothers with type 1 diabetes vs 99.2 in the control group; $p = 0.002$.

The meta-analysis of studies using the Bayley Scales of Infant Development, 1st and 2nd Editions, is found in ESM Figs 1, 2. When multiple assessment times were available, we chose the oldest age group as it is a better predictor of later IQ [31]. There was no significant difference in Mental Developmental Index (pooled mean difference -2.79 [95% CI $-7.82, 2.24$] using the ‘early entry’ Sells et al cohort, and -4.50 [95% CI $-9.06, 0.06$] using the ‘late entry’ cohort) (ESM Fig. 1a, b) [30]. There was also no significant difference in Psychomotor Developmental Index (pooled mean difference -5.95 [95% CI $-14.16, 2.26$] using the ‘early entry’ Sells et al cohort and -4.62 [95% CI $-16.73, 7.50$] using the ‘late entry’ cohort) (ESM Fig. 2a, b) [30].

Exposure to maternal pre-existing diabetes and ASD Five studies examining the association between maternal pre-existing diabetes and ASD were found. All were large database studies [10, 16, 19, 23, 25] (Table 3). Exposure to maternal pre-existing diabetes was associated with an increased risk of ASD. When women with type 1 diabetes from the Xiang et al cohort were included, the effect estimate was 1.98 (95% CI 1.46, 2.68; $I^2 = 0\%$) (Fig. 3) [10]. When the analysis was re-run, substituting women with type 2 diabetes from the same Xiang et al cohort for Xiang’s cohort of women with type 1 diabetes, this effect estimate was 1.46 (95% CI 1.26, 1.69; $I^2 = 0\%$) (Fig. 3). Because Kong et al performed a stratified analysis by BMI, it could not be included in the overall analysis [23].

Exposure to maternal pre-existing diabetes and ADHD Four studies assessed the relationship between exposure to maternal pre-existing diabetes and ADHD [18, 21, 23, 25] (Table 3), three of which were included in a meta-analysis [21, 23, 25]. The Bytoft et al study was not included as it assessed for ADHD by history of medication use and used the Conners’ Continuous Performance test version 2 but did not report an RR, OR or HR [18]. They found that, while there was higher self-reported ADHD medication use (2.2 vs 0%; $p = 0.01$), there was no significant difference in regression analyses with the Conners’ Continuous Performance test.

Pooled adjusted HR for the diagnosis of ADHD after exposure to maternal pre-existing diabetes was 1.36 (95% CI 1.19, 1.55; $I^2 = 0\%$) (Fig. 4). Again, the data from Kong et al were not included as they were only presented as a stratified analysis [23].

Assessment of the role of maternal glycaemic control Seven studies reported on the association of maternal glycaemic control with neurocognitive or behavioural measures in offspring [7, 8, 17, 22, 24, 27, 29] (Table 3). Only three studies found glycaemic control to be associated with offspring outcomes [22, 24, 27]. Knorr et al noted that lower HbA_{1c} was associated with higher average school grades; however, they highlight the strong correlation between maternal education level and glycaemic control [22]. Kowalczyk et al found that a first trimester HbA_{1c} of >64 mmol/mol (8%) was associated with an increased risk of developmental abnormalities [24]. Lastly, Ornoy et al noted a positive correlation between maternal glucose concentrations and results on the Bender Visual Gestalt test (a test used to evaluate hand–eye coordination) and Wechsler Intelligence Scales for Children, Revised [27]. Despite adjustment for parental education, Sells et al

Fig. 3 Forest plot of ASD in offspring exposed to maternal pre-existing diabetes compared with control participants. This analysis includes all types of pre-existing diabetes, and includes a pooling of RR and HR. Weights are from random-effects analysis. ES, effect size

Fig. 4 Forest plot of attention deficit disorders in offspring exposed to maternal pre-existing diabetes compared with control participants. This analysis includes all types of pre-existing diabetes, and includes a pooling of HR for attention deficit disorders. Weights are from random-effects analysis. ES, effect size

identified poorer ($p < 0.05$) scores in the Peabody Picture Vocabulary Test and the Vineland Communication Subscale but no difference in the Mean Length of Utterance at 3 years among children of mothers with ‘late study entry’ who had significantly higher first and second trimester HbA_{1c} compared with mothers with ‘early study entry’ [30].

Evaluation for small-study effect and publication bias An assessment for small-study effect was only performed on the meta-analysis of IQ since all other pooled analyses had very few studies. The funnel plots for the main analysis (Fig. 2a, b) were symmetrical, suggesting that there was no evidence of small-study effects (ESM Fig. 3a, b). However, given that the effect estimates are similar across studies we cannot rule out the possibility that larger studies are more often published, whereas smaller studies are only published if they report positive findings.

For the ASD meta-analysis, most studies included had a lower CI limit that was close to the null. This may indicate a bias to publish studies with a significant finding.

Discussion

This systematic review and meta-analysis found that in utero exposure to maternal pre-existing diabetes was associated with poorer neurocognitive and behavioural outcomes including lower pooled IQ, an increased risk of ASD and an increased risk of ADHD. It was unclear whether exposure was associated with lower academic achievement or lower infant development scores.

There was a significantly lower pooled IQ in offspring exposed to maternal pre-existing diabetes compared with comparator groups. While the overall effect (−3.07 to −3.92 IQ points) in an individual child may not be clinically meaningful, when applied at a population level this difference is noteworthy and demands further investigation. It is important to note that this pooled IQ is unadjusted. There are many important potential confounders in examining IQ such as parental IQ/education, socioeconomic status, gestational age at delivery and perinatal complications such as preterm delivery and neonatal

hypoglycaemia [32] which may be different in offspring of mothers with diabetes compared with those without.

Some studies matched for some important confounders, though residual confounding likely exists even after matching [7, 17, 27]. It is noteworthy that the two studies that were limited to women with type 1 diabetes had the largest difference in IQ between groups [7, 17]. Interestingly, in the study by Bytøft et al [17] this difference remained significant after adjustment for many confounders, whereas in the study by Clausen et al, this difference was lost [7]. This may be due to the larger sample size in the Bytøft cohort ($n = 578$) vs the Clausen cohort ($n = 276$), as both were in Denmark and had very similar adjusted analyses performed.

Offspring exposure to maternal pre-existing diabetes was associated with an increased risk of ASD and ADHD in most analyses in this review. This is consistent with previously published meta-analyses examining ASD [33, 34]. The impact of the ASD effect size is currently unknown but is large enough to prompt further investigation of this association. To our knowledge, no other published meta-analyses have examined the risk of ADHD in this population. The risk of ASD with maternal obesity has been previously reported [35]. However, the associations between these outcomes and maternal pre-existing diabetes and how they are modulated by maternal blood glucose levels are interesting and merit further study. We identified one study that examined the risk of attention deficits in a cohort including only type 1 diabetes offspring [18]. It found a significant difference in ADHD medication use but no difference in direct measures. However, these results may be a result of the much smaller sample size ($n = 269$ offspring) in this prospective cohort study compared with larger retrospective database studies.

Our review was unable to identify evidence definitively suggesting a difference in academic achievement or Bayley Scale of Infant Development scores between infants exposed to maternal pre-existing diabetes and those who were not. Only two studies investigated difference in academic achievement and the results were mixed. The study by Fraser et al was large but only included 26 offspring exposed to maternal pre-existing diabetes [9]. The study by Knorr et al had a larger

number of diabetes-exposed offspring ($n = 707$) and did not find a difference between groups [22]. Only three studies, all performed over 20 years ago, examined performance on the Bayley Scale of Infant Development, 1st and 2nd Editions [20, 29, 30]. While these studies found lower scores on both the mental and psychomotor development indexes, none were statistically significant. The small number of studies as well as the small number of participants included ($n = 72$ –199) may have contributed to this negative result.

The literature was also discordant regarding the role of maternal glycaemic control and offspring neurocognitive and behavioural outcomes. Only seven of the 19 studies included in this review reported on this and the results were variable [7, 8, 17, 22, 24, 27, 29]. Assessment of glycaemic control in these studies was limited to HbA_{1c} or mean glucose, both of which are surrogate measures of glycaemic control and are inadequate in assessing daily glucose excursions, especially during pregnancy. There may also be important confounding in relating glycaemic control measures to intelligence and/or academic achievement. Knorr et al, for example, found that lower HbA_{1c} was strongly correlated with maternal education [22]. For this reason, it is especially important to adjust for maternal education and socioeconomic status in future studies. A more detailed examination of the relationship between maternal glycaemic control and offspring neurocognitive and behavioural outcomes using continuous glucose monitoring data should be performed. Continuous glucose monitoring allows for an assessment of direct fetal exposure to maternal hyper- and hypoglycaemia and may be more informative for assessing in utero glycaemic exposure.

Our review has both similarities and differences to previously published reviews in the area [11, 12]. Unlike recent systematic reviews, ours is restricted to offspring exposed to pre-existing diabetes and does not include women with gestational diabetes, which is a less severe form of glycaemic disturbance and of shorter duration. Our review also included studies that assessed outcomes into adulthood and seven additional studies published in the last few years. As with our systematic review and meta-analysis, both of these reviews highlight the important role of confounding when interpreting the data [11, 12].

This systematic review and meta-analysis benefits from its rigorous methodology and broad inclusion criteria, allowing for a comprehensive assessment of existing literature. To our knowledge, it is also the first review to perform a pooled analysis of the risk for ADHD in offspring exposed to maternal pre-existing diabetes. It is further strengthened by our inclusion of only women with pre-existing diabetes in pregnancy. However, there are also limitations to acknowledge. Diabetes was included in our search terms and therefore we may have missed studies that were not specific to diabetes [16, 19]. We have mitigated that limitation with a reference review of all included studies and relevant reviews. Many of the prospective cohort studies had inadequate or unreported assessments of neurocognitive and behavioural outcomes, which makes them particularly

prone to bias. Also, they may be underpowered to show a difference in outcomes. Unfortunately, most studies did not report an assessment of power. In addition, many studies were unadjusted or minimally adjusted. Knowing that there are many important confounders, these findings must be interpreted with caution. Additionally, the pooled analysis for ADHD included only two studies of vastly varying sample sizes and, therefore, this analysis must be interpreted carefully. Heterogeneity between studies calculated using the I^2 statistic should also be interpreted cautiously as our power was limited given the small number of studies included in each presented analysis. Lastly, few studies reported on the role of glycaemic control and no studies reported detailed measures of glycaemic control.

When taken together, these data suggest there is a signal that exposure to maternal pre-existing diabetes is associated with adverse neurocognitive and behavioural outcomes past the neonatal period. However, caution must be exercised when interpreting these findings. While some of these analyses were highly adjusted, it remains unclear what the roles of perinatal factors such as preterm delivery and neonatal hypoglycaemia are and the degree to which other environmental factors may contribute to these findings. It is essential that future studies focus on identifying potentially modifiable risk factors such as maternal glycaemic control, which may assist women and their care providers in preventing neurocognitive or behavioural complications associated with prenatal exposure to maternal pre-existing diabetes.

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Data availability All data used in this systematic review and meta-analysis are published and referenced.

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Contribution statement JMY, JLB, LED, DSF, HRM, JJS and DD conceived and designed the study. JMY and JLB performed the search, data extraction and data analysis. JMY wrote the initial manuscript draft. JMY, JLB, LED, DSF, HRM, JJS and DD all participated in the critical revision of the manuscript for important intellectual content and approved the final version. JMY is the guarantor of this work, had full access to all of the study data and takes responsibility for the integrity of the data.

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