Diabetes in Pregnancy and Childhood Cognitive Development: A Systematic Review

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abstract

CONTEXT: The effect of diabetes during pregnancy on the cognitive development of offspring is unclear because of inconsistent findings from limited studies.

OBJECTIVE: This review was aimed to provide the best available scientific evidence on the associations between maternal pregnancy diabetes and the cognitive development of offspring.

DATA SOURCES: A search was conducted in the Embase, CINAHL, PubMed, PsycINFO, and Scopus databases.

STUDY SELECTION: Studies addressing the cognitive development of offspring (aged ≤12 years) as outcome and any diabetes in pregnancy as an exposure were included.

DATA EXTRACTION: Data were extracted and evaluated for quality by 2 independent reviewers.

RESULTS: Fourteen articles were eligible for the review. Ten studies investigated the associations between maternal pregestational diabetes or both pregestational and gestational diabetes and offspring's cognitive development; 6 studies found at least 1 negative association. Four studies exclusively examined the relationships between gestational diabetes and offspring's cognitive development; 2 studies found a negative association, 1 a positive association, and 1 a null association. The use of diverse cognitive and diabetes assessment tools/criteria, as well as statistical power, contributed to the inconsistent findings.

LIMITATIONS: The English-language restriction and publication bias in the included studies are potential limitations.

CONCLUSIONS: Although there are few data available regarding the associations between maternal pregnancy diabetes and offspring's cognitive development, this review found that maternal diabetes during pregnancy seems to be negatively associated with offspring's cognitive development. Large prospective studies that address potential confounders are needed to confirm the independent effect of maternal diabetes during pregnancy.

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REVIEW ARTICLE

Globally, the prevalence of both pregestational diabetes mellitus (PDM) and gestational diabetes mellitus (GDM) are increasing significantly due to the rising rates of obesity, aging, and population growth.[1–4] In women, the global prevalence of age-adjusted diabetes increased from 7.5% in 1980 to 9.2% in 2008.[4] An increasing future trend in the prevalence of diabetes is also projected across all countries worldwide. For instance, in 2011, there were 366 million people with diabetes, and over the next 19 years, this figure is expected to rise to 552 million. Substantial increases are expected in developing countries related to lifestyle changes after rapid urbanization, globalization, and aging.[5]

Any type of diabetes during pregnancy is associated with poor maternal and perinatal outcomes. For instance, congenital malformation,[6] preterm birth,[7,8] large for gestational age at birth/macrosomia,[7,9–11] and stillbirth[6,10,11] are significantly more common in offspring of diabetic mothers than nondiabetic mothers. Even offspring of mothers with borderline GDM have been found to be born too early and to be macrosomic.[12]

Due to advances in medical care, offspring of mothers with diabetes are increasingly surviving the perinatal period. Consequently, the long-term effects of diabetes during pregnancy on later childhood health such as obesity/adiposity, mainly via large for gestational age at birth, has been clearly established.[13–15] In contrast, data regarding the long-term effects of maternal diabetes during pregnancy on the offspring's cognitive development are relatively limited and, when data are available, the findings are inconclusive.[16–23]

The mechanisms by which maternal diabetes during pregnancy is associated with the offspring's cognitive development are unclear. Excess glucose levels in patients with diabetes, a condition known as hyperglycemia, is hypothesized to cause cognitive impairment.[24] Animal models have shown that maternal diabetes during pregnancy is usually associated with hyperglycemia and that more glucose will pass to the fetus, and this action may hinder the cognitive development of the offspring.[25] Although not always found,[26] metabolic complications related to diabetes during pregnancy such as acetonuria,[27,28] ketoacidosis,[20] and glycosuria[16] are also associated with offspring's cognitive impairment. It has been suggested by some investigators that offspring born to either mothers with PDM or GDM are more likely to have poorer cognitive and language development than those born to nondiabetic mothers.[28–33]However, other investigators have either found no such associations[17,18,20,22] or report contradictory findings.[23]

To the best of our knowledge, systematically synthesized information on the associations between maternal diabetes during pregnancy and offspring's cognitive development, particularly in childhood, is lacking. The implications of such information are twofold: (1) it would provide decision-makers/clinicians with comprehensive information to deliver preconception counseling; and (2) it would enable the early identification of infants at future risk of cognitive development. It would also avail information for researchers to identify research gaps and guide future research development. Thus, the goal of the present systematic review was to provide the best available scientific evidence regarding the possible associations between maternal diabetes in pregnancy and the cognitive development of offspring.

METHODS

Data Sources and Search Strategies

The PubMed database was searched by using combinations of key words: (((((offspring) OR child*)) AND (((((((((((("cognitive development") OR "cognitive functions") OR "school performance") OR "educational outcomes") OR "language development") OR "neuropsychological tests") OR "mental development") OR neurodevelopment) OR "child development") OR cognition) OR intelligence) OR " IQ") OR "intelligence tests")) AND (((mother*) OR pregnan*) OR women)) AND ((((((("type I diabetes") OR "type Il diabetes") OR "gestational diabetes") OR "diabetes insipidus") OR "diabetes mellitus") OR diabetes). Similarly, systematic searches were conducted in the Embase, CINHAL, PsycINFO, and Scopus databases using the same key word combinations tailored to each database until June 2015. These searches were limited to studies in the English language with human domain restrictions. Moreover, the reference list of all identified relevant records were searched for additional studies. The authors were not contacted for additional studies or data.

Study Selection

Studies addressing the cognitive and/or language development of offspring (aged ≤12 years) as outcome and either PDM or GDM or both as a main exposure or confounder were included in this systematic review. Reviews, commentaries, and case or descriptive studies lacking relevant control groups were excluded.

Records deemed relevant from the title screening were further evaluated by using the information available in the abstract by 2 independent reviewers (A.A.A. and L.R.T.) using the eligibility criterion. The same authors further evaluated the full records of those eligible articles from the abstract review. Disagreements were resolved by face-to-face discussions and through joint review of the records. The third author helped resolve any disagreement between the first 2 reviewers (Fig 1).

Data Extraction

Data on the first author, publication year, country, study design, sample size, offspring's age at follow-up, diabetes type and assessment, cognitive type and measurement, confounders accounted/adjusted for, and main findings between maternal pregnancy diabetes and offspring's cognitive development were extracted by the reviewers by using a standardized data extraction format (Table 1).

Quality Assessment

The Newcastle-Ottawa quality assessment scale for case-control and cohort studies[34] was used to assess the quality of included studies. Two modifications were made: a "nonblind standard assessment" option was included in the outcome subsection of the cohort studies assessment scale and "the length of follow-up for the outcome to occur" criteria was omitted because the goal of this systematic review was to examine the effect of any diabetes during pregnancy on cognitive development of offspring to the age of 12 years. Consequently, a slightly modified score ranging from 0 (most likely biased) to 8 (highly unlikely to be biased) was calculated for each study.

Data Synthesis and Analysis

Meta-analysis was not performed because of heterogeneous cognitive outcomes and having too few studies that adjusted for potential confounders. Instead, a narrative review and qualitative summarizations were undertaken (Table 2).

RESULTS

A total of 1295 records were identified with English-language and human domain restrictions. After removal of duplicates, the titles of
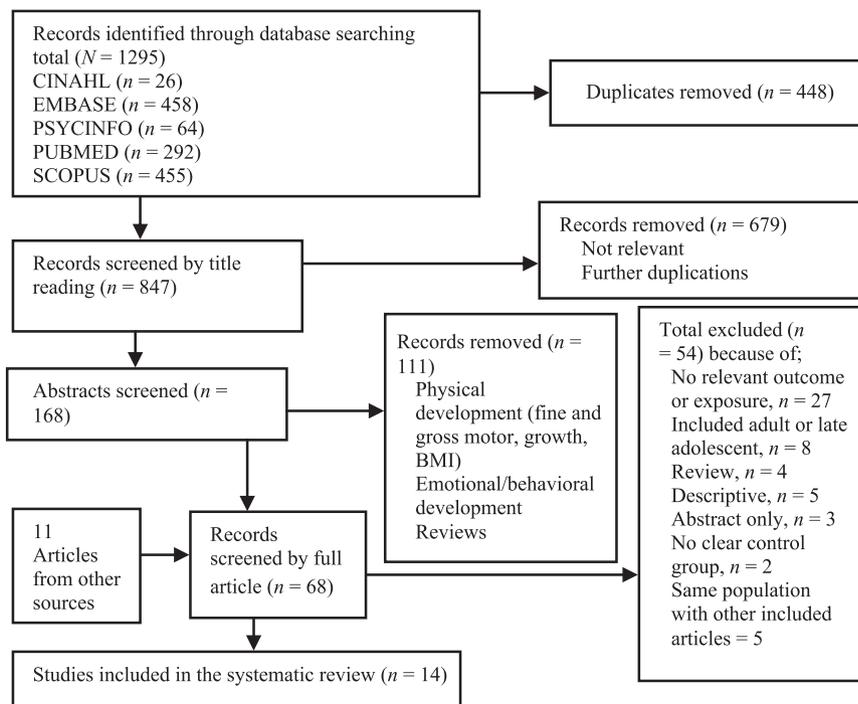

FIGURE 1
Flow diagram of studies included in the systematic review of maternal diabetes during pregnancy and childhood cognitive development.

847 articles were screened; 679 were identified as not relevant or as further duplicates. The abstracts of 168 articles were then evaluated independently, and 111 records were excluded. Subsequent full-record evaluations of 68 articles resulted in a total of 19 eligible studies. However, 2 studies[35,36] were further excluded because they were published with the same populations used in 2 included studies.[18,20] In addition, 5 relatively different studies[22,32,37–39] were conducted by using the same cohort study with varied sample sizes. All reported global cognitive development as a secondary outcome or confounder at the age of 1 year[32,37–39] and 4 years.[22] None of these studies primarily aimed to evaluate the global cognitive development of offspring of mothers with diabetes mellitus (ODM). Therefore, we included Nelson et al[32] (ie, better sample size and relatively recent) and Townsend et al[22] (ie, cognitive development was measured at the age of 4 years by using the Wechsler Intelligence Scale

for Children) in the review. Overall, 14 studies[16–23,28–33] were eligible for the present review.

Quality Assessment

Using the adapted Newcastle-Ottawa quality assessment scale, the scores for each study ranged from 2 to 6 (from a total of 8). In addition to low overall scores, the following quality concerns were observed: one-half of the studies reported unadjusted results; in all studies (except 1 report[30]) the population was obtained from unrepresentative populations, mainly from hospital facilities; and 7 of 14 studies[16,17,22,23,29,31,33] reported the use of standard cognitive development assessment tools but failed to provide or report blind assessment.

Study Characteristics

The 14 studies were conducted between 1969 and 2015. The offspring's age at cognitive assessment ranged from 6 months

TABLE 1 Characteristics of Studies Reporting the Association Between Maternal Diabetes During Pregnancy and Cognitive Development of Offspring

First Author/Year	Country	Study Design	Sample Size	Age at Follow-up	Diabetes Type	Diabetes Diagnosis	Cognitive Assessment	Cognitive Outcome	Main Findings on Maternal Pregnancy Diabetes and Offspring's Cognitive Development (95% CI)	Effect Size: Cohen's d (95% CI)
Bonilla et al, 2012[29]	UK	Cohort study	6272 mother–child pairs	8 y	PDM + GDM	Record-based	WISC-III	IQ	DM associated with lower IQ (MD), −3.5 (−5.6, −1.5); P = .001)	No sufficient data
Churchill et al, 1969[28]	US	Retrospective cohort study	237 ODM and control subjects	8 mo and 4 y	PDM + GDM	Somogyi-Nelson glucose tolerance curves	BSID at 8 mo and SBIS at 4 y	IQ (n = 121) and MDI (n = 231)	DM associated with lower IQ (96 vs 103; P = .001) and MDI (78 vs 81; P = .001). DM without acetone has no association with MDI (81.0 vs 81.0), PDI (33.4 vs 34.2), and IQ (101.3 vs 100.8); all, P > .05	No sufficient data
Dionne et al, 2008[30]	Canada	Retrospective cohort study	221 OGDM and 2612 control subjects — QNTS (n ranges from 721 to 861) and QLSCD (n varies from 955 to 1728)	1.5–7 y	GDM	OGTT	MCDI at 18 and 30 mo, PPVT at 48 mo, expressive and receptive vocabulary at 60 mo, and EDI teacher-assessed communication at 72 and 84 mo	Language, NVIQ, and RM	QNTS GDM associated with lower (mean); expressive vocabulary at 18 mo (−0.25 ± 0.96 vs 0.02 ± 0.99) and at 30 mo (−0.33 ± 1.22 vs 0.04 ± 0.96), expressive grammar at 30 mo (−0.28 ± 1.18 ± 0.96) and oral communication at 72/84 mo (−0.30 ± 1.21 vs 0.05 ± 0.96); all, P < .05 No association with (mean) receptive vocabulary (−0.06 ± 1.00 vs 0.00 ± 0.99) and receptive grammar (−0.10 ± 1.16 vs 0.02 ± 0.98) at 18 mo, receptive grammar at 30 mo (0.04 ± 0.97 vs 0.01 ± 1.01), expressive vocabulary (−0.12 ± 0.90 vs 0.04 ± 0.99) and receptive vocabulary at 60 mo (−0.09 ± 0.86 vs 0.01 ± 1.01), math (−0.10 ± 1.02 vs 0.05 ± 0.93) and reading (−0.04 ± 0.96 vs 0.03 ± 0.99) scores at 72/84 mo; all, P > .05 QLSCD GDM associated with lower (mean); expressive vocabulary (−0.28 ± 1.09 vs 0.02 ± 0.99) and grammar at 30 mo (−0.38 ± 1.21 vs 0.03 ± 0.97) but not with receptive vocabulary at 30 mo (−0.18 ± 1.10 vs 0.01 ± 0.98) and at 42 mo (−0.16 ± 0.81 vs 0.02 ± 1.00)	Expressive vocabulary Effect size varies from 0.27 to 0.41 Expressive grammar Effect size varies from −0.37 to −0.30 Expressive vocabulary Effect size varies from −0.34 to −0.17 Receptive vocabulary

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TABLE 1 Continued

First Author/Year	Country	Study Design	Sample Size	Age at Follow-up	Diabetes Type	Diabetes Diagnosis	Cognitive Assessment	Cognitive Outcome	Main Findings on Maternal Pregnancy Diabetes and Offspring's Cognitive Development (95% CI)	Effect Size: Cohen's d (95% CI)
									GDM associated with language impairment (OR), 2.2 (1.4,3.5), RM (F = 5.31; P = .02), and NVIQ (F = 3.73; P = .05) but not with short-term memory (F = 2.86; P = .09)	Effect size varies from −0.18 to −0.06 Receptive grammar Effect size varies from −0.11 to 0.03 Oral communication Effect size (d) = −0.32 Math Effect size (d) = −0.15 Reading Effect size (d) = −0.07 For the others, no sufficient data
Fraser et al, 2012[16]	UK	Cohort study	SEA 24 0GDM, 21 0PDM, and 5804 control subjects IQ 23 0GDM, 20 0PDM, and 5079 control subjects	4 and 8 y	PDM + GDM	Record based	SEA at 4 y and WISC-III at 8 y	Educational attainment and IQ	PDM has no association with (MD) SEA, 0.04 (−1.68, 1.75); FIQ, −0.54 (−9.61, 8.52); VIQ, 1.5 (−7.63 ,10.74); and PIQ, −4.01 (−13.80, 5.78) GDM associated with (MD) lower VIQ, −9.92 (−18.34, −1.50); not associated with FIQ, −5.93 (−14.24, 2.38); PIQ, −0.19 (−9.17, 8.78); or SEA, 0.30 (−1.12, 1.72)	PDM SEA, −0.13 (−0.51,0.26) FIQ, −0.13 (−0.51,0.26) VIQ, −0.01 (−0.40,0.37) PIQ, −0.27 (−0.66,0.11) GDM SEA, −0.03 (−0.37,0.31) FIQ, −0.40 (−0.75, −0.06) VIQ, −0.43 (−0.78, −0.09) PIQ, −0.19 (−0.53,0.15)
Hod et al, 1999[31]	Israel	Cohort study	31 0PDM and 41 control subjects	1 y	PDM	OGTT	BSID-II	MDI	PDM associated with lower MDI (91 ± 9.0 vs 98 ± 12.1; P < .05)	MDI, −0.64 (−1.12,−0.17)
Nelson et al, 2003[32]	US	Cohort study	52 0DM and 75 control subjects	1 y	PDM + GDM	OGTT	BSID-II	MDI	DM associated with lower MDI (100 ± 9 vs 104 ± 8; P < .03)	MDI, −0.49 (−0.94,−0.03)
Nomura et al, 2012[17]	US	Cohort study	21 0GDM and 191 control subjects	3–4 y	GDM	Self-reported	WPPSI-III, developmental; neuropsychologic assessment	IQ, language	GDM associated with lower FIQ (109.2 ± 1.4 vs 113.6 ± 3.5), VIQ (110.5 ± 1.5 vs 113.6 ± 4.2), language (108.8 ± 1.4 vs 112.9 ± 3.9), and memory (96.6 ± 1.4 vs 101.1 ± 3.8); all, P < .05; No association with PIQ (109.8 ± 1.5 vs 111.9 ± 3.8); P = .14	FIQ, −1.30 (−2.01,−0.60) VIQ, −0.76 (−1.46,−0.07) Language, −1.09 (−1.79, −0.39) Memory, −1.23 (−1.93, −0.52) PIQ, −0.57 (−1.26,0.12)

TABLE 1 Continued

First Author/ Year	Country	Study Design	Sample Size	Age at Follow-up	Diabetes Type	Diabetes Diagnosis	Cognitive Assessment	Cognitive Outcome	Main Findings on Maternal Pregnancy Diabetes and Offspring's Cognitive Development (95% CI)	Effect Size: Cohen's d (95% CI)
Ornoy et al, 1999[19]	Israel	Retrospective cohort study	32 OGDM and 57 control subjects	5–12 y	GDM	Blood glucose concentration test	WISC-Revised	IQ	Young age (5–8 y) GDM associated with lower FIQ (111 ± 14 vs 121 ± 8) and VIQ (107 ± 11 vs 115 ± 11); both, $P < .05$; Not associated with PIQ (114 ± 17 vs 123 ± 11); $P > .05$ Older age (9–12 y) No association with FIQ (115 ± 13 vs 116 ± 12), VIQ (109 ±12 vs 113 ± 13), or PIQ (119 ± 15 vs 117 ± 12); all, $P > .05$	Young group IQ, −0.95 (−1.40,−0.49) VIQ, −0.73 (−1.17,−0.28) PIQ, −0.67 (−1.11,−0.23) Older group FIQ, −0.08 (−0.51,0.35) VIQ, −0.32 (−0.75, 0.11) PIQ, 0.15 (−0.28,0.58)
Ornoy et al, 2001[18]	Israel	Retrospective cohort study	57 OPDM, 32 OGDM, and 57 control subjects	5–12 y	PDM + GDM	Blood glucose concentration test	WISC-Revised	IQ	PDM has no association with FIQ (117.7 ± 12 vs 118.5 ± 11), VIQ (112.4 ± 12 vs 114.4 ± 12), and PIQ (120.4 ± 19 vs 119.7 ± 11.5) GDM has no association with FIQ (113.5 ± 14.3 vs 118.5 ± 11), VIQ (108.0 ± 11.5 vs 114.4 ± 12), and PIQ (116.0 ± 16.0 vs 119.7 ± 11.5); all, $P > .05$	PDM IQ, −0.08 (−0.44,0.30) VIQ, −0.17 (−0.53,0.20) PIQ, 0.05 (−0.32,0.41) GDM IQ, −0.41 (−0.84,0.03) VIQ, −0.54 (−0.98,−0.10) PIQ, −0.28 (−0.71,0.16)
Rizzo et al, 1991[20]	USA	Cohort study	80 OPDM, 82 OGDM, and 29 control subjects	2–5 y	PDM + GDM	OGTT- O'Sullivan and Mahan criteria	BSID at 2 y SBIS at 3–5 y	MDI, IQ	PDM has no association with MDI (89 ± 18 vs 89 ± 13) and IQ (89 ± 14 vs 92 ± 10) GDM has no association with MDI (90 ± 14 vs 89 ± 13) and IQ (93 ± 13 vs 92 ± 10)	PDM MDI, 0 (−0.43,0.43) IQ, −0.23 (−0.67,0.20) GDM MDI, 0.07 (−0.35,0.50) IQ, 0.08 (−0.36, 0.52)

TABLE 1 Continued

First Author/ Year	Country	Study Design	Sample Size	Age at Follow-up	Diabetes Type	Diabetes Diagnosis	Cognitive Assessment	Cognitive Outcome	Main Findings on Maternal Pregnancy Diabetes and Offspring's Cognitive Development (95% CI)	Effect Size: Cohen's d (95% CI)
Sells et al, 1994[21]	US	Cohort study	109 OPDM (70 early entry and 39 late entry), and 90 control subjects	6, 12, 24, and 36 mo	PDM	Not stated	BSID at 6, 12, and 24 mo; SBIS; spontaneous language sample; and PPVT at 36 mo revised Vineland Adaptive Behavior scales at 12, 24, and 36 mo	MDI, IQ, and language	PDM associated with lower PPVT scores (114 ± 11.0 vs 111 ± 10.1 vs 105 ± 11.4) and Vineland Communication subscale (111 ± 10.2 vs 110 ± 9.2 vs 103 ± 11.5) PDM has no association with mean length of utterance (4.1 ± 1.0 vs 4.0 ± 0.86 vs 3.7 ± 0.91) MDI at 6 mo (107 ± 12.1 vs 104 ± 14.4 vs 106 ± 13.7), at 12 mo (117 ± 12.5 vs 113 ± 15.3 vs 112 ± 3.5) and at 24 mo (118 ± 18.4 vs 118 ± 19.4 vs 112 ± 16.8) SBIS Verbal reasoning (114 ± 12.4 vs 110 ± 10.2 vs 105 ± 14.2), abstract reasoning (104 ± 11.8 vs 104 ± 8.7 vs 103 ± 9.7), quantitative reasoning (105 ± 9.5 vs 104 ± 9.1 vs 96.5 ± 8.7), short-term memory (110 ± 12.1 vs 110 ± 10.5 vs 108 ± 9.6) and composite score (110 ± 9.6 vs 109 ± 7.9 vs 103 ± 11.0). All comparisons are control versus early entry versus late entry	PPVT Early entry, −0.28 (−0.65, 0.09) Later entry, −0.81 (−1.30, −0.32) Communication Early entry, −0.10 (−0.48, 0.27) Later entry, −0.76 (−1.25, −0.27) Length of Utterance Early entry, −0.11 (−0.48, 0.27) Later entry, −0.41 (−0.89, 0.07) MDI Early entry, ranges −0.29 to 0 Later entry, ranges −0.33 to −0.08 SBIS Early entry, ranges −0.35 to 0 Later entry, ranges −0.70 to −0.09
Townsend et al, 2005[22]	US	Cohort study	15 ODM and 15 control subjects	4 y	PDM + GDM	Not stated	WPPSI-Revised at 4 y	IQ	DM has no association with FIQ (118 ± 16 vs 121 ± 21), VIQ (116 ± 16 vs 115 ± 19), or PIQ (116 ± 14 vs 121 ± 18)	FIQ, −0.16 (−0.88,0.56) VIQ, 0.06 (−0.66,0.77) PIQ, −0.31 (−1.03,0.41)

TABLE 1 Continued

First Author/ Year	Country	Study Design	Sample Size	Age at Follow-up	Diabetes Type	Diabetes Diagnosis	Cognitive Assessment	Cognitive Outcome	Main Findings on Maternal Pregnancy Diabetes and Offspring's Cognitive Development (95% CI)	Effect Size: Cohen's d (95% CI)
Veena et al, 2010[23]	India	Cohort study	32 OGDM and 483 control subjects	9–10 y	GDM	OGTT	KABC-II (learning, long- term retrieval/ storage)	Learning long-term retrieval/ storage	GDM associated with higher mean cognitive scores of long-term retrieval/ storage (β), 0.38 (0.01,0.75), verbal ability–names, 0.46 (0.09, 0.83)	Long-term retrieval/ storage, 0.49 (0.13,0.85)
							Word order	Short-term memory	GDM has no association with: attention and concentration, 0.32 (−0.04, 0.67); visuospatial ability, 0.01 (−0.36,0.39); verbal ability–animals, 0.22 (−0.16,0.61); reasoning ability, 0.14 (−0.23,0.51); and short-term memory, 0.03 (−0.35,0.40)	Verbal ability– names, 0.45 (0.09, 0.81)
							Pattern reasoning	Reasoning ability		Attention and concentration, 0.54 (0.19,0.90)
							Verbal ability	Reasoning ability		Verbal ability—animals, 0.34 (−0.02,0.69)
							Kohs block-design	Verbal fluency		Short-term memory, 0.23 (−0.13,0.59)
							Coding WISC-III	Visuospatial ability		All effect sizes are unadjusted
								Attention and concentration		
Yamashita et al, 1996[33]	Japan	Cohort study	33 OPDM, 3 OGDM, and 34 control subjects	3–4 y	PDM + GDM	OGTT	Tanaka-Binet intelligence scale	IQ	DM associated with lower IQ (98 ± 17 vs 113 ± 15)	IQ, −0.93 (−1.43,−0.44)

BSID, Bayley Scales of Infant Development; CI, confidence interval; DM, diabetes mellitus; EDI, Early Development Instrument; FIQ, full IQ; KABC, Kaufman Assessment Battery for Children; MCDI, MacArthur Communicative Development Inventory; MD, mean difference; NVIQ, nonverbal IQ; OGTT, oral glucose tolerance test; OR, odds ratio; PIQ, performance IQ; PPVT, Peabody Picture Vocabulary Test; QLSCD, Quebec Longitudinal Study of Child Development; QNTS, Quebec Newborn Twin Study; RM, recognition memory; SBIS, Stanford-Binet Intelligence Scale; SEA, school entry assessment; VIQ, verbal IQ; WISC, Wechsler Intelligence Scale for Children; WPPSI-III, Wechsler Preschool and Primary Scale of Intelligence, Third Edition.

to 12 years. Most of the studies were conducted in the United States, Israel, and the United Kingdom; 3 were conducted in India, Japan, and Canada. The majority of the studies (n = 10) were prospective cohorts. Although the measurement tools were diverse, offspring's IQ according to several different IQ scales was the most commonly assessed cognitive outcome, followed by the mental development index (MDI) of the Bayley Scales of Infant Development. Overall, 10 of 14 studies[16,18,20–22,28,29,31–33] investigated the associations between maternal PDM or both PDM and GDM with cognitive development of offspring. The remaining 4 studies[17,19,23,30] exclusively examined the associations between maternal GDM and offspring's cognitive development (Table 1).

Association Between PDM and Offspring's Cognitive Development

In 1969, Churchill et al[28] reported the negative associations between maternal diabetes in pregnancy (ie, both PDM and GDM) and offspring's cognitive development. They administered the MDI at age 8 months (n = 121) and the Stanford-Binet Intelligence Scale at age 4 years (n = 231). In this study, maternal diabetes during pregnancy with acetonuria was associated with lower MDI and IQ scores. ODM, complicated by acetonuria, scored ~2.5 and 7 points lower in MDI and IQ scores, respectively, compared with offspring of mothers without diabetes. However, in the absence of acetonuria, ODM had MDI and IQ scores similar to control subjects.

In 1991, Rizzo et al[20] conducted a cohort study of 89 offspring of mothers with pregestational diabetes mellitus (OPDM), 99 offspring of mothers with gestational diabetes mellitus

(OGDM), and 35 control subjects aged 2 to 5 years. The study examined the correlation between maternal metabolism during pregnancy and offspring's cognitive and behavioral functioning. Accordingly, the MDI scores of the offspring correlated inversely with the mother's third-trimester plasma β-hydroxybutyrate levels, and the Binet's IQ scores correlated inversely with the mother's third-trimester plasma β-hydroxybutyrate and free fatty acid levels. However, the investigators found similar MDI and Binet's IQ scores among groups. In support of this outcome, Ornoy et al,[18] using 32 OGDM, 57 OPDM, and 57 control subjects matched on age, socioeconomic status (SES), gestational age, birth order, and family size, reported similar Wechsler's IQ scores across these groups. Despite lack of statistical significance, OGDM scored 5 points below control subjects.

Nelson et al[32] aimed to evaluate cross-modal recognition memory of infants, and they provided a simple MDI score comparison (unadjusted) between 52 ODM and 75 control subjects at the age of 1 year. They found a significant difference between these groups (mean ± SD, 100 ± 9 vs 104 ± 8; P < .03). However, using a small subset (15 ODM and 15 control subjects) of the same population but at the age of 4 years, Townsend et al[22] supported the null association between maternal diabetes during pregnancy and offspring's cognitive development as measured by using Wechsler's IQ scale. The investigators failed to provide explanations for this discrepancy except for the cognitive measurement variations.

In another study, Sells et al[21] examined the neurodevelopmental outcomes of offspring born to mothers with insulin-dependent PDM. The study included 109 OPDM (70 early entry and 39 late entry) and 90 control subjects, and the

investigators administered various cognitive and language development measures at 6 to 36 months of age. In this study, PDM was significantly associated with lower scores of language development in late-entry groups, although this association was not observed between maternal PDM and offspring's MDI and the Binet IQ scores.

Hod et al[31] confirmed the negative association in 31 OPDM and 41 control subjects at 1 year of age between maternal PDM and offspring MDI; OPDM scored 7 points below control subjects (91 ± 9 vs 98 ± 12; P < .05). Similarly, Yamashita et al[33] found significantly lower Tanaka-Binet IQ scores in 15 OPDM (98 ± 17) compared with 15 control subjects (113 ± 15; P < .0001). However, both studies failed to account for any potential confounder.

Bonilla et al[29] (n = 6272) and Fraser et al[16] examined the cognitive development of offspring born to women with PDM and GDM at the age of 4 and 8 years in 2 different large cohort studies. Bonilla et al reported that maternal diabetes during pregnancy was negatively associated with Wechsler's IQ scores; ODM scored 3.5 (95% confidence interval, –5.6 to –1.5; P = .001) points lower compared with offspring of women without diabetes. The investigators did not report the outcomes according to diabetes type, failed to account for potential confounders such as SES and prepregnancy BMI, and did not provide information about the nature and size of the control group. Fraser et al also reported that both PDM and GDM were associated with lower offspring school entry assessment (age 4 years, ~5849 children) and Wechsler's IQ (age 8 years, ~5124 children) scores. However, after full adjustments were made for various confounders, the negative associations persisted only between maternal GDM and verbal IQ (mean

TABLE 2 Summary of the Associations Between Diabetes in Pregnancy and Offspring's Cognitive Development, and Confounders and Covariates

Study/Year	Association	Potential Confounders/Covariates												
		Maternal									Birth Weight	Offspring		
		Age	BMI	SES	Education	HDP	Depression	Lifestyle Behaviors	Parity	Duration of Breastfeeding		GA	Age	Gender
Bonilla et al, 2012[29]	→	✓									✓	✓	✓	✓
Churchill et al, 1969[28]	→	✓		✓									✓	✓
Dionne et al, 2008[30]	→	✓	✓	✓				✓		✓	✓	✓		✓
Fraser et al, 2012[16]	→	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓		✓
Hod et al, 1999[31]	→	✓										✓		
Nelson et al, 2003[32]	→	✓					✓	✓			✓			
Nomura et al, 2012[17]	↔		✓	✓										✓
Ornoy et al, 1999[19a]	↔			✓								✓		
Ornoy et al, 2001[18]	↔			✓								✓	✓	
Rizzo et al, 1991[20]	→		✓	✓										
Sells et al, 1994[21]	↔				✓									
Townsend et al, 2005[22]														
Veena et al, 2010[23]	←	✓	✓	✓	✓						✓	✓	✓	
Yamashita et al, 1996[33]	→	✓											✓	✓

↓, significant negative association; ↑, significant positive association; ↔, no significant association; GA, gestational age; HDP, hypertensive disorder of pregnancy.
a Found significant association between GDM and IQ scores in young age (5–8 years) groups only.

difference, 9.92) scores. Despite full model adjustment, Fraser et al acknowledged the presence of the small number of mothers with diabetes (∼44) and a significant loss to follow-up (ie, IQ data were available for ∼49% of the cohort).

Association Between GDM and Offspring's Cognitive Development

Although the associations between maternal GDM and offspring's cognitive development was separately reported in 7 studies,[16–20,23,30] only 4 studies[17,19,23,30] exclusively addressed GDM. Hence, to avoid repetition, only the last 4 studies are presented here.

In a retrospective cohort study, Ornoy et al[19] compared the neuropsychological function of 32 school-aged children born to mothers with well-controlled GDM and 57 control subjects matched according to age, birth order, and parental SES. Although the study was underpowered and lacked any adjustment for confounders, the younger aged (ie, 5–8 years) OGDM scored 8 points (107 ± 11 vs 115 ± 11) and 10 points (111 ± 14 vs 121 ± 8) lower in Wechsler's verbal IQ and full-scale IQ scores, respectively, than control subjects; such associations were not observed in older children (aged 9–12 years) or on the performance IQ scale.

Dionne et al[30] compared OGDM and control subjects (aged 1.5–7 years) in various language development measures. In this study, OGDM scored between 0.27 and 0.41 SD below control subjects on expressive vocabulary and grammar at 18 and 30 months. At 72 and 84 months, maternal GDM was also associated with lower mean scores in oral communication. In both cases, the model was adjusted for gender, gestational age, birth weight, Apgar score, gestational

hypertension, alcohol use, and smoking in pregnancy. The same authors also reported an odds ratio of 2.2 (95% confidence interval, 1.4 to 3.5) for the risk of language impairment. At 42 and 60 months of age, no differences between OGDM and control subjects on expressive and receptive vocabulary were observed. In addition, the groups did not differ in mean reading and math scores.

In contrary, Veena et al[23] reported that maternal GDM was associated with higher mean cognitive scores of long-term retrieval/storage, verbal ability, attention, and concentration; these scores were measured by using the Kaufman Assessment Battery for Children, the Wechsler Intelligence Scale for Children, and other cognitive tests in 32 school-aged OGDM and 483 control children after adjustments were made for various confounders. The investigators acknowledged the relatively small number of OGDM and requested larger studies.

More recently, Nomura et al[17] examined the independent and synergistic effect of maternal GDM and low SES on the cognitive and language development of 21 OGDM and 191 control subjects. They compared preschool-aged children (aged 3–4 years) exposed to 1 of 4 conditions: neither mother's GDM nor low SES (n = 97); mother's GDM but not low SES (n = 12); no mother's GDM but low SES (n = 94); and both mother's GDM and low SES (n = 9). From these pairwise comparisons, they found that children born to both diabetic and low SES mothers had lower verbal and full-scale IQ and language composite scores on the Wechsler Preschool and Primary Scale of Intelligence. Compared with the first group, maternal GDM alone was also significantly associated with lower cognitive (full and verbal IQ)

and language development but with attenuated effect sizes.

DISCUSSION

To our knowledge, this article is the first systematic review to examine the associations between maternal diabetes during pregnancy and childhood cognitive development. We found a few geographically limited studies, the majority of which were small and did not adjust for important confounders. Although not conclusive, 8 of the 14 studies seemed to support the negative association between maternal diabetes during pregnancy and offspring's cognitive and language development. Generally, the effect sizes were heterogeneous, varying from –1.30 to 0.54. Effect sizes were consistently larger for language development compared with performance IQ, suggesting that the latter is less likely to be affected by maternal diabetes during pregnancy. The finding has relevant clinical implications because the prevalence of GDM and type 2 diabetes mellitus are increasing.[3,40] It is worth noting, however, that the evidence is from limited observational studies (ie, whether the observed association was exclusively due to diabetes during pregnancy, its complications, or confounders was unclear with the available evidence).

Most of the studies[16,29,30] conducted with relatively larger sample sizes, totaling ≥2833 offspring, produced consistent negative associations. Others that failed to detect such associations were conducted with smaller sample sizes[18,20,22] and therefore had less power to detect true differences between groups.

Only 2 of the 14 eligible studies[16,23] fully accounted for potential confounders such as maternal prepregnancy BMI, SES, maternal age, alcohol use, and smoking during pregnancy and offspring-related

covariates. Maternal prepregnancy overweight/obesity is a well-known strong predictor of both maternal PDM (particularly type 2 diabetes mellitus) and GDM.[41] For instance, in the United States, >80% and 49% of patients with diabetes were found to be overweight and obese, respectively.[42] Together with the increasing trend of overweight and obesity and the subsequent effect of these conditions on maternal diabetes,[5] the relationship between these factors and later cognitive development of the offspring must be better understood. To date, there have been only a few studies to show the independent associations of maternal prepregnancy obesity and offspring's cognitive development.[43–45] Hence, studies in the present review that perceived a negative association between maternal diabetes during pregnancy and offspring's cognitive development could have been confounded by maternal prepregnancy obesity.

Studies in young offspring consistently found that both maternal PDM and GDM reduced their cognitive and language development, whereas the majority of the studies in older children showed no effect of maternal diabetes on their cognitive development. This outcome suggests that either the intrauterine effect of diabetes may diminish as children get older or postnatal factors such as SES[30] accounted for the association. Alternatively, the effect of diabetes in pregnancy may be reversible as the cognitive abilities in young children are prone to changes, mainly to their home environment.[46]

Maternal SES, measured according to maternal education, occupation, and income, is a powerful determinant of health. In a recent systematic review,[47] SES was a significant confounder in the association between preterm birth and cognitive deficit, and these investigators recommended the

need to adjust the role of SES in studies reporting child cognitive development. Similarly, Nomura et al,[17] included in this systematic review, revealed a negative synergistic effect of maternal low SES and GDM on offspring's IQ and language development. Moreover, a large cohort study[48] using data from Swedish population registers found lower IQ scores in nonsibling men born to diabetic mothers, but no such association was seen within sibships discordant in their exposure to maternal diabetes in pregnancy; these findings reflect the role of the shared environment (specifically SES). However, few of the included studies matched control subjects on the basis of SES[19] or adjusted for SES[16] in the relationships between maternal diabetes during pregnancy and offspring's cognitive development. Likewise, other potential confounders, including maternal age,[49,50] alcohol use,[51,52] and smoking during pregnancy,[53] and offspring-related covariates, such as gestational age[54] and birth weight,[27,55] were rarely adjusted for in these studies.

A review by Ornoy[56] concluded that the cognitive ability of offspring born to mothers with well-controlled diabetes is usually normal. Despite substantial challenges, maternal metabolism control has multiple benefits, including but not limited to reduction of perinatal adverse outcomes and long-term effects in offspring exposed to maternal diabetes in pregnancy.[57] However, the conclusion was offered from limited, mainly small[18,20,21] and descriptive[26,27,58] studies. In addition, mixed results have been reported, with null or positive associations between different measures of maternal metabolic control and diverse measures of cognitive ability.[26,29,33,39] Even with well-controlled maternal diabetes, offspring's cognitive development has been found to be significantly

impaired.[19,31] Regardless of maternal metabolic control, in our systematic review, 1 study[16] fully adjusted for potential confounders with relatively good power, as well as other studies[19,21,29–33] that partially adjusted for potential confounders, reported significantly impaired cognitive development in offspring born to mothers with either PDM or GDM.

In contrast, in school-aged Indian children born to a population with higher rates of diabetes in pregnancy (6.9%), Veena et al[23] reported higher cognitive scores on a variety of cognitive measurements in OGDM compared with offspring of women without GDM. The investigators reported that GDM has been positively associated with higher SES, unlike in developed nations, and hence the observed association could be attributable to residual SES confounders. Although there are no data regarding the maximum threshold of maternal glucose level that is deleterious to the growing fetus, Veena et al and others[29,48] reported positive associations between maternal glucose levels during pregnancy and offspring's cognitive scores. An optimal maternal glucose level during pregnancy is vital for the growing fetus. However, tight glycemic control is usually associated with hypoglycemia, a condition which, if it occurs repeatedly, could lead to impaired cognitive development.[59]

The observed discrepancies between some of the studies that found negative,[30,33] null,[18,20,22] and positive associations[23] could also be partly due to cognitive test variations and the subsequent different cognitive outcomes. The effect of maternal diabetes in pregnancy may vary according to specific types of cognitive domains, as reflected by heterogeneous effect sizes. However, we are unaware

of any evidence supporting this suggestion. Various cognitive development measurements of offspring, obtained from self-report to highly standardized and blindly administered tools, were used. In addition, despite the utilization of standard cognitive measurement tools, one-half of the studies[16,17,22,23, 29,31,33] failed to provide or report blind outcome assessment. Assessors' awareness of exposure status in randomized controlled trials has been found to be a source of information bias[60]; it may also be a problem in observational cohort studies that did not commence as case-control designs. Likewise, maternal diabetes status was obtained either from hospital records, interview, or from objectively measured but varied glucose tolerance test results. These variations in measurement may also have contributed to the observed inconsistencies (eg, between Nomura et al[17] and Fraser et al[16]). Moreover, universal GDM screening was not available in these studies,[16,17] and it is possible that control subjects could have GDM. If so, this finding may have diluted the associations.

Some of the strengths of this systematic review are that it included studies without time restriction, employed independent reviewers, and used a standardized quality assessment tool. However, publication bias in the included studies is an inevitable limitation. A recent systematic review revealed a strong tendency for publication of positive or significant results.[61] In addition, we restricted our systematic review to published articles and did not contact experts for additional data. Although we excluded limited studies through language restriction, relevant studies could have been missed from this restriction. More importantly, meta-analysis was not performed because of the limited number of studies

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with diverse cognitive outcomes and model adjustment.

CONCLUSIONS

Few data are available regarding the influence of maternal diabetes during pregnancy on the subsequent cognitive development of offspring. The present review found that maternal diabetes during pregnancy seems negatively associated with offspring's childhood cognitive development. The effect was substantial in the offspring's language development during a young age, particularly verbal IQ. However, the extent to which the observed association is due to potential confounders such as prepregnancy obesity, maternal SES, or other confounders is unclear. The use of diverse cognitive and diabetes assessment tools and criteria, sample size, and population differences contributed to the inconsistent findings. Larger prospective studies that address potential confounders are needed to confirm the independent effect of maternal diabetes on cognitive development of offspring. Future research must also determine whether the negative association is due to maternal diabetes itself or to metabolic complications.

ABBREVIATIONS

DM: diabetes mellitus
GDM: gestational diabetes mellitus
MDI: mental development index
ODM: offspring of mothers with diabetes mellitus
OGDM: offspring of mothers with gestational diabetes mellitus
OPDM: offspring of mothers with pregestational diabetes mellitus
PDM: pregestational diabetes mellitus
SES: socioeconomic status

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Diabetes in Pregnancy and Childhood Cognitive Development: A Systematic Review

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