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Maternal glycemic control in diabetic pregnancies and neurodevelopmental outcomes in preschool aged children. A prospective cohort study.

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Introduction.

There are conflicting reports regarding the relationship between maternal glycemic control during diabetic pregnancy and neurodevelopmental outcomes of the offspring. Some studies found no association between maternal glycemic control and their children's intellect.[1–3] Others found an adverse association between poor maternal glycemic control and intellect, [4,5] developmental quotient,[6] hand-eye coordination,[7] motor test scores,[7,8] school grades [9] and cognitive scores in adult males.[10] However, participants in most of these studies were born in the 1960s through to 1990s and management of diabetes in pregnancy has evolved since that time.[11–15] Furthermore, many studies did not adjust for confounding factors such as obesity, parental education or socioeconomic status,[1,2,6–8,16] or were not large enough to compare outcomes between children of mothers with different types of diabetes.

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RG, JA and JH drafted the manuscript and designed the tables. All authors critically revised the manuscript for important intellectual content and approved the final manuscript. JA is the guarantor of this work and takes responsibility for the contents of this article and the integrity of the data and the accuracy of the data analysis.

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Conflicts of interest

Declarations of interest: none

The socioeconomic status of a child's family is a well-known influence on their development [17] and there is increasing evidence that maternal obesity has an adverse effect on their children's neurodevelopment.[18–27] Obesity is associated with increased risk of diabetes in pregnancy [28] and with poorer socioeconomic status [29,30]. The variation in findings from previous studies could thus be due to confounding.

Reports of the effect of intrapartum glycemic control on risk of neonatal hypoglycemia also yield conflicting results. In cohorts with a high percentage of diabetic women maintaining blood glucose concentrations within target ranges of 3–6 mmol/L or 4–7 mmol/L during labor,[31,32] no association was found between maternal intrapartum and neonatal blood glucose concentrations. However, other studies found higher maternal blood glucose concentrations during labor were associated with an increased likelihood of neonatal hypoglycemia,[33–37] Since neonatal hypoglycemia can itself lead to adverse neurodevelopmental outcomes, it is possible that an interaction between maternal glycemic control and neonatal hypoglycemia determines later outcomes.

We sought to determine the relationship between maternal glycemic control during pregnancy and labor in diabetic pregnancy and offspring neurodevelopmental outcomes, accounting for a range of potential confounders and also any interaction with neonatal hypoglycemia.

Materials and Methods

Sample

Eligible children were born to mothers with either pre-existing or gestational diabetes who were part of a prospective cohort study, the CHYLD Study, which recruited infants at risk of neonatal hypoglycemia (maternal diabetes, late preterm birth between 32 and 36 weeks' gestation, birthweight less than 10th centile or less than 2500g (small) or birthweight greater than 90th centile, or greater than 4500g (large)) between 2006 and 2010 at Waikato Hospital, Hamilton, New Zealand.[38,39] Children born 35 weeks' gestation were eligible for assessment at 2 years' corrected age, and all children were eligible for assessment at 4.5 years' corrected age.

Measures

Gestational diabetes was diagnosed by a fasting blood glucose concentration of ≥ 5.5 mmol/L or 1-hour blood glucose concentration of >11 mmol/L after 50 g carbohydrate load. Measures of maternal glycemic control were collected from electronic and paper records, including diabetes type; the last available HbA1c concentration during the second and third trimesters; blood glucose concentration 1 hour after 50 g polycose load administered between 20 and 32 weeks' gestation to screen for gestational diabetes; and blood glucose concentrations in the 6 hours prior to the birth. Infant blood glucose concentrations were measured by the glucose oxidase method on heel-prick capillary blood samples at one hour of age, then before feeds two to four hourly for at least 12 hours. In infants receiving intravenous dextrose, blood glucose concentrations were measured 4 hourly for 12 hours, and then as clinically indicated.

Assessment at 2 and 4.5 years

At each age, children underwent a comprehensive neurocognitive, motor and vision assessment as previously reported [38,39], including caregiver completed questionnaires about the child's health, home environment and everyday executive function (BRIEF-P parent rating form). Assessors were blinded to the reason for risk of hypoglycaemia and neonatal history and were trained to ensure reliability on all assessments.

Neurosensory impairment at 4.5 years was defined as any of: visual impairment (visual acuity >0.5 log MAR in the better eye); deafness requiring hearing aid; cerebral palsy; Wechsler Preschool and Primary Scale of Intelligence 3rd edition[40] (WPPSI-III) score <85 ; Beery Visual-Motor Integration 6th edition[41] (Beery VMI) score more than 1 SD below the test mean; Movement Assessment Battery for Children-2nd Edition[42] (MABC-2) total Score <15 th centile; Motion coherence threshold[43] or Executive function composite score worse than 1.5 SD from the cohort mean. Neurosensory impairment at 2 years was defined as any of: blindness (visual acuity >1.4 log MAR in the better eye); deafness requiring hearing aids; cerebral palsy; Bayley Scale of Infant Development 3rd Edition[44] cognitive, language or motor score more than 1 SD below the test mean.

The regional ethics committee approved the neonatal (NTY/08/03/025) and follow-up (NTY/10/03/021) studies. Written informed consent was obtained from a parent or guardian at study entry and at follow-up.

Statistical Analysis

Analysis was performed using JMP software version 12.1 (SAS Institute, Cary, NC). The primary outcome was neurosensory impairment at 4.5 years, or if this was not available, neurosensory impairment at 2 years of age. The secondary outcomes were the components of the primary outcome.

HbA1c results were categorized into quartiles: Q1 <36.6 mmol/mol (5.5 %); Q2 36.6 mmol/mol (5.5 %) – 39.9 mmol/mol (5.8%); Q3 40 mmol/mol (5.8 %) – 46.5 mmol/mol (6.4 %); Q4 >46.5 mmol/mol (6.4 %). Polycose results were categorized into quartiles: Q1 <8.2 mmol/L; Q2 8.2 – 8.9 mmol/L; Q3 9.0 – 10.0 mmol/L; Q4 >10.0 mmol/L. Maternal blood glucose concentrations in the 6 hours preceding birth were categorized as remaining in the recommended range of 4–7 mmol/L or out of range. Maternal BMI at booking was categorized into healthy (<25 kg/m²), overweight (25– 30 kg/m²) or obese (>30 kg/m²). Socioeconomic status was categorized using the New Zealand Deprivation Index (NZDPI) [45] and analysed using quintiles. Neonatal hypoglycemia was defined as a blood glucose concentration <2.6 mmol/L (47 mg/dL); severe hypoglycemia as <2 mmol/L (36 mg/dL). Children were categorized as having experienced no neonatal hypoglycemia, a single episode, or severe or recurrent episodes.[38]

Maternal and neonatal characteristics were compared between diabetes types using ANOVA or Chi-square test, with Tukey-Kramer *post hoc* adjustment for multiple comparisons. Logistic regression was used to assess univariate associations between measures of maternal glycemic control and risk of neurosensory impairment. Multivariate models were then constructed to identify potential confounders (NZDPI and maternal BMI) and mediators

(gestation and birthweight z score). Thus, Model 1 adjusted for NZDPI. Model 2 adjusted for NZDPI, gestation and birthweight z score. Model 3 adjusted for NZDPI, and maternal body mass index (BMI) at booking. Model 4 adjusted for NZDPI, maternal BMI at booking, gestation and birthweight z score.

Exploratory analyses were performed on the fully adjusted multivariate model (Model 4) to examine any interaction effect between sex or neonatal hypoglycemia and the relationship between maternal glycemic control and neurodevelopmental outcomes.

Results

Primary outcome data were available for 196/229 (86%) eligible children (196/231, 85% of recruited children) (Figure). The majority of children (155/196, 79%) were born to mothers with gestational diabetes. As expected, diabetes management varied by diabetes type (Table 1). Mothers with type 1 diabetes had the lowest BMI at booking, followed by those with gestational and then type 2 diabetes. Babies of mothers with gestational diabetes were born half a week later, on average, than those born to mothers with type 1 or type 2 diabetes. Mothers with type 1 diabetes were most likely to have a baby who developed hypoglycemia, followed by those with type 2 and then gestational diabetes.

Neurosensory impairment was present in 81/196 children (41%) (Table 2). Only one child was deaf and none were blind at follow-up. The risk of neurosensory impairment did not differ by type of diabetes (gestational 64/155 [41%], type 1 7/20 [35%], type 2 10/21 [48%], $p=0.71$).

The risk of neurosensory impairment was not related to maternal HbA1c or polycose results in univariate or multivariate models (Tables 3, 4). There was wide variation in the timing and frequency of monitoring of intrapartum blood glucose concentrations. Although 17 mothers had an intrapartum blood glucose concentration below 4 mmol/L and 26 mothers had an intrapartum blood glucose concentration above 7 mmol/L, there was no association between poorer intrapartum glycemic control and the risk of neurosensory impairment in children in univariate or multivariate models (Table 4).

There was no significant interaction effect of sex ($p>0.15$) or neonatal hypoglycemia ($p>0.7$) on the relationships between polycose, HbA1c, or Intrapartum glucose concentration in/out of range and neurosensory impairment. Sensitivity analysis excluding data from 17 children without 4.5-year outcomes did not alter the results (Appendix).

The secondary outcomes also did not vary by maternal diabetes type, HbA1c or polycose quartile, nor intrapartum blood glucose range (Tables 2, 3).

Discussion:

We sought to examine the relationship between maternal glycemic control in pregnancy and labor, and neurosensory impairment in the children of diabetic mothers. We found that maternal glycemic control in pregnancy and labor was not associated with offspring neurodevelopment at preschool ages.

Our findings agree with some studies which found no association between IQ at three years of age and maternal HbA1c,[2,3] but are contrary to others, which found an association between HbA1c and offspring neurodevelopment between the ages of five and sixteen years. [5,8,9] However, these studies included exclusively or a large proportion of mothers with pre-existing diabetes.[5,8,9] Although pre-existing diabetes alters the intrauterine environment throughout pregnancy [46], whereas gestational diabetes, has its onset later pregnancy [47], we found no association between the type of maternal diabetes and the risk of neurosensory impairment in their children. Most mothers in our study had gestational diabetes rather than pre-existing type 1 or type 2 diabetes, so these results largely reflect the effect of glycemic control in mothers with gestational diabetes on their offspring, and we had limited power to detect small differences in outcomes between offspring of mothers with different types of diabetes.

As with our study, a large population based study adjusted for confounders including socioeconomic status, and although an association between maternal diabetes and offspring cognitive outcome was demonstrated, after comparing within sibships, this relationship was lost. [48]

One reason that our findings differ from previous studies might be that management of diabetes, and particularly gestational diabetes, has altered since earlier studies of participants born in the 1960s through to the 1990s [2–5,7–9,16,17]. For example, there are new insulin formulations and metformin is now used in gestational diabetes.[11–13] The definitions of abnormal glucose tolerance in pregnancy and recommended targets for glucose management [14,15] have also all changed since that time.

We used HbA1c as one indicator of maternal glycemic control. Although HbA1c is easily retrieved from medical records, it will not necessarily reflect stability or variability of maternal glucose concentrations.[49,50] Polycose results give an indication of postprandial glucose concentration, but only at one point in time. Previous studies have found no association between post prandial or 2 hour post carbohydrate load blood glucose concentrations and adult cognitive outcomes.[10,17] Nevertheless, there is evidence from animal studies that intermittent maternal hyperglycemia results in a greater increase in fetal insulin secretion than constant stable hyperglycemia.[51] Thus, additional parameters of maternal glycemic profile such as a series of fasting and postprandial blood glucose concentrations would give a more accurate reflection of variability in blood glucose concentration which might have a greater influence on fetal metabolism and neurodevelopment, and should be examined in future studies.

We found no relationship between intrapartum blood glucose concentration and risk of neurosensory impairment. However, intrapartum blood glucose monitoring was intermittent and highly variable in timing and frequency as no clinical guideline was in use at the time. We chose 6 hours prior to birth as the timeframe in which maternal blood glucose concentration was most likely to influence neonatal glycemic profile, and not simply reflect longer term maternal glycemic stability. NICE guidelines recommend hourly blood glucose monitoring during labor in mothers with all types of diabetes.[52] Hourly measurements would provide a profile for analysis of any relationship between time in recommended range

and risk of neonatal hypoglycemia, and its relationship to neurodevelopmental outcomes. However, it might be expected that mothers with poorer glycemic control and a wider range of blood glucose concentrations during pregnancy might also have poorer control during labor [53], meaning intrapartum blood glucose concentrations might simply reflect overall maternal glycemic control.

One limitation of our study was that we did not have a control group to compare their outcomes with those of children born to non-diabetic mothers, but our aim was to explore the associations between indicators of maternal glycemic control and offspring neurodevelopment. Another limitation was that HbA1c and polyose data were missing for 40 and 50 mothers respectively, and this missing data may have reduced the likelihood of detecting relationships between these measures of glycemia and outcomes. Nevertheless, this is the largest prospective, follow up study of children of diabetic mothers of which we are aware, and includes children born between December 2008 and November 2010, so is a useful representation of relatively recent practice.

We found a high rate of neurosensory impairment (41%) in the children born to mothers with diabetes in pregnancy, but no association with measures of maternal glycemic control. The research measures were intentionally broad (including motion coherence and executive function) to detect a wide range of possible effects of glycaemic control. The interaction of glucose with amino acid and lipid metabolic pathways might influence fetal neurodevelopment. Given no association with glycemic control, but a high risk of neurosensory impairment in this group, it is important that future studies examine any relationship between offspring neurodevelopmental outcomes and indicators of broader metabolic processes in mothers with diabetes. These might include not only blood glucose concentrations, but also amino acid, triglyceride, fatty acid and cholesterol measurements. Management of diabetic mothers to improve infant outcomes might then be directed towards better control of interrelated metabolic processes. Randomized controlled trials comparing tighter control of indicators of these metabolic processes with usual management should be carried out to determine the effect on neurodevelopmental outcomes of the children. Longitudinal studies are also required to determine if any early adverse neurodevelopmental outcomes persist with advancing age.

Conclusions

Children born to mothers with diabetes during pregnancy have a high rate of neurosensory impairment at preschool ages, but this is not associated with measures of maternal glycemic control during pregnancy or the intrapartum period.

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Appendix.: Primary and secondary childhood outcomes for 17 children at age 2 years

<i>Outcome</i>	<i>Number (%)</i>
Neurosensory impairment	10 (59)
Bayley cognitive <85	5 (29)
Bayley Language <85	7 (42)
Bayley motor <85	4 (24)
Executive function performance poor	2 (13) ^a
BRIEF P Executive function poor	6 (35)
Motion coherence threshold poor	1 (8) ^b

Number (%) per column

^aData missing for 2

^bData missing for 4

No children were blind nor deaf, nor had cerebral palsy.

Poor EF task performance score: > 1.5 SD below cohort mean

Poor BRIEF P executive function: global executive composite t score >65

Poor motion coherence threshold: >1.5 SD above cohort mean (higher threshold indicates worse performance)

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Highlights

Neurosensory impairment is common in children born to diabetic mothers

Neurosensory impairment was not associated with maternal glycemic control

There was no interaction effect of sex or neonatal hypoglycaemia on this relationship

Figure:
Participant flow to four-and-a-half-year follow-up

Table 1

Characteristics of mothers with different types of diabetes in pregnancy and their babies.

<i>Characteristic</i>	<i>Total</i>	<i>Gestation al diabetes</i>	<i>Type 1 diabetes</i>	<i>Type 2 diabetes</i>	<i>P value</i>
Mothers	192	153	20	19	
Maternal age, years	31.1 (6.1)	31.1 (6.3)	29.3 (5.6)	33.2 (4.9)	0.14
Booking BMI^a	31.2 (7.8)	31.5 (7.9)	25.3 (4.0)	34.7 (5.9)	<0.01 ¹
Gestational weight gain, kg^b	10.8 (7.1)	11.1 (7.1)	9.2 (7.5)	9.6 (5.9)	0.48
Parity^c	1 (0–9)	1 (0–9)	1 (0–4)	1 (0–4)	0.75
Diabetes management					<0.01 ²
Diet/lifestyle only	58 (30)	58 (38)	0 (0)	0 (0)	
Metformin	24 (13)	22 (14)	0 (0)	2 (11)	
Insulin	110 (57)	73 (48)	20 (100)	17 (89)	
HbA1c in 2nd or 3rd trimester mmol/mol and %^d					<0.01 ³
Polycose 1 hour result, mmol/L and mg/dL^e		9.3 (2.4)	N/A	N/A	
NZDPI quintiles^f					0.70
1	25 (12.8)	18 (11.6)	3 (15.0)	4 (19.1)	
2	27 (13.8)	23 (14.8)	2 (10.0)	2 (9.5)	
3	45 (23.0)	34 (21.9)	5 (25.0)	6 (28.6)	
4	44 (22.5)	32 (20.7)	6 (30.0)	6 (28.6)	
5	55 (28.1)	48 (31.0)	4 (20.0)	3 (14.3)	
Babies	196	155	20	21	
Twins	9 (5)	4 (3)	0 (0)	5 (24)	0.02 ²
Female	98 (50)	79 (50)	10 (50)	12 (57)	0.78
Ethnicity					0.43
Maori	73 (37.2)	54 (34.8)	8 (40.0)	11 (52.4)	
Pacific	7 (3.6)	7 (4.5)	0 (0)	0 (0)	
Asian	15 (7.7)	12 (7.7)	1 (5)	2 (9.5)	
NZ European	101 (51.5)	82 (52.9)	11 (55.0)	8 (33.1)	
Gestation	38.3 (33.1–42.5)	38.3 (33.1–42.5)	37.4 (34.2–40.6)	37.6 (35.2–40.0)	<0.01 ⁴
Birthweight z score	0.70 (1.44)	0.63 (1.34)	1.45 (2.02)	0.55 (1.39)	0.05 ⁵
Hypoglycemia	101 (52)	72 (46)	16 (80)	13 (62)	0.01 ²
Severe/recurrent hypoglycemia	48 (24)	29 (19)	13 (65)	6 (29)	<0.01 ²

<i>Characteristic</i>	<i>Total</i>	<i>Gestation al diabetes</i>	<i>Type 1 diabetes</i>	<i>Type 2 diabetes</i>	<i>P value</i>
Other risk factors for hypoglycemia					
Preterm	37 (19)	21 (14)	6 (30)	10 (53)	<0.01 ²
Small	13 (7)	7 (5)	2 (10)	4 (21)	0.08
Large	59 (30)	44 (29)	10 (50)	5 (26)	0.13

Data are mean (SD) or median, (range), or number (%) of column.

^a data available 148 gestational, 18 type 1, 16 type 2 diabetic mothers.

^b data available for 138 gestational, 14 type 1, 15 type 2 diabetic mothers.

^c data available for 19 type 1 diabetic mothers.

^d data available for 147 gestational, 16 type 1, 16 type 2 diabetic mothers

^e data available for 118 gestational diabetic mothers

^f New Zealand Deprivation Index, 1=least deprived

¹ p 0.003 for the comparison gestational vs type 1 and p 0.001 type 2 vs type 1

² chisquare

³ p 0.0001 for the comparison type 1 vs gestational and p 0.05 type 2 vs gestational

⁴ p 0.035 for the comparison gestational vs type 1 and p 0.042 gestational vs type 2

⁵ p 0.04 for the comparison type 1 vs gestational

Table 2

Primary and secondary childhood outcomes in children of mothers with different types of diabetes

<i>Outcome</i>	<i>All types</i>	<i>Gestational diabetes</i>	<i>Type 1 diabetes</i>	<i>Type 2 diabetes</i>	<i>P value</i>
Neurosensory impairment	81 (41) [196]	64 (41) [155]	7(35) [20]	10 (48) [21]	0.71
Low IQ	26 (15) [178]	19 (13) [142]	2 (11) [19]	5 (29) [17]	0.24
Low Visual Motor Integration score	7 (4) [178]	6 (4) [142]	1 (5) [19]	0 (0) [17]	0.48
Low Movement ABC score	50 (29) [172]	40 (29) [137]	5 (27) [18]	5 (29) [17]	0.99
Cerebral palsy	2 (1) [195]	2 (1) [154]	0 (0) [20]	0 (0) [21]	0.62
Executive function performance poor	13 (7) [186]	12 (8) [146]	0 (0) [19]	1 (5) [21]	0.20
BRIEF P Executive function poor	40 (21) [194]	3 (22) [153]	3 (15) [20]	4 (19) [21]	0.77
Motion coherence threshold poor	11 (6) [187]	8 (5) [148]	1 (5) [20]	2 (11) [19]	0.71
Deaf	2 (1) [196]	2 (1) [148]	0 (0) [19]	0 (0) [19]	0.79

Data are number (%) [number for whom data are available]

No children were blind. The two children with cerebral palsy were classified as level 1 on the Gross Motor Function Classification System.

Low IQ: > 1 SD below test mean

Low VMI score: > 1 SD below test mean

Low MABC score: <15th centile

Poor EF task performance score: > 1.5 SD below cohort mean

Poor BRIEF P executive function: global executive composite t score >65

Poor motion coherence threshold: >1.5 SD above cohort mean (higher threshold indicates worse performance)

Table 3

Primary and secondary childhood outcomes according to HbA1c quartile, polycose quartile, and prepartum blood glucose range.

<i>HbA1c quartile</i>	<i>1</i>	<i>2</i>	<i>3</i>	<i>4</i>	P value
Neurosensory impairment	10 (27) [37]	17 (39) [44]	13 (33) [39]	20 (54) [37]	0.10
		1.70 (0.66–4.38), 0.27	1.35 (0.50–3.61), 0.55	3.18 (1.20–8.39), <0.02	
Low IQ	2 (6) [35]	4 (9) [43]	2 (6) [33]	6 (19) [31]	0.27
		1.69 (0.29–9.83), 0.58	1.06 (0.14–8.03), 0.95	3.96 (0.74–21.3), 0.11	
Low Visual Motor Integration score	2 (6) [35]	1 (2) [43]	0 (0) [33]	1 (3) [30]	0.43
		0.39 (0.03–4.52), 0.45	Not calculable	0.57 (0.05–6.60), 0.65	
Low Movement ABC score	7 (21) [33]	14 (33) [42]	8 (24) [33]	8 (28) [29]	0.64
		1.93 (0.67–5.51), 0.22	1.23 (0.39–3.90), 0.72	1.47 (0.46–4.70), 0.52	
Cerebral palsy	0 (0) [32]	1 (2) [41]	0 (0) [33]	0 (0) [31]	0.49
		Not calculable	Not calculable	Not calculable	
Executive function performance poor	2 (6) [36]	3 (7) [43]	0 (0) [37]	1 (3) [34]	0.25
		1.28 (0.20–8.08), 0.80	Not calculable	0.52 (0.04–5.96), 0.60	
BRIEF P Executive function poor	6 (16) [37]	6 (14) [43]	6 (15) [39]	6 (19) [31]	0.65
		0.84 (0.25–2.86), 0.78	0.94 (0.27–3.22), 0.92	1.66 (0.52–5.26), 0.39	
Motion coherence threshold poor	3 (8) [37]	0 (0) [43]	4 (11) [37]	3 (9) [34]	0.07
		Not calculable	1.37 (0.29–6.61), 0.69	1.10 (0.21–5.84), 0.91	
Deaf	0 (0) [34]	0 (0) [43]	0 (0) [33]	1 (3) [31]	0.38
		Not calculable	Not calculable	Not calculable	
<i>Polycose quartile</i>	<i>1</i>	<i>2</i>	<i>3</i>	<i>4</i>	
Neurosensory impairment	10 (42) [24]	10 (36) [28]	10 (42) [24]	11 (44.0) [25]	0.94
		0.78 (0.25–2.39), 0.66	1 (0.31–3.15), 1	1.1 (0.35–3.41), 0.89	
Low IQ	3 (14) [22]	3 (11) [27]	3 (13) [23]	4 (18) [22]	0.92
		0.79 (0.14–4.38), 0.79	0.95 (0.17–5.30), 0.95	1.41 (0.28–7.18), 0.68	
Low Visual Motor Integration score	1 (5) [22]	2 (7) [27]	1 (4) [23]	0 (0) [21]	0.50
		1.68 (0.14–19.85), 0.68	0.95 (0.06–16.27), 0.97	Not calculable	
Low Movement ABC score	5 (24) [21]	7 (28) [25]	6 (26) [23]	6 (30) [20]	0.97
		1.24 (0.38–4.71), 0.74	1.13 (0.29–4.44), 0.86	1.37 (0.34–5.49), 0.66	
Cerebral palsy	0 (0) [20]	0 (0) [27]	0 (0) [19]	0 (0) [21]	
		Not calculable	Not calculable	Not calculable	
Executive Function performance poor	1 (5) [20]	5 (20) [25]	2 (9) [23]	0 (0) [20]	0.07
		2.38 (0.41–13.7), 0.33	0.91 (0.12–7.07), 0.93	Not calculable	
BRIEF P Executive function poor	3 (14) [21]	4 (15) [27]	2 (10) [21]	4 (19) [21]	0.85
		0.79 (0.17–3.59), 0.76	0.69 (0.13–3.43), 0.64	1.85 (0.46–7.40), 0.39	
Motion coherence threshold poor	0 [21]	2 (8) [25]	2 (9) [22]	1 (5) [22]	0.37

<i>HbA1c quartile</i>	<i>1</i>	<i>2</i>	<i>3</i>	<i>4</i>	P value
		Not calculable	Not calculable	Not calculable	
Deaf	0 (0) [21]	1 (4) [27]	0 (0) [23]	0 (0) [22]	0.48
		Not calculable	Not calculable	Not calculable	
<i>Prepartum blood glucose 4–7mmol/L</i>	<i>In range</i>		<i>Out of range</i>		
Neurosensory impairment	38 (41) [92]		14 (36) [39]		0.56
			0.80 (0.37–1.73), 0.56		
Low IQ	12 (13) [91]		5 (13) [39]		0.95
			0.97 (0.32–2.96), 0.95		
Low Visual Motor Integration score	3 (3) [92]		1 (3) [38]		0.85
			0.80 (0.81–7.96), 0.85		
Low Movement ABC score	25 (28) [88]		10 (27) [37]		0.87
			0.93 (0.39–2.21), 0.88		
Cerebral palsy	2 (2) [89]		0 (0) [36]		0.36
			Not calculable		
Executive function performance poor	8 (9) [89]		0 (0) [38]		<0.02
			Not calculable		
BRIEF P Executive function poor	14 (16) [89]		9 (23) [39]		0.33
			1.61 (0.63–4.12), 0.32		
Motion coherence threshold poor	4 (5) [86]		1 (3) [39]		0.57
			0.54 (0.06–4.99), 0.59		
Deaf	1 (1) [92]		0 (0) [39]		0.40
			Not calculable		

Data are number (%) in quantile [number for which data available] and unadjusted OR (95% CI), p value, where quartile 1 or blood glucose in range is used as referent

No children were blind

Low IQ: > 1 SD below test mean

Low VMI score: > 1 SD below test mean

Low MABC score: <15th centile

Poor EF task performance score: > 1.5 SD below cohort mean

Poor BRIEF P executive function: gec t >65

Poor motion coherence threshold: > 1.5 SD above cohort mean (higher threshold indicates worse performance)

Table 4

Relationship between HbA1c, polycose and prepartum blood glucose and neurosensory impairment adjusted for confounders and mediators

HbA1c quartile	2	3	4	P value
Model 1	1.65 (0.62, 4.53)	1.08 (0.38, 3.05)	2.36 (0.87, 6.64)	0.27
Model 2	1.76 (0.65, 4.96)	1.14 (0.81, 3.37)	2.32 (0.77, 7.34)	0.36
Model 3	1.42 (0.52, 3.97)	0.86 (0.30, 2.52)	1.60 (0.55, 4.74)	0.57
Model 4	1.49 (0.53, 4.30)	0.82 (0.27, 2.50)	1.32 (0.40, 4.47)	0.62
Polycose quartile	2	3	4	
Model 1	0.65 (0.19, 2.15)	0.85 (0.25, 2.86)	0.89 (0.26, 2.98)	0.91
Model 2	0.69 (0.20, 2.34)	0.95 (0.27, 3.34)	0.95 (0.28, 3.22)	0.93
Model 3	0.71 (0.20, 2.52)	0.98 (0.28, 3.43)	0.86 (0.24, 3.03)	0.95
Model 4	0.77 (0.21, 2.76)	0.97 (0.26, 3.51)	0.85 (0.23, 3.06)	0.97
Prepartum blood glucose 4– 7mmol/L	Out of range: in range			
Model 1	0.80 (0.35, 1.80)			0.59
Model 2	0.76 (0.32, 1.73)			0.51
Model 3	0.78 (0.33, 1.78)			0.56
Model 4	0.74 (0.31, 1.70)			0.48

Data are odds ratio with 95% confidence interval

Referent is quartile 1 for HbA1c and polycose.

Model1 adjusted for New Zealand Deprivation Index (NZDPI). Model 2 adjusted for NZDPI, gestation, birthweight z score. Model 3 adjusted for NZDPI, maternal BMI category at booking. Model 4 adjusted for NZDPI, maternal BMI category at booking, gestation, birthweight z score.

Maternal HbA1c results available for 152 mothers of 157 children.

Polycose results available for 142 mothers of 144 children.

Prepartum blood glucose concentrations available for 130 mothers of 131 children.