National Institutes of Health
Turning Discovery Into Health

NIHMS PDF Receipt

Journal title:	Early human development
Manuscript title:	Maternal glycemic control in diabetic pregnancies and neurodevelopmental outcomes in preschool aged children. A prospective cohort study
Submitter:	Author support, Elsevier
NIHMSID:	1520547

Manuscript Files

Type	Label	File Name	Upload Date
Manuscript		EHD_4731.pdf	2019-02-01 23:34:24

This PDF receipt will be used only as the basis for generating PubMed Central (PMC) documents and will not appear on PMC. The PMC-ready documents will be made available for review after conversion. Any necessary corrections can be made at that time. No materials will be released to PMC without the Reviewer's approval.

Accepted Manuscript

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

Rebecca J. Griffith, Jane E. Harding, Christopher J.D. McKinlay, Trecia A. Wouldes, Deborah Harris, Jane M. Alsweiler

PII: S0378-3782(18)30263-9
DOI: doi:10.1016/j.earlhumdev.2019.01.010
Reference: EHD 4731

Published in: *Early Human Development*

Received date: 11 May 2018
Revised date: 3 January 2019
Accepted date: 14 January 2019

Cite this article as: Griffith RJ, Harding JE, McKinlay CJD, Wouldes TA, Harris D, Alsweiler JM, Maternal glycemic control in diabetic pregnancies and neurodevelopmental outcomes in preschool aged children. A prospective cohort study, *Early Human Development*, doi:10.1016/j.earlhumdev.2019.01.010

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2019 Published by Elsevier Ltd.

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

Rebecca J. Griffith MBChB [1], Jane E. Harding DPhil [2], Christopher J.D. McKinlay PhD [1,2], Trecia A. Wouldes PhD [3], Deborah Harris PhD [2,4], Jane M. Alsweiler PhD [1,2] for the CHYLD Study Team.

[1]Department of Paediatrics, University of Auckland, Auckland, New Zealand

[2]Liggins Institute, University of Auckland, Auckland, New Zealand

[3]Department of Psychological Medicine, University of Auckland, Auckland, New Zealand

[4]Newborn Intensive Care Unit Waikato District Health Board, Hamilton, New Zealand

Conflicts of interest

Declarations of interest: none

Author contributions. RG, JA had full access to all of the data in the study. RG, DH, JA, JH and TW were involved with the acquisition of data. RG, JA, JH, and CM were involved in the analysis, interpretation and statistical analysis of data.
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.

The results of this study were presented at the Perinatal Society of Australia and New Zealand Annual Congress, Canberra, 2nd -5th April 2017.

Corresponding author: Jane Alsweiler

Department of Paediatrics: Child and Youth Health, University of Auckland, Private Bag 92019, Auckland 1142, New Zealand

Phone: +649 373 7599

Fax: +649 373 7486

Email: j.alsweiler@auckland.ac.nz

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.

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 <15th 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 <8.2mmol/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/m^2), overweight (25-30 kg/m^2) or obese (>30 kg/m^2). 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 polycose 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.

Sources of funding:

Funding/Support. RG held a research fellowship from the New Zealand Diabetes Foundation. The CHYLD study was supported by grant R01HD069622 from the Eunice Kennedy Shriver National Institute of Child Health and Human Development, by grant 10-399 from the Health Research Council of New Zealand, by the Auckland Medical Research Foundation, and by Gravida, National Research Centre for Growth and Development, New Zealand. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Eunice Kennedy Shriver National Institute of Child Health and Human Development or the National Institutes of Health. None of the funders had any role in the study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the article for publication.

Acknowledgements. We are grateful to the children and families who participated in the CHYLD study and The Children with Hypoglycemia and Their Later Development (CHYLD) Study Team:

Liggins Institute, The University of Auckland, Auckland, New Zealand: Judith Ansell, PhD, Anne Jaquiery, PhD, Kelly Jones, PhD, Sapphire Martin, BNurs, Christina McQuoid, DipEdPsych, Jenny Rogers, MHSc, Heather Stewart, Anna Tottman, MBBS, Kate Williamson, MBBS, Ellen Campbell, PhD, Coila Bevan, BA, Tineke Crawford, Kelly Fredell, BNurs, Kate Sommers, Claire Hahnhaussen, BSc, Safayet Hossin, MSc, Karen Frost, BSc, Grace McKnight, Janine Paynter, PhD, Jess Wilson, MSc, Rebecca Young, BEd, Anna Gsell, PhD, and Jessica Brosnahan, MHSc.

Waikato Hospital, Hamilton, New Zealand: Anna Timmings, MBChB, Arun Nair,MD, Alexandra Wallace, PhD, and Phil Weston, MBChB. University of Canterbury, Christchurch, New Zealand: Aaron Le Compte, PhD, and Matthew Signal, PhD. Canterbury District Health Board, Christchurch, New Zealand: Nicola Austin, DM. Bay of Plenty District Health Board, Tauranga, New Zealand: Jeremy Armishaw, MBChB. Mid-Central District Health Board, Palmerston North, New Zealand: Nicola Webster, MBBS. Women's and Children's Hospital, Adelaide, Australia: Ross Haslam, MBBS, and Pat Ashwood, BSc. Royal Women's Hospital, Melbourne, Australia: Lex Doyle, MD, and Kate Callanan. John Hunter Children's Hospital, Newcastle, Australia: Ian Wright, MBChB.

Steering Group

University of Auckland (Auckland, New

Zealand): Jane Alsweiler, MBChB, PhD, Jane Harding, MBChB, DPhil (Chair), Ben Thompson, BSc, PhD, Trecia Wouldes, BA, MA, PhD; University of Canterbury (Christchurch, New Zealand): J. Geoffrey Chase, BS, MS, PhD; Waikato District Health Board (Hamilton, New Zealand): Deborah Harris, Dip Nursing, MHSc (Hons), PhD.

International Advisory Group

Stanford University School of Medicine (Stanford, California): Heidi Feldman, MD, PhD, Darrell Wilson, BS, MD; University of Colorado School of Medicine (Denver, Colorado): William Hay, BA, MD; McGill University (Montreal, Canada): Robert Hess, BSc, MSc, PhD, DSc.

Conflict of Interest Statement: None declared

References

[1] R.C. Temple, M. Hardiman, M. Pellegrini, L. Horrocks, M.-T. Martinez-Cengotitabengoa, Cognitive function in 6- to 12-year-old offspring of women with Type 1 diabetes., Diabet. Med. 28 (2011) 845–8. doi:10.1111/j.1464-5491.2011.03285.x.

[2] Y. Yamashita, Y. Kawano, N. Kuriya, Y. Murakami, T. Matsuishi, K. Yoshimatsu, H. Kato, Intellectual development of offspring of diabetic mothers., Acta Paediatr. 85 (1996) 1192–6. http://www.ncbi.nlm.nih.gov/pubmed/8922082.

[3] C.J. Sells, N.M. Robinson, Z. Brown, R.H. Knopp, Long-term developmental follow-up of infants of diabetic mothers, J. Pediatr. 125 (1994) S9–S17. doi:10.1016/S0022-3476(94)70170-9.

[4] B.L. Silverman, T. Rizzo, O.C. Green, N.H. Cho, R.J. Winter, E.S. Ogata, G.E. Richards, B.E. Metzger, Long-term prospective evaluation of offspring of diabetic mothers., Diabetes. 40 Suppl 2 (1991) 121–125. doi:10.2337/diab.40.2.S121.

[5] B.L. Silverman, T.A. Rizzo, N.H. Cho, B.E. Metzger, Long-term effects of the intrauterine environment: The northwestern university diabetes in pregnancy center, in: Diabetes Care, 1998.

[6] M. Brinciotti, M. Matricardi, A. Colatrella, F. Torcia, F. Fallucca, A. Napoli, Visual evoked potentials in infants of diabetic mothers: relations to clinical and metabolic status during pregnancy and delivery, Clin Neurophysiol. 120 (2009)

563–568. doi:https://doi.org/10.1016/j.clinph.2008.12.028.

[7] A. Ornoy, N. Ratzon, C. Greenbaum, E. Peretz, D. Soriano, M. Dulitzky, Neurobehaviour of school age children born to diabetic mothers., Arch. Dis. Child. Fetal Neonatal Ed. 79 (1998) F94-9. doi:10.1136/fn.79.2.F94.

[8] N. Ratzon, C. Greenbaum, M. Dulitzky, A. Ornoy, Comparison of the motor development of school-age children born to mothers with and without diabetes mellitus, Phys. Occup. Ther. Pediatr. 20 (2000) 43–57. doi:10.1080/J006v20n01_04.

[9] S. Knorr, T.D. Clausen, Z. Vlachová, B. Bytoft, P. Damm, H. Beck-Nielsen, D.M. Jensen, S. Juul, C.H. Gravholt, Academic achievement in primary school in offspring born to mothers with type 1 diabetes (the EPICOM study): A register-based prospective cohort study., Diabetes Care. 38 (2015) 1238–44. doi:10.2337/dc15-0223.

[10] G.L. Nielsen, E. Andersen, S. Lundbye-Christensen, Maternal blood glucose in diabetic pregnancies and cognitive performance in offspring in young adulthood: A Danish cohort study, Diabet. Med. 27 (2010) 786–790. doi:10.1111/j.1464-5491.2010.03024.x.

[11] M.B. Landon, S.G. Gabbe, L. Sachs, Management of diabetes mellitus and pregnancy: a survey of obstetricians and maternal-fetal specialists., Obstet. Gynecol. 75 (1990) 635–640. http://www.ncbi.nlm.nih.gov/pubmed/2179778 (accessed July 16, 2018).

[12] N.W. Cheung, The management of gestational diabetes., Vasc. Health Risk Manag. 5 (2009) 153–64. http://www.ncbi.nlm.nih.gov/pubmed/19436673 (accessed March 15, 2018).

[13] K.P. Singh, F. Rahimpanah, M. Barclay, Metformin for the management of

gestational diabetes mellitus, Aust. New Zeal. J. Obstet. Gynaecol. 55 (2015) 303–308. doi:10.1111/ajo.12311.

[14] D.R. Coustan, L.P. Lowe, B.E. Metzger, A.R. Dyer, The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study: paving the way for new diagnostic criteria for gestational diabetes mellitus, Am. J. Obstet. Gynecol. 202 (2010) 654.e1-6. doi:10.1016/j.ajog.2010.04.006.

[15] WHO, Diagnostic Criteria and Classification of Hyperglycaemia First Detected in Pregnancy, n.d. http://apps.who.int/iris/bitstream/10665/85975/1/WHO_NMH_MND_13.2_eng.pdf?ua=1 (accessed March 2, 2018).

[16] G.L. Nielsen, C. Dethlefsen, H.T. Sørensen, J.F. Pedersen, L. Molsted-Pedersen, Cognitive function and army rejection rate in young adult male offspring of women with diabetes: a Danish population-based cohort study, Diabetes Care. 30 (2007) 2827–2831. doi:10.2337/dc07-1225.

[17] T.D. Clausen, E.L. Mortensen, L. Schmidt, E.R. Mathiesen, T. Hansen, D.M. Jensen, P. Damm, Cognitive function in adult offspring of women with gestational diabetes-the role of glucose and other factors, PLoS One. 8 (2013) 2–9. doi:10.1371/journal.pone.0067107.

[18] J.M. Kerstjens, A.F. de Winter, K.M. Sollie, I.F. Bocca-Tjeertes, M.R. Potijk, S.A. Reijneveld, A.F. Bos, Maternal and pregnancy-related factors associated with developmental delay in moderately preterm-born children., Obstet. Gynecol. 121 (2013) 727–733. doi:10.1097/AOG.0b013e3182860c52.

[19] P. Krakowiak, C.K. Walker, A.A. Bremer, A.S. Baker, S. Ozonoff, R.L. Hansen, I. Hertz-Picciotto, Maternal metabolic conditions and risk for autism and other neurodevelopmental disorders, Pediatrics. 129 (2012) e1121–e1128.

doi:10.1542/peds.2011-2583.

[20] E. Basatemur, J. Gardiner, C. Williams, E. Melhuish, J. Barnes, A. Sutcliffe, Maternal prepregnancy BMI and child cognition: a longitudinal cohort study., Pediatrics. 131 (2013) 56–63. doi:10.1542/peds.2012-0788.

[21] M. Casas, L. Chatzi, A.-E. Carsin, P. Amiano, M. Guxens, M. Kogevinas, K. Koutra, N. Lertxundi, M. Murcia, M. Rebagliato, I. Riano, C.L. Rodriguez-Bernal, T. Roumeliotaki, J. Sunyer, M. Mendez, M. Vrijheid, Maternal pre-pregnancy overweight and obesity, and child neuropsychological development: two Southern European birth cohort studies, Int. J. Epidemiol. 42 (2013) 506–517. doi:10.1093/ije/dyt002.

[22] J.B. Helderman, T.M. O'Shea, K.C.K. Kuban, E.N. Allred, J.L. Hecht, O. Dammann, N. Paneth, T.F. McElrath, A. Onderdonk, A. Leviton, ELGAN study Investigators, Antenatal antecedents of cognitive impairment at 24 months in extremely low gestational age newborns., Pediatrics. 129 (2012) 494–502. doi:10.1542/peds.2011-1796.

[23] S. Hinkle, L. Schieve, A. Stein, D. Swan, U. Ramakrishnan, A. Sharma, Associations between maternal prepregnancy body mass index and child neurodevelopment at 2 years of age HHS Public Access, Int J Obes. 36 (2012) 1312–1319. doi:10.1038/ijo.2012.143.

[24] M. Bliddal, J. Olsen, H. Støvring, H.-L.F. Eriksen, U.S. Kesmodel, T.I.A. Sørensen, E.A. Nøhr, Maternal pre-pregnancy BMI and Intelligence Quotient (IQ) in 5-year-old children: A cohort based study, PLoS One. 9 (2014) e94498. doi:10.1371/journal.pone.0094498.

[25] S.H. Gage, D.A. Lawlor, K. Tilling, A. Fraser, Associations of maternal weight gain in pregnancy with offspring cognition in childhood and adolescence:

Findings from the Avon Longitudinal Study of Parents and Children, Am. J. Epidemiol. 177 (2013) 402–410. doi:10.1093/aje/kws239.

[26] L. Huang, X. Yu, S. Keim, L. Li, L. Zhang, J. Zhang, Maternal prepregnancy obesity and child neurodevelopment in the Collaborative Perinatal Project, Int. J. Epidemiol. 43 (2014) 783–792. doi:10.1093/ije/dyu030.

[27] Y.H. Neggers, R.L. Goldenberg, S.L. Ramey, S.P. Cliver, Maternal prepregnancy body mass index and psychomotor development in children, Acta Obstet. Gynecol. Scand. 82 (2003) 235–240. doi:10.1034/j.1600-0412.2003.00090.x.

[28] D. Shin, W.O. Song, Prepregnancy body mass index is an independent risk factor for gestational hypertension, gestational diabetes, preterm labor, and small- and large-for-gestational-age infants, J. Matern. Neonatal Med. 28 (2015) 1679–1686. doi:10.3109/14767058.2014.964675.

[29] L. Mclaren, Socioeconomic Status and Obesity, Epidemiol. Rev. 29 (2007) 29–48. doi:10.1093/epirev/mxm001.

[30] Y. Wang, M.A. Beydoun, The Obesity Epidemic in the United States Gender, Age, Socioeconomic, Racial/Ethnic, and Geographic Characteristics: A Systematic Review and Meta-Regression Analysis, Epidemiol. Rev. 29 (2007) 6–28. doi:10.1093/epirev/mxm007.

[31] E. Njenga, T. Lind, R. Taylor, Five year audit of peripartum blood glucose control in type 1 diabetic patients, Diabet. Med. 9 (1992) 567–570. doi:10.1111/j.1464-5491.1992.tb01840.x.

[32] H.L. Barrett, J. Morris, A. McElduff, Watchful waiting: A management protocol for maternal glycaemia in the peripartum period, Aust. New Zeal. J. Obstet. Gynaecol. 49 (2009) 162–167. doi:10.1111/j.1479-828X.2009.00969.x.

[33] R. Taylor, C. Lee, D. Kyne-Grzebalski, S.. Marshall, J.. Davison, Clinical outcomes of pregnancy in women with type 1 diabetes, Obstet. Gynecol. 99 (2002) 537–541. doi:10.1016/S0029-7844(01)01790-2.

[34] J.A. Flores-le Roux, E. Sagarra, D. Benaiges, E. Hernandez-Rivas, J.J. Chillaron, J. Puig de Dou, A. Mur, M.A. Lopez-Vilchez, J. Pedro-Botet, A prospective evaluation of neonatal hypoglycaemia in infants of women with gestational diabetes mellitus., Diabetes Res. Clin. Pract. 97 (2012) 217–22. doi:10.1016/j.diabres.2012.03.011.

[35] S.C. Brown, D. Kyne-Grzebalski, B. Mwangi, R. Taylor, Effect of management policy upon 120 Type 1 diabetic pregnancies: policy decisions in practice, Diabet. Med. 16 (1999) 573–578. doi:10.1046/j.1464-5491.1999.00124.x.

[36] G.A. Kline, A. Edwards, Antepartum and intra-partum insulin management of type 1 and type 2 diabetic women: Impact on clinically significant neonatal hypoglycemia, Diabetes Res. Clin. Pract. 77 (2007) 223–230. doi:10.1016/j.diabres.2006.10.024.

[37] M. Balsells, R. Corcoy, J.M. Adelantado, A. Garcia-Patterson, O. Altirriba, A. de Leiva, Gestational diabetes mellitus: metabolic control during labour., Diabetes. Nutr. Metab. 13 (2000) 257–262.

[38] C.J.D. McKinlay, J.M. Alsweiler, J.M. Ansell, N.S. Anstice, J.G. Chase, G.D. Gamble, D.L. Harris, R.J. Jacobs, Y. Jiang, N. Paudel, M. Signal, B. Thompson, T. a. Wouldes, T.-Y. Yu, J.E. Harding, Neonatal glycemia and neurodevelopmental outcomes at 2 years, N. Engl. J. Med. 373 (2015) 1507–1518. doi:10.1056/NEJMoa1504909.

[39] C.J.D. McKinlay, J.M. Alsweiler, N.S. Anstice, N. Burakevych, A. Chakraborty, J.G. Chase, G.D. Gamble, D.L. Harris, R.J. Jacobs, Y. Jiang, N. Paudel, R.J.

San Diego, B. Thompson, T.A. Wouldes, J.E. Harding, Association of neonatal glycemia with neurodevelopmental outcomes at 4.5 years, JAMA Pediatr. 85 (2017) 172–176. doi:10.1001/jamapediatrics.2017.1579.

[40] D. Wechsler, The Wechsler Preschool and Primary Scale of Intelligence-3rd edition, The Psychological Corporation, San Antonio, Texas, 2002.

[41] K. Beery, N. Buktenica, N. Beery, The Beery–Buktenica Developmental Test of Visual–Motor Integration: Administration, scoring, and teaching manual (6th ed.), Pearson, Minneapolis, 2010.

[42] S. Henderson, D. Sugden, A. Barnett, Movement Assessment Battery for Children-2, Harcourt Assessment, London, England, 2007.

[43] T.-Y.Y. Yu, R.J. Jacobs, N.S. Anstice, N. Paudel, J.E. Harding, B. Thompson, CHYLD Study Team, Global motion perception in 2-year-old children: a method for psychophysical assessment and relationships with clinical measures of visual function., Invest. Ophthalmol. Vis. Sci. 54 (2013) 8408–8419. doi:10.1167/iovs.13-13051.

[44] N. Bayley, Bayley Scales of Infant and Toddler Development—Third Edition, Harcourt Assessment, San Antonio, Texas, 2006.

[45] C. Salmond, P. Crampton, J. Atkinson, NZDep2006 Index of Deprivation, 2007. http://www.otago.ac.nz/wellington/otago020348.pdf (accessed August 23, 2017).

[46] N.D.C. Sturrock, T.N. Fay, N. Pound, B.A. Kirk, L.E. Danks, Analysis of 44 279 blood glucose estimations in relation to outcomes in 80 pregnant diabetic women, J. Obstet. Gynaecol. (Lahore). 21 (2001) 253–257.

[47] T. Rizzo, N. Freinkel, B.E. Metzger, R. Hatcher, W.J. Burns, P. Barglow, Correlations between antepartum maternal metabolism and newborn behavior,

Am J Obs. Gynecol. 163 (1990) 1458–1464.

[48] A. Fraser, C. Almqvist, H. Larsson, N. Långström, D. a. Lawlor, Maternal diabetes in pregnancy and offspring cognitive ability: Sibling study with 723,775 men from 579,857 families, Diabetologia. 57 (2014) 102–109. doi:10.1007/s00125-013-3065-z.

[49] A. Kerssen, H.W. de Valk, G.H.A. Visser, Do HbA1c levels and the self-monitoring of blood glucose levels adequately reflect glycaemic control during pregnancy in women with type 1 diabetes mellitus?, Diabetologia. 49 (2006) 25–28. doi:10.1007/s00125-005-0057-7.

[50] R. Derr, E. Garrett, G.A. Stacy, C.D. Saudek, Is HbA1c affected by glycemic instability?, Diabetes Care. 26 (2003) 2728–2733. http://care.diabetesjournals.org/content/26/10/2728 (accessed August 27, 2017).

[51] T.D. Carver, S.M. Anderson, P.W. Aldoretta, W.W. Hay, Effect of low-level basal plus marked “pulsatile” hyperglycemia on insulin secretion in fetal sheep, Am. J. Physiol. - Endocrinol. Metab. 271 (1996) E865–E871. http://ajpendo.physiology.org/content/271/5/E865 (accessed June 3, 2017).

[52] NICE guideline NG3, Diabetes in pregnancy: management from preconception to the postnatal period | Guidance and guidelines | NICE, Natl. Inst. Heal. Care Excell. (2015). https://www.nice.org.uk/guidance/ng3 (accessed August 11, 2016).

[53] J.A. Flores-Le Roux, J.J. Chillaron, A. Goday, J. Puig De Dou, A. Paya, M.A. Lopez-Vilchez, J.F. Cano, Peripartum metabolic control in gestational diabetes, Am. J. Obstet. Gynecol. 202 (2010) 568.e1-568.e6. doi:10.1016/J.AJOG.2010.01.064.

Appendix.

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

Outcome	***Number (%)***
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

[a]Data missing for 2

[b]Data 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)

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.

Characteristic	***Total***	***Gestational diabetes***	***Type 1 diabetes***	***Type 2 diabetes***	***P value***
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]	42.4 (10.4) 6.0% (1.0)	40.7 (8.6) 5.9% (0.8)	52.4 (17.0) 7.0% (1.6)	48.0 (10.6) 6.5% (1.0)	<0.01[3]
Polycose 1 hour					

result, mmol/L and mg/dL[e]		9.3 (2.4) 188 (42)	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]
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

Outcome	***All types***	***Gestational diabetes***	***Type 1 diabetes***	***Type 2 diabetes***	***P value***
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.

HbA1c quartile	***1***	***2***	***3***	***4***	**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	
Polycose quartile	*1*	*2*	*3*	*4*	
Neurosensory	10 (42) [24]	10 (36) [28]	10 (42) [24]	11 (44.0)	0.94

impairment				[25]	
		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
		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	
Prepartum blood glucose 4-7mmol/L	*In range*		*Out of range*		
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.

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

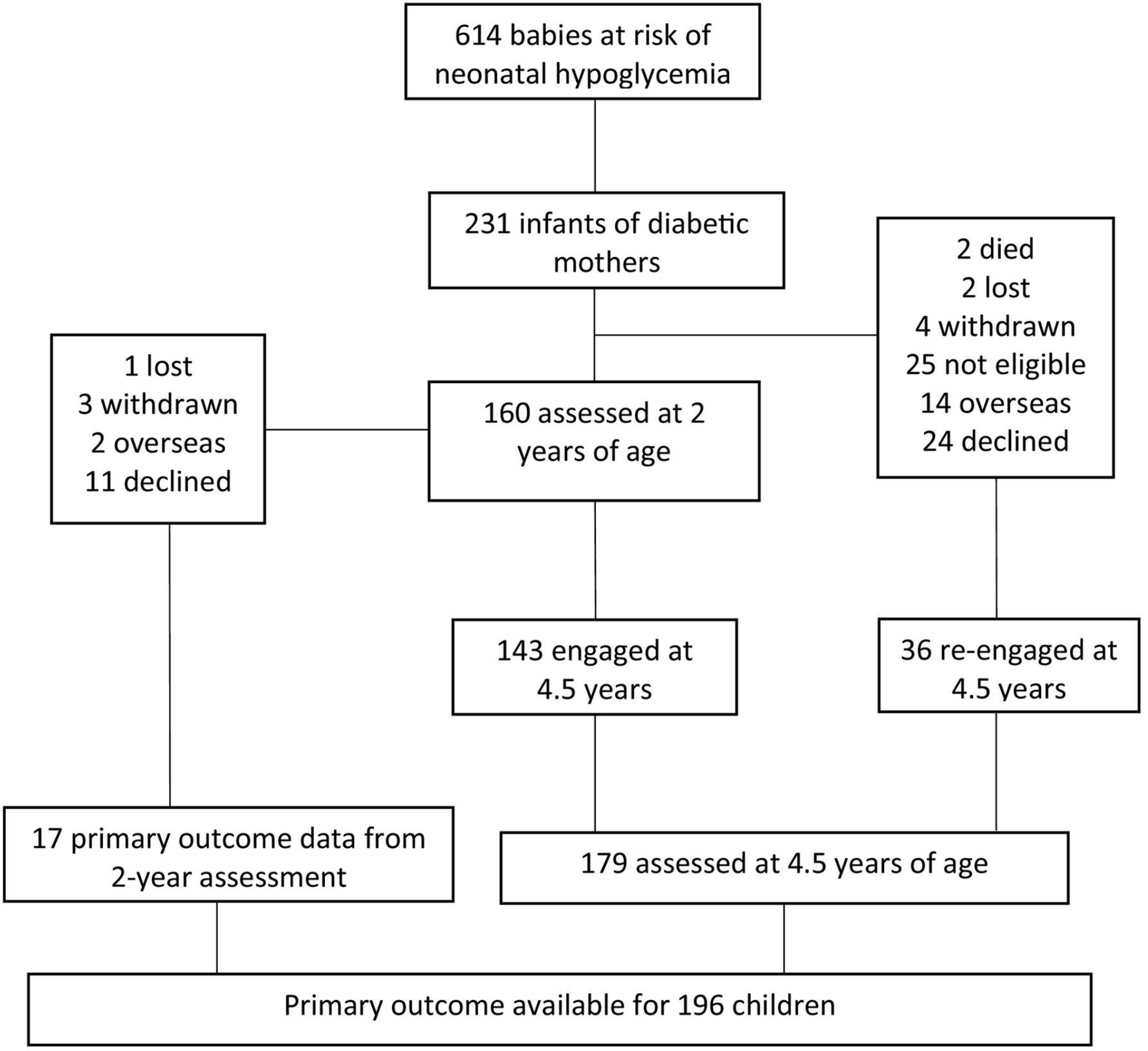
614 babies at risk of neonatal hypoglycemia
231 infants of diabetic mothers
2 died
2 lost
4 withdrawn
25 not eligible
14 overseas
24 declined
1 lost
3 withdrawn
2 overseas
11 declined
160 assessed at 2 years of age
143 engaged at 4.5 years
36 re-engaged at 4.5 years
17 primary outcome data from 2-year assessment
179 assessed at 4.5 years of age
Primary outcome available for 196 children

Figure 1