The prevention of adverse neurodevelopmental outcomes in children born to diabetic mothers

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Abstract

Diabetes during pregnancy, mainly due to gestational diabetes mellitus (GDM), is common and associated with a higher risk of impaired neurodevelopment in the offspring in later life. Currently, there are no interventions to reduce the risk of neurodevelopmental impairment in children born to mothers with diabetes. The studies in this thesis aimed to determine if there were antenatal interventions that could reduce the incidence of GDM, if maternal glycaemic control during pregnancy and labour was associated with later neurodevelopment and if prophylactic dextrose gel one hour after birth to prevent neonatal hypoglycaemia improved neurodevelopment in early childhood.

In a prospective cohort study of infants born to mothers with diabetes, glycaemic control in pregnancy was not associated with the children's neurodevelopment at four and half years of age. This suggests that preventing the development of GDM may be a better alternative than interventions during pregnancy to improve neurodevelopmental outcomes. However, as part of our Cochrane overview investigating effective strategies for the prevention of GDM, we found no interventions that were of clear benefit in reducing the incidence of GDM. In particular, there were no trials of interventions before or between pregnancies to reduce the risk of GDM.

The prospective follow-up of children from two randomised controlled trials of prophylactic oral dextrose gel to prevent neonatal hypoglycaemia, one of different doses of dextrose gel and one in children of diabetic mothers, showed that these interventions did not result in improved neurodevelopmental outcomes at age two years but, reassuringly, did not cause adverse effects. Neonatal hypoglycaemia in infants of diabetic mothers was associated with neurosensory impairment at age two years.

These studies suggest that in children born to mothers with GDM the risk of neurosensory impairment is higher in the context of neonatal hypoglycaemia but is not associated with maternal glycaemic control in pregnancy or labour. Prophylactic oral dextrose gel, which previously has been shown to reduce neonatal hypoglycaemia, did not reduce the incidence of neurosensory impairment. Interventions to prevent GDM pre-conception should be tested in randomised controlled trials to reduce the number of children born at risk of impaired neurodevelopment.

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Table of Contents

List of Tables

List of Figures

Abbreviations

ACTRN	Australian clinical trials registration number
BABIES	Babies and blood sugar's influence on EEG study
BGC	Blood glucose concentration(s)
BMI	Body mass index
BRIEF	Behaviour rating inventory of executive function
BRIEF-P	Behaviour rating inventory of executive function- preschool version
BSID	Bayley scales of infant development
Chi^2	Chi-squared test
CHYLD	Children with hypoglycaemia and their later development study
CI	Confidence interval
cm	Centimetre
df	Degrees of freedom
DHA	Docosahexaenoic acid
EEG	Electroencephalogram
EF	Executive function
EPA	Eicosapentaenoic acid
g	Gram
GDM	Gestational diabetes mellitus
GEC	Global executive composite
GRADE	Grades of recommendation, assessment, development and evaluation
HbA1c	Glycated haemoglobin
hPOD	Hypoglycaemia prevention in newborns with oral dextrose study

I^2	Fraction of variance due to heterogeneity in meta-analyses
IDM	Infant of diabetic mother
IgG	Immunoglobulin G
IQ	Intelligence quotient
kg	Kilogram
L	Litre
LGA	Large for gestational age
logMAR	Logarithm of the minimum angle of resolution
m	Metre
MBAC-2	Movement assessment battery for children
MD	Mean difference
mg	Milligram
ml	Millilitre
mmol	Millimole
MSML	Multi-search multi-location task
NA	Not available
NC	Not calculable
NHI	National health index number, assigned to each user of health services in NZ
NICE	The national institute for health and care excellence (UK)
NICU	Neonatal intensive care
NZDPI	New Zealand deprivation index
OR	Odds ratio
PCOS	Polycystic ovarian syndrome

p value	Probability value
pre-hPOD	Hypoglycaemia prevention in newborns with oral dextrose dosage study
RCT	Randomised controlled trial
RDK	Random dot kinematograms
ROBIS	Risk of bias in systematic reviews assessment tool
RR	Relative risk
SCORAD	Severity Scoring of Atopic Dermatitis index
SD	Standard deviation
SDQ	Strength and difficulties questionnaire
SEIFA	Socio-economic indexes for areas, Australian bureau of statistics
SGA	Small for gestational age
SComQ	Social Communication Questionnaire
SQL	Structured query language database
T score	Standard score, t= (z-score x10) + 50
WHO	World health organisation
WPPSI	Wechsler Preschool and Primary Scale of Intelligence
z-score	Standard score

1 Introduction

1.1 Diabetes in pregnancy

Diabetes prevalence has been increasing since the 1960s with an estimated 450 million adults having diabetes worldwide (Ogurtsova et al., 2017). The increasing number of women of child-bearing age with diabetes means that diabetes in pregnancy has also become increasingly common. Approximately 17% of pregnancies (20.9 million live births) worldwide are complicated by diabetes (Goldenberg, McClure, Harrison, & Miodovnik, 2016) with an estimated 85% having their onset during pregnancy, known as gestational diabetes mellitus (GDM) (Ogurtsova et al., 2017). The incidence of GDM varies according to the diagnostic threshold as well as country and ethnicity (Farrar et al., 2016; HAPO Study Cooperative Research Group, 2008; Pu et al., 2015) with 12% of pregnancies affected in 2019 in New Zealand (National Women's Health, 2019), an increase from 6.2% in 2010 (R. L. Lawrence, Wall, & Bloomfield, 2019).

The incidence of GDM is strongly correlated with the prevalence of obesity (Chu et al., 2007), which has been increasing worldwide (Flegal, Carroll, Ogden, & Curtin, 2010; Jones Nielsen et al., 2013) including obesity in pregnant women (Fisher, Kim, Sharma, Rochat, & Morrow, 2013). Nearly a third of New Zealand adults are now obese, but the proportion affected is higher in Pacific Islander (63%) and Māori (48%) adults (Ministry of Health, 2020).

Complications of diabetes in pregnancy include an increased risk of pre-eclampsia and induction of labour (Dodd, Crowther, Antoniou, Baghurst, & Robinson, 2007). The infants are at increased risk of being born large for gestational age (Sacks, Black, Li, Montoro, & Lawrence, 2015) with higher risk of birth injuries, and also at higher risk of developing respiratory distress syndrome, jaundice and hypoglycaemia (Crowther et al., 2005; González-Quintero et al., 2007; Landon et al., 2009). Longer term complications for the mother include an increased risk of developing type 2 diabetes (Bellamy, Casas, Hingorani, & Williams, 2009) and for the children: obesity; metabolic syndrome and diabetes (Boney, Verma, Tucker, & Vohr, 2005) and possibly adverse neurodevelopment (Bolaños, Matute, Ramírez-Dueñas, & Zarabozo, 2015).

1.1.1 Maternal metabolism during pregnancy

In order to provide the necessary nutrition to the growing fetus, maternal metabolism, including insulin sensitivity, alters over the course of pregnancy with changes in glucose, lipid and amino acid metabolism (Q. Wang et al., 2016). During the first trimester of pregnancy, there is normal or increased insulin sensitivity (Catalano, Tyzbir, Roman, Amini, & Sims, 1991; Catalano et al., 1993, 1992). Adipocytes hypertrophy with increasing numbers of insulin receptors on the cells as fat stores are laid down during the first two trimesters. All plasma lipid components increase after the first trimester (Butte, 2000), but the largest increase is seen in triglycerides. ß-cell adaptation occurs (Van Assche, Aerts, & De Prins, 1978) with cell proliferation, hypertrophy and hyperplasia (Van Assche et al., 1978), increased insulin synthesis (Weinhaus, Stout, & Sorenson, 1996) and secretion (Sorenson, Brelje, & Roth, 1993), leading to improved utilisation and oxidation of glucose. By 14 weeks' gestation, the first phase of insulin secretion in response to a glucose load increases by approximately 120% (Bowes et al., 1996; Catalano et al., 1993). The plasma glucose concentration falls by 0.6-0.8 mmol/L with the increased insulin secretion (Catalano et al., 1992).

The increased insulin sensitivity of the first trimester is followed by increasing insulin resistance in the 2nd and 3rd trimesters (Catalano et al., 1991, 1993, 1992; Ryan, O'Sullivan, & Skyler, 1985). In late pregnancy, there is reduced expression of the glucose transporter (GLUT) 4 in adipocytes (Okuno et al., 1995) with resulting reduced maternal uptake of glucose from the circulation. Skeletal muscle insulin resistance is more affected than adipose tissue in experimental animals (Leturque et al., 1986). Oestrogen, progesterone and human placental lactogen increase during pregnancy and are associated with changes in maternal metabolic parameters (Desoye, Schweditsch, Pfeiffer, Zechner, & Kostner, 1987). Additionally, circulating concentrations of cortisol double during pregnancy, which reduce insulin receptor signalling (Giorgino, Almahfouz, Goodyear, & Smith, 1993). Progesterone (Parker Jr, Everett, Quirk, Whalley, & Gant, 1979) reduces insulin binding and glucose transport and impairs insulin suppression of hepatic gluconeogenesis in experimental animals (T. Nelson, Shulman, Grainger, & Diamond, 1994). Despite the rising progesterone concentrations, gluconeogenesis rates in late gestation are increased compared to early gestation (Catalano et al., 1992; Kalhan, Rossi, Gruca, Burkett, & O'Brien, 1997) providing for increased fetal requirements. High circulating oestrogen concentrations in pregnancy induce increased synthesis and reduction in clearance of triacylglyerols in experimental animals (Ginci, Arezzini, Terzuoli, Pizzichini, &

Marinello, 1997). Human placental lactogen, promotes production of insulin like growth factors and reduces insulin sensitivity while stimulating insulin production and secretion and increasing lipolysis in adipocytes (Handwerger & Freemark, 2000). The overall result is lipid component concentrations are higher in mid and late pregnancy compared to non-pregnant normal concentrations (Dathan-Stumpf et al., 2019). Glucagon concentrations also increase after the first trimester potentially adding to insulin resistance (Luyckx, Gerard, Gaspard, & Lefebvre, 1975).

There is evidence of a difference in maternal metabolism during pregnancy between those carrying male and female fetuses. Higher blood glucose concentrations (BGC) are seen in overweight or obese mothers carrying female fetuses compared to male fetuses (Seneviratne et al., 2017), but there are conflicting results in regard to the relationship between fetal sex and maternal insulin resistance or future risk of diabetes (Jaskolka, Retnakaran, Zinman, & Kramer, 2015; Retnakaran et al., 2015; Retnakaran & Shah, 2015; Seneviratne et al., 2017; Walsh, Segurado, Mahony, Foley, & McAuliffe, 2015; H. Yamashita et al., 2020).

1.1.2 Maternal metabolism in gestational diabetes mellitus

During pregnancy maternal insulin resistance increases as the pregnancy advances (Catalano, Drago, & Amini, 1998). With pre-existing diabetes mellitus or the development of GDM, insulin resistance is further increased with resultant increased BGC, and glycated haemoglobin (HbA1c). Increased insulin resistance in GDM is partially mediated by a further reduction of tyrosine phosphorylation of IRS-1 in skeletal muscle compared to that seen in normal pregnancy (Friedman et al., 1999). In pregnancies complicated by GDM, the increase in first phase insulin secretion in response to a glucose load is attenuated compared to normal pregnancies despite similar responses in the pre-conception period (Catalano et al., 1993). Inadequate adaptation of ß-cells leads to impaired glucose homeostasis as insulin secretion is no longer able to keep up with the increasing insulin resistance (Buchanan, 2001). Suppression of endogenous hepatic glucose production is impaired in GDM leading to postprandial hyperglycaemia (Catalano et al., 1993). Plasma leptin concentration, which correlates with maternal adipose mass and insulin concentration during pregnancy is higher still in women with GDM (Kautzky-Willer et al., 2001). As such, it is a marker of insulin resistance.

Circulating lipid concentrations also change with the course of pregnancy. By the 12th week of gestation, circulating lipid concentrations, particularly triglycerides are increased further compared to normal pregnancy (Koukkou, Watts, & Lowy, 1996), as there is increased synthesis in the liver and reduced activity of lipoprotein lipase and hepatic lipase (Sattar et al., 1997). The transfer of long-chain polyunsaturated fatty acids (LCPUFA), critical in fetal and neonatal central nervous system development, is altered in GDM without the normal rise in docosahexanoic acid (DHA) or 3n- LCPUFA (J. Zhao et al., 2016), potentially impairing development in offspring of diabetic pregnancy. Cord concentrations of DHA and arachidonic acid are lower in infants born to mothers with GDM (Wijendran et al., 2000; J.-P. Zhao et al., 2014). Indeed, altered mRNA expression of genes involved in fatty acid uptake or metabolism is found in placentas of pregnancies complicated by gestation diabetes or obesity resulting in altered transfer of fatty acids compared to healthy controls with unknown effects on offspring neurodevelopment (Segura et al., 2017).

1.1.3 Definition of gestational diabetes mellitus

GDM is diabetes with onset during pregnancy and is screened for, or diagnosed, in various ways: fasting plasma glucose or 1 hour plasma glucose after screening with a 50g glucose load (polycose test), or 1 hour or 2 hour plasma glucose concentration after a 75g oral glucose tolerance test (OGTT). The definition of GDM remains controversial with some groups advocating lower thresholds for diagnosis: fasting plasma glucose 5.1 mmol/L or plasma glucose 8.5 mmol/L at 2 hours after an OGTT (Hadar & Hod, 2010; Nankervis et al., 2014)) or a fasting plasma glucose 5.6 mmol/L or 7.8 mmol/L at 2 hours after an OGTT (National Institute for Health and Care Excellence, 2015)) than the previously applied criteria of a fasting plasma glucose 5.8 mmol/L or 2 hour plasma glucose 11.1 mmol/L after a OGTT (Carpenter & Coustan, 1982; Coustan, Lowe, Metzger, & Dyer, 2010; HAPO Study Cooperative Research Group, 2008; World Health Organisation, 2013a). In 2003, the American Diabetes Association reduced the recommended lower threshold for impaired fasting glucose from a plasma glucose concentration of 110 mg/dl (6.1 mmol/l) to 100 mg/dl (5.6 mmol/l) (American Diabetes Association, 2010). The American Diabetes Association later included strategies for screening and diagnosing GDM using thresholds of a plasma glucose > 5.1 mmol/L fasting or 2 hour post 75g OGTT > 8.5 mmol/L or using a 2 step process with a 50g glucose load and if the 1 hour plasma glucose was > 7.2, 7.5 or 7.8 mmol/L to proceed to a 100g OGTT with a choice of criteria for 1 hour, 2 hour and 3 hour results (American Diabetes Association, 2018).

Adverse pregnancy outcomes (pre-eclampsia, Caesarean section, large for gestational age, shoulder dystocia or birth injury, premature delivery) are associated with progressively increasing glucose intolerance in a linear manner (HAPO Study Cooperative Research Group, 2008). Treating these milder degrees of glucose intolerance improves perinatal outcomes (Crowther et al., 2005), but it remains unclear what the criteria should be for diagnosis and treating GDM, with untreated women, and their infants, who would otherwise have received a diagnosis of GDM based on the International Association of Diabetes and Pregnancy Study Groups (IADPSPG) criteria (fasting plasma glucose ≥ 5.1, ≥ 10 at 1 hour or ≥ 8.5 mmol/L at 2 hours post 75g OGTT) being at higher risk of adverse perinatal outcomes (B. R. Shah & Sharifi, 2020). In New Zealand, where guidelines now recommend all women are screened between 24 and 28 weeks' gestation (Ministry of Health, 2014), GDM is diagnosed if OGTT fasting blood glucose is ≥ 5.5mmol/l or 2 hour glucose ≥ 9.0mmol/l (Ministry of Health, 2014). However, the New Zealand based GEMS trial is seeking to determine if using the lower IADPSG diagnostic criteria to detect and treat GDM reduces infant morbidity without increasing maternal morbidity (Crowther et al., 2020). In many countries, screening for GDM is based on the presence of risk factors, a strategy that misses more than a third of women with GDM (Benhalima et al., 2019).

1.1.4 Prevention of gestational diabetes mellitus

Risk factors for GDM include a past history of GDM (C. Kim, Berger, & Chamany, 2007), advanced maternal age, maternal high or low birthweight, high parity (Petry, 2010), polycystic ovarian syndrome (Toulis et al., 2009), a family history of first-degree relatives with GDM or type 2 diabetes (Petry, 2010), maternal overweight or obesity (Morisset et al., 2010; Torloni et al., 2009), physical inactivity before or during early pregnancy (Dempsey et al., 2004; Tobias, Zhang, van Dam, Bowers, & Hu, 2011) gestational weight gain (Morisset et al., 2010) and a past history of a macrosomic baby or a stillbirth (Petry, 2010). Some of these factors e.g. obesity and levels of physical activity are potentially modifiable through interventions initiated in the pre-conception period or during pregnancy.

Weight reduction and improved insulin sensitivity may be achieved in overweight males or females through dietary interventions to reduce calorie intake and increasing physical activity (Larson-Meyer et al., 2006). However calorie restriction is not recommended during pregnancy

(Health Service Executive, 2010; National Institute for Health and Care Excellence, 2010) due to concerns about adverse effects on offspring neurodevelopment associated with ketonaemia with severe calorie restriction (Rizzo, Metzger, Burns, & Burns, 1991). Higher fibre diets are associated with improved insulin sensitivity (Liese et al., 2005). Exercise not only increases energy consumption, but also increases insulin sensitivity through translocation of GLUT-4 receptors to the surface in skeletal muscle cells and increased glucose uptake into the cells (Etgen, Memonll, Thompson, & Ivy, 1993; Reichkendler et al., 2013).

A variety of dietary supplements may have beneficial effects contributing to reduced risk of GDM. Myo-inositol has insulin mimetic properties causing increased translocation of GLUT-4 receptors in skeletal muscle (Dang, Mukai, Yoshida, & Ashida, 2010) with increased glucose uptake into the cells. Probiotics have produced varying results in studies with some demonstrating improved glucose concentrations and body mass index (BMI) in participants with metabolic syndrome (Tenorio-Jiménez, Martínez-Ramírez, Gil, & Gómez-Llorente, 2020). Vitamin D supplementation is associated with improved insulin sensitivity and ß-cell function (Lemieux et al., 2019). Higher intakes of vitamin D prior to pregnancy are associated with reduced risk of developing GDM compared to lower intakes (Bao et al., 2017) and insulin sensitivity is inversely associated with serum vitamin D concentrations in healthy and diabetic women (Esteghamati, Aryan, Esteghamati, & Nakhjavani, 2014). Fish oils or n-3 fatty acid supplementation have had mixed results with improved serum glucose concentrations and HbA1c (Jacobo-Cejudo et al., 2017) after supplementation in adults with type 2 diabetes, but unaltered peripheral insulin sensitivity, postprandial plasma glucose, and insulin secretion in insulin resistant adults (Lalia et al., 2015).

In order to determine effective interventions to prevent GDM, pooled data from multiple high quality trials are needed to assess the size of effect and confidence in the data. An overview of published systematic reviews with meta-analysis for specific interventions related to the prevention of GDM is presented in Chapter 3.

1.1.5 Management of gestational diabetes mellitus

An overview of Cochrane systematic reviews found only one intervention, among 14 reviews of 128 trials, deemed to be of clear benefit in treating women with GDM (Martis et al., 2018). This was lifestyle change of diet and exercise which was associated with a reduced risk of

infants being born large for gestational age. Insulin therapy compared to oral medication was associated with a higher risk of hypertensive disorders in pregnancy, indicating a potential adverse effect, though whether this was due to the insulin or an association with poorer diabetic control is unclear. The American Diabetes Association recommends lifestyle change, such as exercise and nutritional changes, as the first line treatment of gestation diabetes, followed by use of insulin if lifestyle changes don't achieve good glycaemic control. Metformin or glyburide are not recommended due to concerns about offspring obesity with metformin use and neonatal hypoglycaemia and macrosomia with glyburide use (American Diabetes Association, 2020). However, the "Metformin in gestational diabetes: the offspring follow-up" study of 221 children did not indicate an increase in total or percentage body fat up to nine years of age despite the children having larger weight, arm and waist measures with maternal metformin versus insulin treatment (Rowan et al., 2018). Outcomes may be different with offspring having a higher BMI if mothers have polycystic ovarian syndrome (PCOS) and metformin is compared to placebo (Hanem et al., 2018).

Glycaemic control during pregnancy is assessed by the monitoring of fasting, preprandial and postprandial BGC (aiming for fasting BGC < 95 mg/dL (5.3 mmol/L), 1 hour postprandial BGC < 140 mg/dL (7.8 mmol/L), 2 hour postprandial BGC < 120 mg/dL (6.7 mmol/L)) and targeting HbA1c at 6–6.5% (42–48 mmol/mol) or < 6% (42 mmol/mol) if achievable without significant hypoglycaemia, but <7% (53 mmol/mol) if necessary to prevent hypoglycaemia (American Diabetes Association, 2016). UK NICE guidelines recommend the maintaining of fasting and 2 hour postprandial BGC below 5.3 mmol/L and 6.4 mmol/L respectively (National Institute for Health and Care Excellence, 2015). The American Diabetes Association and New Zealand Ministry of Health guidelines advise maintaining the fasting BGC ≤ 5.0 mmol/L and 2 hour postprandial blood glucose ≤ 6.7 mmol/L (Guerin et al., 2015; Ministry of Health, 2014). UK guidelines advise not allowing pregnancy to continue beyond 40 weeks and 6 days in mothers with GDM (National Institute for Health and Care Excellence, 2015) and New Zealand guidelines do not recommended delivery before 40 weeks in well controlled GDM without complications (Ministry of Health, 2014), but these guidelines are based on limited evidence.

It remains unclear if tighter glycaemic control in GDM is of benefit to mothers or their infants. A Cochrane systematic review found insufficient data from only one trial on the effect of different intensities of glycaemic control for women with GDM (Martis, Brown, Alsweiler, Crawford, & Crowther, 2016). The ongoing TARGET trial is designed to determine if there

are differences in outcomes for mothers and infants with tighter targets (fasting blood glucose ≤5.0 mmol/L, 1 h ≤7.4 mmol/L; 2 h postprandial ≤6.7 mmol/L) compared to less tight targets (fasting blood glucose <5.5 mmol/L; 1 h <8.0 mmol/L; 2 h postprandial <7.0 mmol/L) (Crowther et al., 2019).

1.2 Fetal and neonatal glucose metabolism

1.2.1 Fetal glucose metabolism

The primary source of energy for the fetus is glucose. With low activity of cytosolic phosphoenolpyruvate carboxykinase (Girard, 1986), gluconeogenesis does not occur in the human fetus until after birth under normal conditions (Kalhan & Parimi, 2000). The supply of glucose to the fetus is via facilitated diffusion using GLUT transporters in the placental syncytiotrophoblast microvillous and basement membranes, from the maternal blood through the placenta to the fetal circulation. There have been 14 GLUT membrane transporter isoforms described to date in humans (Illsley & Baumann, 2020; Mueckler & Thorens, 2013) with differing substrates and distribution across different cell types.

GLUT 1 is the predominant isoform in human placental membranes (Barros, Yudilevich, Jarvis, Beaumont, & Baldwin, 1995), and is also found in erythrocytes, brain endothelial cells, and brain astrocytes. The level of GLUT 1 in the placenta increases over the course of pregnancy (Sakata et al., 1995) allowing increased transfer of glucose across the placenta to the fetus. The glucose transport capacity of the placental syncytiotrophoblast microvillous membrane is approximately 20 times that of the basement membrane, due to increased density of transporters and increased surface area of the microvillous membrane (Jansson, Wennergren, & Illsley, 1993). In the second to early third trimesters, the density of GLUT 1 transporters in the basement membrane doubles, leading to an increase in the transport of glucose delivery to the fetus (Jansson et al., 1993), providing for an increased rate of fetal growth over this time. Fetal glucose consumption is associated with the maternal-fetal glucose gradient (Michelsen et al., 2019). The maternal-fetal glucose gradient is dependent on the maternal glucose concentration (Osmond, King, Brennecke, & Gude, 2001), placental glucose metabolism, placenta GLUT 1 density and uteroplacental and umbilical blood flows (Holme, Roland, Lorentzen, Michelsen, & Henriksen, 2015). GLUT 1 transfer rates do not become saturated until maternal glucose concentrations are well above the normal range (Day, Cleal, Lofthouse, Hanson, & Lewis, 2013). Despite the facilitated glucose transport, fetal glucose concentrations

are typically 1mmol/L below those of the mother due to placental glucose consumption (Jansson et al., 1993). In mothers with either pre-existing diabetes or GDM, the syncytiotrophoblast cells of the placenta have higher levels of GLUT 1 and hence higher glucose transfer (Borges et al., 2019; Gaither, Quraishi, & Illsley, 1999; Jansson, Wennergren, & Powell, 1999), and there is increased glucose transfer to the fetus with increasing maternal glucose concentration (Osmond et al., 2001).

In contrast to GLUT 1, GLUT 3 levels in the placenta decrease with advancing pregnancy with approximately half the levels of GLUT 3 seen in the second trimester and 34% in the third trimester compared to the first trimester levels (K. Brown, Heller, Zamudio, & Illsley, 2011) suggesting a role in early fetal life. GLUT 3 is the main neuronal transporter of glucose in dendrites and axons, and found in heart muscle (Mantych, James, Chung, & Devaskar, 1992; P. R. Shepherd et al., 1992).

Insulin sensitive GLUT 4 is expressed in the placenta (Stanirowski et al., 2019), adipocytes, skeletal muscle, cardiomyocytes and a small group of neurons. Similar to GLUT 3, the placental concentrations of GLUT 4 decrease significantly from the first trimester to negligible concentrations at term (Ericsson, Hamark, Powell, & Jansson, 2005) suggesting a role in early fetal life. GLUT 9 is also found in the syncytiotrophoblast, and along with GLUT 1 and GLUT 4 is seen in higher quantities in diabetic pregnancies (Bibee, Illsley, & Moley, 2011; Stanirowski et al., 2019). GLUT 12 is found in the placenta (Gude et al., 2003), skeletal muscle, adipose tissue (Rogers et al., 2002) and heart muscle (Waller et al., 2013). Rising insulin concentrations cause a redistribution of GLUT 4 and GLUT 12 receptors from intracellular to the cell membranes in muscle (Stuart, Howell, Zhang, & Yin, 2009) resulting in increased glucose uptake and metabolism in these cells, thereby regulating glucose homeostasis.

Maternal insulin does not cross the placenta under normal conditions, but fetal insulin is detectable by the end of the first trimester (Adam, Teramo, Raiha, Gitlin, & Schwartz, 1969). There is a positive correlation between maternal blood glucose and maternal insulin concentrations (Holme et al., 2015). However, in the term fetus in uncomplicated pregnancies, there is no significant correlation between fetal BGC and fetal insulin concentrations, rather the fetal plasma insulin concentration is correlated with placental weight, birthweight and the fetal venous-arterial glucose difference (Holme et al., 2015). These findings suggest that there is a different regulation and function of insulin in the fetus. In the sheep fetus, lack of insulin

following a pancreatectomy leads to a slowing in growth, both of length and weight, whilst in fetuses post pancreatectomy receiving insulin, growth is maintained (Fowden, Hughes, & Comline, 1989), suggesting insulin has a significant role in fetal growth.

Maternal episodes of hyperglycaemia lead to an acute rise in the fetal glucose concentration, with fetuses of diabetic mothers having a lower plateau and exaggerated insulin response compared to fetuses of healthy mothers (Oakley, Beard, & Turner, 1972). The effect of maternal hypoglycaemia on fetal glucose metabolism is less clear, although it is known that fetal glucose concentrations don't fall as low as maternal glucose concentrations (Bozzetti et al., 1988). While in non-diabetic mothers, there is a linear relationship between maternal and fetal glucose concentrations in mid to late gestation, in diabetic mothers low maternal BGC in mid gestation are associated with fetal glucose concentrations that can exceed maternal and are independent of maternal glucose concentration. (Bozzetti et al., 1988). *In vitro* work demonstrates that glucose flux occurs down a gradient across the placental membranes from the fetal to maternal side only at much steeper gradients than flux down a gradient from maternal to fetal circulations (Schneider, Reiber, Sager, & Malek, 2003). Therefore, the fetus appears to have a degree of protection from at least shorter periods of maternal hypoglycaemia. The fetal umbilical cord plasma glucose to insulin ratio is lower in those born to diabetic mothers compared to those born to non-diabetic mothers and higher maternal oral glucose tolerance test results correlate with a lower cord plasma glucose to insulin ratio (Luo et al., 2010). Thus, even before birth, there appears to be increased insulin secretion in babies born to diabetic mothers compared to those born to non-diabetic mothers. Supporting this finding are animal studies, demonstrating pulsatile hyperglycaemia, such as one might expect in maternal diabetes, is associated with a larger increase in fetal insulin secretion than sustained maternal hyperglycaemia or hypoglycaemia or controls (Carver, Anderson, Aldoretta, & Hay, 1996).

1.2.2 Transitional changes in metabolism from fetal to neonatal period

Following birth, the infant's metabolism has to transition from a constant glucose supply via the maternal blood to a regime of intermittent supply from enteral feeding. A rapid drop in blood and plasma glucose concentrations occurs in the 1- 2 hours after birth (Heck et al., 1987; Srinivasan et al., 1986). There is surge in glucagon, catecholamines, cortisol and growth

hormone after birth and plasma insulin concentrations progressively fall relative to glucose concentrations (Sperling, Ganguli, Leslie, & Landt, 1984).

There follows a gradual increase in plasma glucose concentrations over the first 18 hours after birth, a plateau then a further gradual increase to typical adult plasma glucose concentrations on the fourth day after birth (Harris, Weston, Gamble, & Harding, 2020). However, even at low BGC, insulin concentrations are not completely suppressed during the first few days after birth (Harris, Weston, & Harding, 2015).

There is also evidence that female infants are more insulin resistant than male infants as demonstrated by higher cord blood leptin and C-peptide (Walsh et al., 2015). Female infants born at risk of neonatal hypoglycaemia are less likely to develop hypoglycaemia than male infants (Harris, Weston, & Harding, 2012). However, mothers carrying female fetuses are less insulin resistant than those carrying male fetuses after adjusting for birthweight and maternal BMI (Retnakaran & Shah, 2015; Walsh et al., 2015). The mechanism for the differing insulin resistance is not yet determined, but placental hormones are a possible cause with placental lactogen concentrations higher in mothers carrying a female fetus (Houghton, Shackleton, Obiekwe, & Chard, 1984).

After birth, the activity of cytosolic phosphoenolpyruvate carboxykinase, which is responsible for converting pyruvate to glucose, increases as a result of the reduced blood insulin/glucagon ratio, leading to glycogenolysis to provide a limited glucose supply via the liver. Once the glycogen stores are exhausted, glucose concentrations must be maintained through feeding or gluconeogenesis. By 6 hours of age, gluconeogenesis is established in term infants (Kalhan et al., 2001). Lactate is also available as an alternative partial supply of fuel for the neonatal brain during the first 12 hours after birth but plasma lactate concentrations fall after this period and lower plasma glucose concentrations are associated with lower plasma lactate concentrations (Harris, Weston, & Harding, 2021; Harris, Weston, et al., 2015). Lactate provides approximately 27% of endogenous glucose during day one after birth (Kalhan et al., 2001) or 25% of the potential energy requirements of the infant (Harris et al., 2021). Ketones, however, remain at low concentrations in blood during the first 12 hours after birth, despite hypoglycaemia (Harris et al., 2021; Harris, Weston, et al., 2015), rising to higher concentrations by 48 – 72 hours and at this time higher concentrations occur when plasma glucose concentrations are lower (Harris et al., 2021; Hawdon, Ward Platt, & Aynsley-Green,

1992). Ketones are therefore not available as an alternative fuel for the brain during the first day after birth. The duration of lower plasma glucose concentrations from day 2 onwards is associated with ketone concentrations: ketone concentrations are higher when interstitial glucose concentrations have been lower than average for more than 18 hours (Harris et al., 2021). Breast fed babies, despite having lower glucose concentrations than babies on formula feeds, have higher concentrations of ketone bodies as an alternative fuel supply for the brain (Hawdon et al., 1992; Heck et al., 1987). During fasting, lipolysis contributes 10-20% of BGC in term infants (Patel & Kalhan, 1992) and alanine contributes approximately 10% of BGC (Frazer, Karl, Hillman, & Bier, 1981) via gluconeogenesis. Pancreatic ß cells transition from secreting insulin in response to raised amino acid concentrations in the fetal state to responding to glucose concentrations in the neonatal period (Helman et al., 2020).

Preterm babies have a greater reduction in BGC than term babies in the first few hours after birth, with basal insulin concentrations higher in preterm infants than term infants at the same glucose concentrations (Hawdon, Weddell, Aynsley-Green, & Ward Platt, 1993) putting preterm infants at higher risk of hypoglycaemia, which occurs in about half of late preterm infants (Harris et al., 2012). They also have reduced ability to produce ketones in the first week after birth (Cornblath & Reisner, 1965; Hawdon et al., 1992) so an alternative energy source is also lacking. Infants of mothers with diabetes (IDM) have higher circulating insulin concentrations in the presence of hypoglycaemia than healthy newborns and those with other risk factors (Harris, Weston, et al., 2015), which may also reduce their ability to mount a counterregulatory response and use alternative fuel sources for the necessary metabolic requirements of the brain.

1.3 Neonatal Hypoglycaemia

1.3.1 Definition of hypoglycaemia

The definition of neonatal hypoglycaemia has varied with the passage of time. Prior to the 1980s, neonatal hypoglycaemia was commonly defined as a BGC below 1.1 mmol/L to 1.7mmol/L (Griffiths & Bryant, 1971; Haworth & MCrae, 1965; Koivisto, Blanco-Sequeiros, & Krause, 1972; Pildes et al., 1974; Sosenko et al., 1982). A UK survey of textbooks and practising neonatologists in 1986 found definitions of hypoglycaemia between 1 and 4 mmol/L with commonly used thresholds of 2 mmol/L for term and 1.1 mmol/L for preterm or small for gestational age (SGA) (Koh, Eyre, & Aynsley-Green, 1988). In 1988, two papers were

published which showed no adverse effect on brainstem auditory or somatosensory evoked potentials or developmental scores at 18 months if the BGC was maintained at or above 2.6 mmol/L (Koh, Aynsley-Green, Tarbit, & Eyre, 1988; Lucas, Morley, & Cole, 1988). Evoked sensory potentials recorded at varying BGC in a small group of children ranging from newborn to 16 years of age found no abnormal sensory evoked potentials when glucose concentrations of at least 2.6 mmol/L were maintained (Koh, Aynsley-Green, et al., 1988). In preterm infants, developmental scores at 18 months of age were inversely associated with the number of days of hypoglycaemia below 2.6 mmol/L. A progressive fall in developmental scores was seen with increasing number of days with both moderate (1.6-2.5 mmol/L) and severe (0-1.5 mmol/L) hypoglycaemia. This association remained after adjusting for multiple additional independent variables that might of themselves affect development. Age of onset of hypoglycaemia did not affect the results (Lucas et al., 1988). This led to the adoption of a higher BGC as the threshold for hypoglycaemia. By 1992, the threshold at which hypoglycaemia was defined was still variable but a greater proportion used definitions of a BGC at least < 2 mmol/L (Koh & Vong, 1996). In 2014 in New Zealand and Australia, 78% of respondents to a survey reported a clinical BGC threshold for treatment of 2.6 mmol/L (Harris, Weston, Battin, & Harding, 2014) and in 2015 in the UK, the definition used by 88% of respondents was a BGC < 2.6 mmol/L, though variation persisted, with definitions between a BGC of < 2 mmol/L and < 4 mmol/L (Dixon et al., 2017). The Pediatric Endocrine Society in 2015 recommended maintaining plasma glucose concentrations > 2.8 mmol/L in the first 48 hours after birth and > 3.3 mmol/L beyond 48 hours in infants with suspected congenital hypoglycaemia disorders (Thornton et al., 2015).

The glycaemic profile of the “normal” newborn infant has been described with a typical nadir in blood or plasma glucose concentration between 1 and 2 hours after birth followed by a stabilisation for approximately 48 hours then increase over the next 3-4 days to BGC seen in older children or adults (Acharya & Payne, 1965; Cornblath & Reisner, 1965; Hawdon et al., 1992; Hoseth, Joergensen, Ebbesen, & Moeller, 2000; Lubchenco & Bard, 1971; Srinivasan et al., 1986). Healthy term infants, the majority receiving breast feeds, have mean plasma glucose concentrations 3.3 +/- 0.6 mmol/L in the first 48 hours after birth, rising to 4.6 +/- 0.7 mmol/L after 72 hours. Continuous glucose monitoring in these infants demonstrates a gradual increase in mean interstitial glucose concentrations from 3.1 +/- 0.6 mmol/L in the first 12 hours after birth to 3.3 +/- 0.5 mmol/L between 12 and 24 hours and from 3.3 +/- 0.6 mmol/L around 48 hours to 4.6 +/- 0.8 mmol/L after 72 hours and a 10^{th} percentile of 2.6 mmol/L (Harris et al.,

2020). Even in these healthy term infants, approximately one third have episodes of plasma glucose concentration below 2.6 mmol/L.

In order to define hypoglycaemia in a meaningful manner, a functional definition is required, aiming for a threshold above which no adverse effects are seen acutely or in the longer term. Defining such a threshold is complicated by the influence of multiple other factors, such as illness and the presence of alternate cerebral fuels (Harris et al., 2021). In children born late preterm, small or large for gestational age, or of a diabetic mother without initial severe hypoglycaemia (BGC ≤ 1.9 mmol/L), there were no detectable differences in Bayley scales of infant development (BSID), 3rd edition cognitive and motor results at 18 months between those in whom a lower treatment threshold of 2 mmol/L versus 2.6 mmol/L was used for asymptomatic hypoglycaemia (van Kempen et al., 2020). However, although similar neurodevelopmental outcomes were also seen at two years' corrected age in babies at risk of hypoglycaemia whose BGC were maintained at 2.6 mmol/L or higher and babies who developed hypoglycaemia (McKinlay et al., 2015), adverse effects associated with hypoglycaemia < 2.6 mmol/L were seen at four and half years of age albeit more commonly with prolonged or severe hypoglycaemia (McKinlay et al., 2017).

1.3.2 Measurement of blood glucose concentration

Plasma glucose concentrations are 10-15% higher than whole BGC due to the higher water content of plasma compared to erythrocytes (Holtkamp, Verhoef, & Leijnse, 1975). Some blood glucose monitors show much greater variation than others in terms of accuracy of results compared to reference laboratory methods (Kermani, Khatony, Jalali, Rezaei, & Abdi, 2017; Klonoff et al., 2018; Scott, Bruns, Boyd, & Sacks, 2009) particularly at the lower BGC in neonates (Kitsommart et al., 2013). In order to avoid the need for further laboratory testing to accurately measure lower BGC and avoid delays in identifying and managing abnormal results, accurate monitoring devices must be used. Using accurate portable enzymatic devices such as the i-STAT® analyser (Abbott. Princeton NJ, USA) or epoc® Blood Analysis system (Siemens, Erlangen, Germany), which use the glucose oxidase method, is also more cost effective than having to repeat tests following abnormal results from less accurate devices (Glasgow, Harding, Edlin, & for the CHYLD study team, 2018).

1.3.3 Incidence of hypoglycaemia

Approximately half of the neonates identified as being at risk of hypoglycaemia < 2.6mmol/L (weight >90th centile or <10th centile, IDM, preterm) are likely to have at least one identified episode of hypoglycaemia, 19% severe hypoglycaemia <2 mmol/L, and 19% more than one episode of hypoglycaemia (Harris et al., 2012). Half of the infants born to mothers with any type of diabetes become hypoglycaemic in the first few days of life including approximately a third of offspring of mothers with GDM (Voormolen et al., 2018). Even in healthy term infants, with no identified risk factors for hypoglycaemia, approximately 39% have plasma glucose concentrations below 2.6 mmol/L during the first 48 hours of life with 73% of infants having interstitial glucose concentrations below 2.6 mmol/L with continuous interstitial glucose monitoring (Harris et al., 2020). With such a high proportion of healthy term infants also found to develop neonatal hypoglycaemia, the question of what is normal or safe remains. It may be that additional adverse factors affecting metabolism in combination with hypoglycaemia put infants at risk of adverse neurodevelopment.

1.3.4 Effect of hypoglycaemia on neurodevelopment

Symptomatic neonatal hypoglycaemia when severe (BGC <1.5 mmol/L), prolonged, or recurrent is associated with brain injury, seizures and poor neurodevelopmental outcome (Burns, Rutherford, Boardman, & Cowan, 2008; Haworth & MCrae, 1965). The effect of asymptomatic neonatal hypoglycaemia is less clear, but retrospective observational data has shown an association between transient neonatal hypoglycaemia and a reduced ability in literacy and mathematics at 10 years of age in children regardless of the presence or absence of risk factors for hypoglycaemia (Kaiser et al., 2015). Hypoglycaemia when treated to maintain BGC of ≥ 2.6 mmol/l in at risk neonates has similar risks of adverse neurodevelopmental outcomes at two years of age, compared with at-risk neonates who do not develop hypoglycaemia (McKinlay et al., 2015). However, by four and half years of age, an association of hypoglycaemia with a higher risk of low executive function and visual motor function becomes apparent (McKinlay et al., 2017) with the greatest risk following recurrent or severe hypoglycaemia respectively. A meta-analysis of six studies on long term outcomes, with low to very low quality evidence found no difference in the risk of neurodevelopmental impairment in early childhood with exposure to neonatal hypoglycaemia, but an increased risk of neurodevelopmental impairment was apparent in mid childhood (R. Shah, Harding, Brown, & McKinlay, 2019). A more rapid or slow rate of recovery after hypoglycaemia may also

contribute to adverse outcomes (Burakevych, McKinlay, Harris, Alsweiler, & Harding, 2019). Children born to mothers with GDM and who have recurrent episodes of hypoglycaemia in the newborn period are more likely to have delayed motor development compared with children with a single or no episodes of hypoglycaemia (Wouldes et al., 2016). IDM who develop neonatal hypoglycaemia have lower developmental quotients and are more likely to be hyperactive, impulsive, and easily distracted compared with those without hypoglycaemia or those born to non-diabetic mothers (Stenninger, Flink, Eriksson, & Sahlen, 1998). Electroencephalogram (EEG) data shows there are lower relative delta power frequency distribution in the frontotemporal region and higher relative alpha power frequency in frontal and parietal regions in the children who had hypoglycaemia, which is consistent with attention deficit and hyperactivity disorders (Stenninger et al., 1998).

The severity of the hypoglycaemia may also contribute to later development as severe neonatal hypoglycaemia (BGC <1.5 mmol/l) in children whose mothers had diabetes in pregnancy is associated with "minor brain dysfunction" (including difficulty standing on one leg or cutting out a paper circle) despite no differences in the standard neurological examination compared to control children of non-diabetic mothers (Stenninger et al., 1998).

1.3.5 Effect of hypoglycaemia on vision development

As symptomatic neonatal hypoglycaemia predominantly affects the parietal and occipital lobes on MRI (Burns et al., 2008), there is a potential risk for visual impairment following hypoglycaemia. However, the association between mild to moderate hypoglycaemia and visual impairment is unclear (Paudel et al., 2017). Children are more likely to have low visual motor integration scores at age four and a half years if they had recurrent or severe neonatal hypoglycaemia (McKinlay et al., 2017). Meta-analysis including two studies (Haworth, McRae, & Dilling, 1976; McKinlay et al., 2017) indicated an increased risk of visual motor impairment in children who had neonatal hypoglycaemia (R. Shah et al., 2019). Other visual parameters such as acuity, binocular vision and motion coherence thresholds are not affected by hypoglycaemia provided regular monitoring of BGC and prompt treatment occurs (McKinlay et al., 2017; Paudel et al., 2017).

1.3.6 The effect of maternal metabolic control during pregnancy on offspring.

The risk of neonatal hypoglycaemia is higher in infants of type 1 diabetic mothers compared to those with type 2 diabetes (Kline & Edwards, 2007; Owens, Sedar, Carmody, & Dunne, 2015). Mothers with diabetes diagnosed early in pregnancy (before 28 weeks' gestation) are more at risk of having an infant with neonatal hypoglycaemia than those diagnosed later in pregnancy (Agrawal, Lui, & Gupta, 2000). Of infants born to gestational diabetic mothers, hypoglycaemia is more likely if the mother required insulin during her pregnancy (Balsells et al., 2000). Higher maternal HbA1c is associated with a higher risk of neonatal hypoglycaemia (Arumugam & Abdul Majeed, 2011; Joshi, Oldmeadow, Attia, & Wynne, 2017; L. P. Lowe et al., 2012; Rowan, Gao, Hague, & McIntyre, 2010). Higher fasting, 1 hour and 2 hour BGC after a 75g oral glucose tolerance test are also associated with increased risk of neonatal hypoglycaemia (Metzger et al., 2010).

The relationship between maternal glycaemic control and later neurodevelopmental outcomes of children of diabetic pregnancies is unclear. Some studies find no effect of the mothers' glycaemic control on their children's intelligence quotient (IQ) or cognitive scores (Ornoy et al., 1998; R. C. Temple, Hardiman, Pellegrini, Horrocks, & Martinez-Cengotitabengoa, 2011). Others find an adverse effect of poor maternal glycaemic control on: IQ (Silverman et al., 1991); adjusted developmental quotient (Brinciotti et al., 2009); intellectual development (Sells, Robinson, Brown, & Knopp, 1994); hand-eye coordination (Ornoy et al., 1998); verbal short term memory (R. Temple, Hardiman, Martinez-Cengotitabengoa, & Alloway, 2010); poorer motor test scores (Ornoy et al., 1998; Ratzon, Greenbaum, Dulitzky, & Ornoy, 2000); reduced hand-eye coordination (Ornoy et al., 1998); video EEG features of abnormal brain development (Castro Conde et al., 2013); school grades (Knorr et al., 2015) and cognitive scores in adult males (Nielsen, Dethlefsen, Sørensen, Pedersen, & Molsted-Pedersen, 2007). When the data is adjusted for confounding variables such as socioeconomic status and parental education, the association becomes non-significant in many cases, but many studies have not performed such adjustments.

HbA1c late in diabetic pregnancy is not associated with infant birthweight (Brans, Huff, Shannon, & Hunter, 1982), but mean HbA1c is associated with increased risk of infants being large for gestational age (LGA) (L. P. Lowe et al., 2012; Rowan et al., 2010). Both fasting BGC and post prandial BGC are associated with increased risk of LGA in diabetic and non-

diabetic pregnancies (Coustan et al., 2010; Durnwald et al., 2011; HAPO Study Cooperative Research Group, 2008; Moses & Calvert, 1995) and with neonatal fat mass in GDM (Durnwald et al., 2011) with a continuous effect rather than threshold effect. However, at two years of age there is not a strong association between maternal BGC and obesity in offspring (Pettitt et al., 2010).

1.3.7 The effect of maternal glycaemic control during labour on the risk of neonatal hypoglycaemia

When pregnant women with diabetes maintain BGC within the target ranges of 3-6 mmol/L or 4-7 mmol/L during labour there is no association between maternal blood glucose and neonatal BGC (Barrett, Morris, & McElduff, 2009; Njenga, Lind, & Taylor, 1992). However, higher maternal BGC during labour are associated with an increased likelihood of neonatal hypoglycaemia (Balsells et al., 2000; S. C. Brown, Kyne-Grzebalski, Mwangi, & Taylor, 1999; Flores-le Roux et al., 2012; Joshi et al., 2017; Kline & Edwards, 2007; Ryan & Al-Agha, 2014; Taylor, Lee, Kyne-Grzebalski, Marshall, & Davison, 2002). There is a dose-response relationship with a higher risk of neonatal hypoglycaemia at higher maternal BGC. Neonatal hypoglycaemia almost invariably occurs when maternal delivery BGC are > 10 mmol/L (S. C. Brown et al., 1999) and the rate of hypoglycaemia is above 80% in infants born to mothers with BGC above 8 mmol/L, (Taylor et al., 2002). Low maternal thresholds below which neonatal hypoglycaemia does not occur varies in studies, BGC between 6.5 mmol/L to 7.1 mmol/L (Andersen, Hertel, Schmølker, & Kühl, 1985; Kline & Edwards, 2007). Despite higher maternal BCC being associated with higher risk of neonatal hypoglycaemia, tighter glycaemic control during labour does not reduce the risk of hypoglycaemia and indeed is associated with lower mean neonatal BGC (Hamel et al., 2019).

British (National Institute for Health and Care Excellence, 2015) and Australasian guidelines (McElduff et al., 2005) for the management of diabetes during pregnancy recommend measuring maternal BGC every 1-2 hours and maintaining intrapartum BGC in the range 4-7 mmol/ L. Intrapartum monitoring is not addressed in the New Zealand diabetes in pregnancy guideline (Ministry of Health, 2014).

1.3.8 Guidelines and recommendations for the management of neonates with hypoglycaemia

Published guidelines and recommendations on the care of neonates with hypoglycaemia typically identify those at risk of hypoglycaemia (Adamkin & Committee on fetus and newborn, 2011; Aziz & Dancey, 2004; British Association of Perinatal Medicine, 2017; Wackernagel et al., 2020) including late preterm infants, those small or large for gestational age, or IDM. Target blood or plasma glucose concentrations are similar, > 2.5-2.6 mmol/L in the American and Canadian guidelines (Adamkin & Committee on fetus and newborn, 2011; Aziz & Dancey, 2004) or > 2 mmol/L in Britain (British Association of Perinatal Medicine, 2017) but guidelines differ on the suggested management according to whether or not infants are symptomatic (Adamkin & Committee on fetus and newborn, 2011; British Association of Perinatal Medicine, 2017; Wackernagel et al., 2020) or no distinction being made (Aziz & Dancey, 2004). When IDM are specifically identified, minimum BGC thresholds are between 2 mmol/L (Adamkin & Committee on fetus and newborn, 2011) and 2.6 mmol/L (Aziz & Dancey, 2004) using an accurate method of measurement (Adamkin & Committee on fetus and newborn, 2011; Aziz & Dancey, 2004; National Institute for Health and Care Excellence, 2015) and early feeding within the first hour after birth is recommended. Canadian Guidelines (Aziz & Dancey, 2004) recognise the nadir in BGC in the first few hours after birth and advocate intervention when lower concentrations after the first few hours after birth are identified. The nature of intervention varies but includes dextrose gel treatment (British Association of Perinatal Medicine, 2017; Wackernagel et al., 2020), refeeding, supplemental feeding with expressed breast milk or formula, or intravenous dextrose bolus and infusions. Repeat measurements are advised within 30-60 minutes of the intervention and ongoing monitoring until consecutive normal results are obtained over approximately 12 hours.

1.3.9 Treatment of hypoglycaemia

Dextrose gel for the treatment of neonatal hypoglycaemia reduces the frequency of treatment failure compared to feeding alone (Harris, Weston, Signal, Chase, & Harding, 2013). No adverse effect of treatment is seen when children's neurodevelopmental measures are evaluated at two years of age, but also no improvement in neurodevelopmental outcomes (Harris et al., 2016). BGC rise following either oral dextrose gel or formula feeding but not breast feeding alone, though infants are less likely to need repeat dextrose gel treatment with breast feeding (Harris, Gamble, Weston, & Harding, 2017). Persistent, severe or symptomatic neonatal

hypoglycaemia is treated with a combination of increased frequency or volume of feeding and intravenous dextrose bolus and infusions (Adamkin & Committee on fetus and newborn, 2011; Aziz & Dancey, 2004; National Institute for Health and Care Excellence, 2015). Intravenous glucose bolus and infusions result in higher interstitial glucose concentrations than formula or breast milk with or without dextrose gel treatments (Burakevych et al., 2019). However, this may not be beneficial as a wider range of glucose concentrations, as seen with intravenous dextrose treatment or formula with oral dextrose gel, is associated with a higher risk of neurosensory impairment (Burakevych et al., 2019). Treatment with intravenous dextrose bolus and infusions typically requires admission of an infant to a special care baby unit or neonatal intensive care thus separating mother and infant.

Persistent hypoglycaemia occurs with prolonged hyperinsulinism and is likely to require additional treatments over and above intravenous dextrose infusions to normalise and maintain BGC. Prolonged neonatal hyperinsulinism, more common in males, is typically treated with diazoxide (Brar et al., 2020), which is effective in the majority of cases (Hoe et al., 2006) and reduces the duration of intravenous fluids and time to achieve full oral feeds (Balachandran, Mukhopadhyay, Sachdeva, Walia, & Attri, 2018). Octreotide may be trialled when hypoglycaemia is resistant to diazoxide treatment (Thornton, Alter, Katz, Baker, & Stanley, 1993).

1.3.10 Prevention of hypoglycaemia

Early feeding reduces the risk of neonatal hypoglycaemia in infants of mothers with GDM (Chertok, Raz, Shoham, Haddad, & Wiznitzer, 2009) but the practice of early feeding does not alter the risk of hypoglycaemia at 1 hour of age in infants born to mothers without diabetes (Sweet, Hadden, & Halliday, 1999). Adding sugar to two-hourly formula feeds for term large for gestational age infants reduces the risk of neonatal hypoglycaemia (Singhal et al., 1991). However, although small amounts of supplemental formula in healthy infants does not reduce breastfeeding rates (Straňák, Feyereislova, Černá, Kollárová, & Feyereisl, 2016), supplemental formula feeds given to infants with risk factors for hypoglycaemia are associated with a reduced duration of breastfeeding (Blomquist, Jonsbo, Serenius, & Persson, 1994). Further progress has been made, with prophylactic dextrose gel now demonstrated to be effective at reducing the incidence of neonatal hypoglycaemia and admission for treatment in at risk infants (Hegarty et al., 2016) as well as being cost effective (Glasgow, Harding, Edlin, Alsweiler, et

al., 2018). Results may differ with alternative dextrose gel preparations as seen in a quasi-randomised trial which found no reduction in risk of neonatal hypoglycaemia (defined as ≤ 40 mg/dL (2.2 mmol/L) in the first four hours or ≤ 45 mg/dL (2.5 mmol/L) thereafter) with prophylactic oral dextrose gel compared to placebo (Coors, Cousin, Hagan, & Kaiser, 2018).

1.4 The outcomes of children born at risk of neonatal hypoglycaemia

1.4.1 Assessment of infant and child neuropsychological development

Standardised assessment tools to gauge general or specific aspects of neuropsychological development may be used to identify the need for developmental intervention and support, monitor progress or predict later neurodevelopment and academic achievement.

Early infancy assessment tools include infant reflexes to varying degrees and observations of neurobehaviour and the Neonatal Intensive Care Unit Network Neurobehavioural Scale (NNNS) (Lester & Tronick, 2004) also includes measures of infant stress. The quality of general movements assessed using Prechtl's Assessment of General Movements (GMs) (Prechtl, 1977) in newborns and infants is predictive of neurodevelopment at two years of age using the Bayley Scales of Infant Development 3rd edition (Bayley, 2006b) and at 10 years of age using the Wechsler Intelligence Scale for Children-III (Einspieler, Bos, Libertus, & Marschik, 2016). The NNNS may be used to determine profiles or patterns of behaviour across domains that predict later motor development (Stephens et al., 2010; Sucharew, Khoury, Xu, Succop, & Yolton, 2012) or externalising behaviours (Sucharew et al., 2012) assessed by the Behavior Assessment System for Children-2 (Reynolds & Kamphaus, 2004).

Repeated assessments in the language domain from early infancy to mid childhood indicates that adverse outcomes persist in children born preterm (Putnick, Bornstein, Eryigit-Madzwamuse, & Wolke, 2017) so identifying early anomalies may help with earlier intervention. However, developmental quotient scores assessed at two years of age using the Bayley Scales of Infant Development, 2nd edition are only moderately predictive of IQ scores assessed using the Wechsler Intelligence Scale for Children, 4th edition (Roberts, Anderson, Doyle, & the Victorian Infant Collaborative Study, 2010) hence the importance of following children at risk of adverse developmental outcomes over longer than just the first two years of childhood.

1.4.1.1 Bayley Scales of Infant Development

The Bayley Scales of Infant Development (BSID), developed for children between the one and 42 months of age (Bayley, 2006b) assess the developmental domains of cognitive, language, motor, social-emotional and adaptive behaviour. These scales assess neurodevelopment and are not a test of intellectual ability. The referent, normative values are a mean of 100 and standard deviation of 15, with abnormal composite scores defined as those more than one standard deviation below the mean (<85) (Bayley, 2006a). Standardisation for the third edition was carried out with a sample of 1700 children in the USA so children from other cultures exposed to different child rearing practices may perform differently (Anderson et al., 2010; Chinta, Walker, Halliday, Loughran-Fowlds, & Badawi, 2014). The first edition of the Bayley Scales of Infant Development was published in 1969 and was designed for infants up to 30 months of age (Bayley, 1969); the second and third editions for children up to 42 months of age. The changes in the structure of the assessment and inclusion of 9.8% of children from special groups in the standardisation process for the 3rd edition (Bayley, 2006b) means that scores are not directly comparable (Bayley, 2006a), and it is suggested that the earlier edition underestimates development and the latter overestimates development (Anderson et al., 2010; Jary, Whitelaw, Walløe, & Thoresen, 2013; Picciolini et al., 2015). BSID, 3rd edition cognitive and language scores at two years of age in infants born preterm at 30 weeks' gestation or earlier are predictive of IQ at four years of age using the Wechsler Preschool and Primary Scale of Intelligence (WPPSI), 3rd edition (Bode, D'Eugenio, Mettelman, & Gross, 2014). Mild or moderate cognitive delay using BSID, 3rd edition is not a sensitive predictor of cognitive impairment on the Differential Ability Scale, 2nd edition, but does have high specificity (Spencer-Smith, Spittle, Lee, Doyle, & Anderson, 2015). BSID 3rd edition motor scores at age two years are poorly predictive of motor difficulties at age four years (Burakevych, Mckinlay, Alsweiler, Wouldes, & Harding, 2017; Spittle et al., 2013). BSID, 3rd edition scores at age 2 years are poorly sensitive at predicting IQ at age 6 years by Wechsler Intelligence Scales for Children, 4th edition but highly specific (Y. F. Kaul et al., 2020). Hence low scores in BSID, 3rd edition may not detect all those children found to have deficits at a later age, but when low scores are found, these are likely to be associated with adverse neurodevelopmental outcomes in later childhood.

The recently released 4th edition of the BSID includes a version specifically standardised for New Zealand and Australian populations (Bayley & Aylward, 2020b). Changes include

involving caregivers in the evaluation and scoring process, polytomous scoring allowing for distinguishing between emerging skills and mastery of skills and adding items that assess precursors to early executive functioning (Bayley & Aylward, 2020a). The predictive value of the 4th edition and how scores compare with the 3rd edition have yet to be determined.

1.4.1.2 The Wechsler Preschool and Primary Scale of Intelligence

The Wechsler Preschool and Primary Scale of Intelligence, third edition (WPPSI) is designed to test intelligence between the ages of two and half years and seven years three months. It is more focused on cognition rather than the broader domains of development covered in the BSID and includes five subscales: verbal IQ; performance IQ; full scale IQ; processing speed and general language composite (Wechsler, 2002). Normal referent values for composite scores are mean 100 with a standard deviation of 15. Earlier BSID 3rd edition cognitive scores categorised as mild, moderate or severe delay are associated with the WPPSI IQ scores at age four years (Bode et al., 2014). The predictive value improves with age with results at six years being more predictive than results at four years of age of later cognitive impairment at 12 years of age (Erdei, Austin, Cherkerzian, Morris, & Woodward, 2020). The association of full scale IQ with academic achievement is predominantly mediated through the verbal IQ component (Kaplan, 1996). Early IQ results from the WPPSI are strongly associated with later IQ results and academic achievement in early and later childhood (J. D. Lowe, Anderson, Williams, & Currie, 1987).

1.4.1.3 Executive function

Executive function is defined as higher order cognitive functioning related to self-regulatory responses including inhibitory control, working memory, mental flexibility, initiating and monitoring behaviour and emotional control (Carlson, 2005; Isquith, Crawford, Espy, & Gioia, 2005). Children develop executive function skills throughout childhood, from inhibitory control and working memory in the first year after birth to basic planning and organisation between three and four years of age and improving regulation of emotional responses throughout childhood (Carlson, 2005; Carlson, Mandell, & Williams, 2004; Espy, Kaufmann, McDiarmid, & Glisky, 1999). Although specific tasks focus on testing specific components of executive function (Carlson, 2005), real life function involves interplay of the different components such as learning new skills requiring attention and working memory. Executive

function in early and later childhood is associated with later academic achievement (Best, Miller, & Naglieri, 2011; Bull, Espy, & Wiebe, 2008) as well as emotional development (Carlson et al., 2004) and behavioural regulation (Espy, Sheffield, Wiebe, Clark, & Moehr, 2011).

Children born preterm have reduced executive function performance which is evident both in infancy and early childhood (Brumbaugh, Hodel, & Thomas, 2013; Hodel et al., 2017). Children born SGA or LGA or to mothers with diabetes during pregnancy have similar executive function test scores to those born late preterm at two years corrected age (Ansell, Wouldes, Harding, & on behalf of the CHYLD Study group, 2017). There is indirect evidence of impaired executive function in children of diabetic mothers amongst a group of children with other risk factors for hypoglycaemia (McKinlay et al., 2017). Otherwise, there are few data available on executive function in children of diabetic mothers.

Executive function is also assessed using questionnaires to collect information on observations of the impact of executive function in everyday situations, which therefore includes overlapping components contributing to observed behaviours. This information is complementary to the information on specific executive function components, which is obtained from performance based assessments (Isquith et al., 2005; Pino Muñoz & Arán Filippetti, 2019).

Behavior Rating Inventory of Executive Function

The Behavior Rating Inventory of Executive Function – Preschool version (BRIEF-P) (Gioia, Espy, & Isquith, 2002) is a questionnaire for children two to five years of age, developed from the original version (Gioia, Isquith, Guy, & Kenworthy, 2000), which was designed for children five to 18 years of age and which included normative data. The BRIEF-P is designed to be completed by the child's caregiver or teacher providing information of the real life impact from observed manifestations of executive function components in everyday life for children aged two to five years of age. The five subscales assess the domains inhibit (ability to resist impulses when needed), shift (ability to switch or transition from one situation or activity to another), emotional control (ability to control emotional responses to events), working memory (ability to keep information in active memory in order to complete tasks) , and plan/ organise (ability to anticipate events and sequence actions or responses to achieve a goal) and contribute

to a summary global executive composite score. T scores are calculated and compared with referent norms of mean of 50 and standard deviation of 10. T scores of 65 or higher are considered abnormal based on standardisation from a US normative sample of 460 children (Gioia et al., 2002).

Executive function testing

A range of tests of components of executive function have been assessed in pre-school aged children at different ages (Carlson, 2005). Verbal ability is associated with executive function performance (Carlson et al., 2004) and therefore executive function scores in the context of delayed language development may not be valid. At two years of age of age, executive function skills are still emerging, but tests of inhibition, attention, working memory and cognitive flexibility are available (Carlson et al., 2004; Kochanska, Murray, & Harlan, 2000; Zelazo, Reznick, & Spinazzola, 1998). Executive function performance in young children is associated with socioeconomic factors, and with sex on certain tasks with girls performing better than boys on inhibitory control tasks but with no difference in overall scores (Ansell et al., 2017). Longitudinal studies of the predictive effect of executive function on later academic achievement are limited, but batteries of tasks for testing executive function two years of age have been shown to be predictive of emerging math and verbal skills and behaviour at three years of age (Mulder, Hoofs, Verhagen, van der Veen, & Leseman, 2014). Early tests of executive function from five months through to six years of age are correlated with each other and are associated with reading achievement at age six years (Blankenship et al., 2019; Gooch, Thompson, Nash, Snowling, & Hulme, 2016). This evidence suggests that executive function influences academic abilities and that early executive function is likely to be predictive of the academic trajectory in later life.

1.4.2 Children born to diabetic mothers

In the perinatal period, IDM are at increased risk of being born preterm or being born macrosomic with a higher risk of birth injuries, respiratory distress syndrome, jaundice, and hypoglycaemia (HAPO Study Cooperative Research Group, 2008). There are also potential longer term neurodevelopmental and health implications for children born to mothers with diabetes (Aberg & Westbom, 2001; W. L. Lowe et al., 2019; Scholtens et al., 2019).

1.4.2.1 Neurodevelopmental outcomes

Prenatal observations in fetuses of diabetic mothers

The effects of diabetes in pregnancy on the neurodevelopment of the offspring can be seen very early on with behavioural changes in fetuses of diabetic mothers related to the degree of diabetic control in pregnancy (Kainer, Prechtl, Engele, & Einspieler, 1997). The fetuses of mothers with type 1 diabetes with lower diabetes optimality score (calculated from the duration and complications of diabetes, and glycaemic control) have more abnormal general movements (poor repertoire and variability) on antenatal ultrasound scan from 20 weeks' gestation onwards. This is significant as infants of mothers with type 1 diabetes with abnormal movements, pre- or postnatally, are more likely to have lower mean BSID (1st edition) mental and psychomotor index scores at 10 months of age (Kainer et al., 1997). Furthermore, fetal habituation to a vibroacoustic stimulus in late gestation in mothers with pre-gestational diabetes is poorer and they are slower to habituate compared to non-diabetic controls matched for gestational age (Gonzalez-Gonzalez et al., 2009).

Neurodevelopment in infancy

The slower habituation persists postnatally, as IDM continue to show reduced ability to habituate and slower rate of habituation to a vibroacoustic stimulus on day one or two of life (Gonzalez-Gonzalez et al., 2009). This behavioural pattern is associated with higher maternal HbA1c (Gonzalez-Gonzalez et al., 2009) as are other abnormal behavioural responses (Rizzo et al., 1990; Silverman et al., 1991). IDM have worse behavioural outcomes using the Brazelton neonatal behavioural scale compared to infants of non-diabetic mothers, with a dose response effect: the poorer the glycaemic control, the poorer the infants' responses (Rizzo et al., 1990). IDM have worse motor development correlating with the maternal HbA1c in the 2nd and 3rd trimesters and worse physiologic responses correlating with the maternal fasting glucose concentrations in the 2nd trimester (Rizzo et al., 1990). IDM also have reduced auditory recognition memory shortly after birth, as assessed by event-related potentials (ERP) (R. A. DeRegnier, Nelson, Thomas, Wewerka, & Georgieff, 2000). Although infants of both diabetic mothers and non-diabetic mothers distinguish between the maternal voice and a stranger's voice, the pattern of the auditory recognition ERP has shorter latencies in IDM indicating a reduced ability to recognise a novel stimulus compared to the infants of non-diabetic mothers. Better recognition memory indicated by the more negative slow wave response is associated with higher BSID (2nd edition) mental developmental index at one year of age in IDM and

control infants, but there were no significant differences in the mental developmental or psychomotor index scores between the control infants and IDM in this study and all children had scores in the normal range. In addition, higher maternal HbA1c is associated with more immature patterns on video EEG in IDM compared to infants of non-diabetic mothers (Castro Conde et al., 2013). At six months of age, memory deficits are evident in IDM (C. A. Nelson et al., 2000). When event related potentials are measured during exposure to pictures of their mother and strangers' faces, IDM are less likely to show evidence of updating memory in response to the stranger compared to infants of non-diabetic mothers. At eight months age, memory deficits persist in IDM with no evidence of cross-modal recognition memory on ERP, which was observed in infants of pregnancies without diabetes (C. A. Nelson, Wewerka, Borscheid, Deregnier, & Georgieff, 2003). Altered ERP on testing attention and distractibility in children aged six and 18 months, born to mothers with GDM, are related to the maternal 2-hour BGC after the 75g OGTT at diagnosis. Abnormal six month ERP results are in turn associated with lower BSID (3rd edition) cognitive scores in children of mothers with GDM (S. Cai et al., 2016). These various findings support an association between the degree of dysfunction in maternal glucose homeostasis and early childhood neurodevelopment.

Neurodevelopment during early childhood

There is delayed maturation of the visual pathways in IDM, with visual evoked potentials to binocular flash stimulation in IDM (pre-existing and gestational) at two months of age having significantly longer mean latencies than infants of non-diabetic mothers (Brinciotti et al., 2009). The visual evoked potentials do not correlate with developmental quotients (ratio between developmental and chronological age) at two months of age, but at 18 months of age, visual evoked potentials in children born to mothers with GDM remain different to those born to non-diabetic mothers, with prolonged latencies, indicating a persistent effect on brain development, and are associated with lower BSID (3rd edition) cognitive scores (Torres-Espínola et al., 2018). The effect is more pronounced in those infants whose mothers who were also overweight or obese.

Cognitive and motor development

Most children born to diabetic mothers have a normal developmental quotient (Rehan, Moddemann, & Casiro, 2002), IQ and neurological system (Persson & Gentz, 1984), with

normal measures of neurodevelopment assessed with the BSID (R. A. DeRegnier et al., 2000; C. A. Nelson et al., 2000; Rizzo, Ogata, Dooley, Metzger, & Cho, 1994), Stanford-Binet (Rizzo et al., 1994), MacArthur Communicative Developmental Inventories (R. A. DeRegnier et al., 2000), and McCarthy Scales of Children's Abilities (Daraki et al., 2017).

Despite most children having normal overall measures of neurodevelopment, differences in specific developmental domains may still be found between children of diabetic and non-diabetic mothers. Memory, essential for learning, follows a delayed pattern of maturation in IDM compared to those born to non-diabetic mothers with poorer recall of actions in the correct temporal order at one year of age (DeBoer, Wewerka, Bauer, Georgieff, & Nelson, 2005). BSID (2^{nd} edition) mental developmental index (MDI) scores are lower for children at one year of age born to diabetic mothers compared to those born to non-diabetic mothers (C. A. Nelson et al., 2003). Differences persist at three to four years of age with ERP patterns indicating persisting impairment in attention and memory in children of non-diabetic mothers despite there being no difference in IQ assessed using the Wechsler Preschool and Primary scale of Intelligence- revised (WPPSI-R) (Cordón, Georgieff, & Nelson, 2009).

Markers of maternal glycaemic control have been investigated for any association with offspring outcomes over many years with an association between acetonuria during pregnancy and reduced IQ in IDM first reported over 40 years ago (Stebhens, J.A; Baker, G; Kitchell, 1977). More recently, lower scores in mental, psychomotor and exploration/orientation scores at one year of age were demonstrated in children of mothers with pre-existing diabetes compared to children of non-diabetic controls, despite good maternal metabolic control during pregnancy (Hod et al., 1999). Although higher HbA1c was associated with reduced head circumference at three years of age in children born to mothers with diabetes compared with those born to mothers with lower HbA1c concentrations or with children of non-diabetic mothers, there were no differences in BSID scores or IQ scores using Stanford-Binet. However, children of mothers with higher HbA1c during pregnancy were more likely to have language delays at three years of age compared to children of mothers with lower HbA1c or controls (Sells et al., 1994).

Poor maternal metabolic control (post prandial BGC and HbA1c in third trimester), is associated with a lower developmental quotient, particularly in mothers with type I diabetes (Brinciotti et al., 2009). Although neurodevelopmental progress is similar in six month old

infants of both diabetic and non-diabetic mothers (Sells et al., 1994; Torres-Espínola et al., 2015), IDM with tighter control of diabetes during pregnancy have higher BSID mental developmental indices at 8-12 months age than those with standard care (Steichen, Steichen Asch, & Tsang, 1987).

Women with GDM are commonly managed using similar approaches to those used in patients with type 2 diabetes, including diet and exercise advice, oral medications and insulin (Martis et al., 2018). Treatment of GDM reduces the short term risks of infant death, shoulder dystocia, bone fracture, and nerve palsy (Crowther et al., 2005). However, data about longer term outcomes of offspring of mothers treated for GDM is limited. The offspring of women with GDM randomised to either insulin or metformin had similar outcomes when assessed using both non standardised methods at 18 months of age (Ijäs, Vääräsmäki, Saarela, Keravuo, & Raudaskoski, 2015) and BSID (2^{nd} edition) at 2 years of age (Wouldes et al., 2016). However, the children in both groups had lower MDI and psychomotor developmental index (PDI) scores (Wouldes et al., 2016) and mild language delay (Ijäs et al., 2015; Tertti, Eskola, Ronnemaa, & Haataja, 2015), compared to standardised normal values. This suggests that even treated GDM impacts on the development of the offspring of affected pregnancies. Perhaps unsurprisingly, given the timing of onset of GDM, there was no relationship between glucose and insulin concentrations at 12 weeks' gestation of mothers with GDM and neurodevelopmental outcomes of their offspring, after adjusting for potential confounders. (Daraki et al., 2017).

When frequent (one- to two- weekly) measurements of maternal fasting glucose, beta hydroxybutyrate and free fatty acids were taken during diabetic pregnancies, there were correlations with longitudinal outcomes in children born to diabetic mothers (Rizzo et al., 1991). Maternal third trimester beta hydroxybutyrate and fasting BGC had an inverse association with BSID (1^{st} edition) MDI scores at two years of age, and third trimester beta hydroxybutyrate, fasting BGC and free fatty acid concentrations inversely correlated with Stanford-Binet IQ scores at three to five years of age in those born to both gestational and pre gestational diabetic mothers (Rizzo et al., 1991; Silverman, Rizzo, Cho, & Metzger, 1998). Even maternal glycosuria, a crude indicator of metabolic control, was inversely related to school entry assessment scores in four year olds in the UK (A. Fraser, Nelson, Macdonald-Wallis, & Lawlor, 2012).

Language

Children of diabetic mothers have weaker language performance, compared to age adjusted normal values at 2 year of age (Tertti et al., 2015). Language impairment, usually mild, is also seen in children of diabetic mothers at 18 months (Dionne, Boivin, Séguin, Pérusse, & Tremblay, 2008), 3 years (Sells et al., 1994) and 6 years of age (Dionne et al., 2008) compared to children of mothers without diabetes. Although genes and maternal education moderate the effect of diabetic pregnancy on language development, the differences remain significant after adjusting for these variables (Dionne et al., 2008), and are not greater in children who developed neonatal hypoglycaemia. IQ assessment tools that do not require verbal communication still demonstrate a difference with IDM having lower IQ than those born to non-diabetic mothers at three years of age (Y. Yamashita et al., 1996). Retrospective data suggest that children of diabetic mothers are more at risk of developing hearing impairment in the first few years of life compared to children of mothers without diabetes but there were very different rates of co-morbidities between groups including diagnoses that might affect hearing outcomes (J. A. Lee, Mehta, Nguyen, & Meyer, 2020) so there is no clear association of increased risk of hearing impairment with delay in language development.

Neurodevelopment during school age

Children of diabetic mothers are at increased risk of hospitalisation for neurological or developmental disorders compared to those born to non-diabetic mothers with a higher risk in pre-existing diabetes compared with GDM (Aberg & Westbom, 2001).

Cognition

Developmental quotient and total IQ at seven to ten years of age are lower in children born to diabetic mothers compared to children born to mothers without diabetes (Bolaños et al., 2015; Bonilla et al., 2012; A. Fraser et al., 2012; Silverman et al., 1998; Stenninger et al., 1998). Not only are children of mothers with pre-gestational diabetes at higher risk of low IQ scores, but also the children of mothers with GDM (Bolaños et al., 2015) There is a dose response effect, with children of non-diabetic mothers with glycosuria having the least reduction in IQ scores followed by the children of gestational diabetic mothers, with the largest reduction in scores seen in children of pre-gestational diabetic mothers (A. Fraser et al., 2012). Maternal HbA1c

and beta-hydroxybutyrate concentrations in the second half of pregnancy are inversely correlated with IQ scores, and free fatty acid concentrations inversely correlated with childhood educational achievement (Silverman et al., 1998). However, the effect of diabetes in pregnancy on cognitive scores may be mitigated by higher levels of maternal education and socioeconomic indices (Veena et al., 2010).

Even when total IQ is found to be similar in children of diabetic and either non diabetic mothers or normative data, the component scores differ between the groups (Ornoy et al., 1998; R. C. Temple et al., 2011), with lower verbal IQ (Ornoy, Wolf, Ratzon, Greenbaum, & Dulitzky, 1999) or poorer working memory scores in those born to type 1 diabetic mothers (R. C. Temple et al., 2011) .

Hippocampal size on MRI is predictive of the time to respond in recognition memory performance in children of diabetic mothers but not in children of unaffected pregnancies (Jabes, Thomas, Langworthy, Georgieff, & Nelson, 2015) suggesting a difference in brain structure. Verbal short term memory performance is worse in children born to mothers with type 1 diabetes compared with those born to non-diabetic mothers, with a worse performance correlating with higher maternal HbA1c concentrations during pregnancy (R. Temple et al., 2010). An increased risk of diagnoses relating to intellectual disability is found in children who were born to diabetic mothers, by three years of age (Mann, Pan, Rao, McDermott, & Hardin, 2013).

Motor development

Motor development is delayed and there are more soft neurological signs at six to nine years of age in children of diabetic mothers compared with those of non-diabetic mothers (Ornoy et al., 1998). Motor scores assessed using the Bruninks-Oseretsky scale in children of diabetic mothers correlate with 2nd and 3rd trimester maternal beta hydroxybutyrate concentrations (Rizzo et al., 1995; Silverman et al., 1998). Motor development is also inversely correlated with maternal HbA1c and urinary acetone concentrations (Ornoy et al., 1998).

Behaviour

Although observable behaviour in everyday life assessed by Conner's behaviour rating scale (Ornoy et al., 1998) or the Child Behaviour Checklist (Rizzo, Silverman, Metzger, & Cho, 1997) is similar in school-aged children of diabetic and non-diabetic mothers, the Pollack tapper test of components contributing to attention deficit demonstrates poorer attention in children of diabetic mothers (Ornoy et al., 1998). The combination of GDM and poor socioeconomic indicators is associated with a markedly increased risk of offspring being affected by Attention Deficit and Hyperactivity Disorder (ADHD) at six years of age, whereas offspring of gestational diabetic mothers in higher socioeconomic groups do not have a significantly increased risk of ADHD (Nomura et al., 2012) indicating that the risk may be ameliorated by higher socioeconomic factors.

School achievement

The higher risk of adverse neurological outcomes in children of diabetic mothers may impact on school achievement. Average school grades are lower for these children at 16 years of age compared to those born to non-diabetic mothers (Dahlquist & Källén, 2007; A. Fraser, Almqvist, Larsson, Långström, & Lawlor, 2014; A. Fraser et al., 2012) and they have a higher rate of not completing school (Dahlquist & Källén, 2007). However, when grades within sibships are compared to those of diabetic and non-diabetic pregnancies, there are no significant differences in grades (A. Fraser et al., 2014), suggesting that mediators such as family environment or maternal IQ influence cognitive outcomes in children of diabetic mothers. Maternal glycaemic control is associated with school grades, with higher HbA1c in mothers with pre-existing diabetes (Knorr et al., 2015) or maternal free fatty acids in the 3rd trimester (Silverman et al., 1998) being associated with children achieving lower school grades. However, if maternal glycaemic control was good, the children achieve higher grades than children of non-diabetic mothers (Knorr et al., 2015) with a strong association between higher education levels in mothers and good glycaemic control.

Adults

At 18 years of age, IQ is lower in men born to mothers with diabetes during pregnancy, but this effect is not observed within sibships (A. Fraser et al., 2014). Maternal glycaemic control

has long-lasting effects, with maternal HbA1c (Nielsen et al., 2007) and fasting BGC in the second half of pregnancy (Nielsen, Andersen, & Lundbye-Christensen, 2010) being inversely associated with cognitive scores in adulthood. In women whose HbA1c was below 7%, the cognitive scores of their adult offspring are similar to those of offspring of mothers without diabetes (Nielsen et al., 2007).

1.4.2.2 Growth outcomes of children born to diabetic mothers

Even in the neonatal period, there are differences in growth parameters of infants born to mothers with diabetes compared to those born after unaffected pregnancies, with increased fat mass, body fat percentage and triceps and subscapular skinfold thickness in IDM (Logan, Gale, Hyde, Santhakumaran, & Modi, 2017). Infants of type 1 and gestational diabetic mothers have higher fat mass (mean difference 62 g, 95% CI 29 g to 94 g, p=0.0002) and body fat percentage (mean difference 1.7%, 95% CI 0.7% to 2.8%. p=0.002) than infants born to non-diabetic mothers (Logan et al., 2017). After adjusting for maternal pre-pregnancy BMI, fat mass remains higher (mean difference 83 g, 95% CI 49 g to 117 g, p<0.0001), but fat-free mass is not different in IDM compared to controls (Logan et al., 2017). Differences remain for neonates born to mothers with GDM, with increased triceps thickness (mean difference 0.47 mm) and subscapular skinfold thickness (mean difference 0.69 mm) than those born to non-diabetic mothers (Logan et al., 2017).

There is a sex specific difference in these risks, with sons of diabetic mothers having a higher fat mass (mean difference 87 g 95% CI 30g to 145g; p=0.003) and fat percentage (mean difference 2.3% 95% CI 1.0% to 3.7%); p=0.0008) than sons of non-diabetic mothers, with no significant association seen in daughters (Logan et al., 2017). Daughters of diabetic mothers have lower fat-free mass than those of non-diabetic mothers (−85 g (−152 to −17); p=0.01) (Logan et al., 2017).

Rapid weight gain by IDM during the first 4 months after birth is associated with an increased risk of being overweight by 4 years of age (Plagemann, Harder, Rodekamp, & Kohlhoff, 2012). Childhood BMI of children born to mothers with diabetes is higher compared to controls after adjusting for maternal pre-pregnancy BMI (Philipps et al., 2011). Waist circumference is longer in children of mothers with GDM and type 1 diabetes (Nehring, Chmitorz, Reulen, von

Kries, & Ensenauer, 2013; Vlachová et al., 2015) and BMI is higher in those born to mothers with type 1 diabetes (Vlachová et al., 2015).

No differences are seen in rates of childhood overweight at age 7 years between children of mothers with type 1 diabetes and national rates but IDM with birthweights > 90th centile are at higher risk of being overweight in childhood, with increased BMI, weight and height, waist and hip circumference and thicker triceps and subscapular skinfolds, compared to IDM born at a healthy weight (Rijpert et al., 2009).

Children born to mothers with GDM are at increased risk of being overweight or obese at 4 years of age (OR 1.81, 95% CI 1.18, 2.86) 5.8 years of age (OR 1.81 (1.23–2.65) and 7 years of age (OR = 1.61 95% CI:1.07, 1.28), but not earlier at 3 years of age, after adjustment for maternal BMI, pregnancy weight gain, family income, and birthweight (Baptiste-Roberts, Nicholson, Wang, & Brancati, 2012; Nehring et al., 2013). Both a higher maternal pre-pregnancy BMI, commonly associated with GDM, and raised maternal free fatty acids are independently positively associated with offspring BMI at age 5-6 years (Gademan et al., 2014). Increased adiposity in offspring exposed to GDM compared to non-exposed persists through adolescence, though adjustment for maternal pre-pregnancy BMI attenuates the association with certain parameters including BMI (Beyerlein, Nehring, Rosario, & von Kries, 2012; Hockett et al., 2019).

Despite treatment of mild GDM reducing the incidence of impaired fasting blood glucose in female offspring, treatment does not result in altered lipid profile, blood pressure or the risk of childhood obesity at five to 10 years of age (Landon et al., 2015). The different treatments, metformin or insulin, for GDM may result in different growth parameters for the offspring. Metformin compared to insulin treatment for GDM increases BMI in mid-childhood (Tarry-Adkins, Aiken, & Ozanne, 2019). However, there is no difference in the ponderal index (Ijäs et al., 2015) or adiposity assessed by skinfold thickness, DEXA and bioimpedance (Rowan et al., 2011) in early childhood.

1.4.2.3 Metabolic and cardiovascular outcomes of children born to diabetic mothers

Maternal pre-pregnancy BMI is associated with increasing insulin resistance in their offspring at 9-10 years of age, independent of GDM and this is not mediated by birthweight or the child's

BMI (Maftei et al., 2015). Children of mothers with type 1 diabetes are not at higher risk of insulin resistance at 7 years of age compared with national reference data, (Rijpert et al., 2009), but insulin resistance is associated with childhood overweight status (Rijpert et al., 2009). However, by 10-16 years of age, children of mothers with pre-existing and gestational diabetes have increased insulin resistance compared to controls, independent of maternal BMI (Sauder, Hockett, Ringham, Glueck, & Dabelea, 2017). Children born to mothers with type 1 diabetes are at increased risk of metabolic syndrome by the time they are teenagers, with higher systolic blood pressure, reduced insulin sensitivity and relative insulin secretion deficiency compared to those born to non-diabetic mothers (Vlachová et al., 2015). Meta-analysis demonstrates higher systolic blood pressure in two to 19 year old offspring of diabetic mothers compared to offspring of non-diabetic mothers, with a greater effect seen in males rather than females and higher diastolic blood pressure in male offspring (Aceti et al., 2012).

These findings may explain why the offspring born to mothers with pre-existing diabetes and GDM are at higher risk of early onset cardiovascular disease up to 40 years of age (Yongfu Yu et al., 2019). How exactly the increased risks are mediated is less clear, although GDM is associated with epigenetic modification with changes in DNA methylation in offspring (Yang et al., 2018).

1.4.2.4 Congenital abnormalities in children born to diabetic mothers

There is an increased risk of congenital abnormalities (5-10% live births) in children born to mothers with pre-gestational diabetes (Ornoy, Reece, Pavlinkova, Kappen, & Miller, 2015) with a prevalence approximately 47% higher in IDM compared to infants of non-diabetic mothers (Agha, Glazier, Moineddin, & Booth, 2016; Garne et al., 2012). Heart defects, renal tract abnormalities and neural tube defects are the most common abnormalities seen in IDM (Garne et al., 2012; Nielsen et al., 2005). Poor diabetic control is associated with increased risk of congenital abnormalities in the infant of mothers with pre-gestational diabetes (Reece, 2012). Maternal hyperglycaemia is thought to mediate the harmful effects through increased oxidative stress (Reece, Homko, Wu, & Wiznitzer, 1998), hypoxia (Ornoy, Tsadok, Yaffe, & Zangen, 2009) and epigenetic changes, hypotheses supported by animal studies (Ornoy et al., 2015). Congenital abnormalities are unlikely in the in those born to mothers with GDM, unless they are also overweight, presumably due to the later onset during pregnancy of GDM, after the critical period of organogenesis (Correa et al., 2008).

1.4.3 Children born to overweight or obese mothers

Maternal obesity and overweight are associated with GDM (Collins, Oehmen, & Mehta, 2018) and diabetes pre pregnancy. There rates of obesity are increasing worldwide and are associated with increasing rates of type 2 diabetes and GDM (Goldenberg et al., 2016).

Children born to obese mothers are more likely to have developmental delay (Kerstjens et al., 2013; Krakowiak et al., 2012), lower cognitive scores (Basatemur et al., 2013; Casas et al., 2013; Helderman et al., 2012; Hinkle et al., 2012) and lower IQ (Bliddal et al., 2014; Gage, Lawlor, Tilling, & Fraser, 2013; Huang et al., 2014; Neggers, Goldenberg, Ramey, & Cliver, 2003) and school grades at age 16 years (Gage et al., 2013) when compared to those born to mothers with a healthy BMI. Lower cognitive scores in children of mothers with obesity are influenced more by non-verbal skills rather than verbal skills (Hinkle et al., 2012; Neggers et al., 2003). At school, reading skills, but not maths skills, are worse (Hinkle, Sharma, Kim, & Schieve, 2013; Tanda, Salsberry, Reagan, & Fang, 2013), with correspondingly lower school examination results in teenagers born to mothers with pre-pregnancy obesity (Gage et al., 2013). The association between maternal pre-pregnancy obesity and cognitive ability remains after adjustment for socioeconomic and maternal factors, including maternal diabetes (Basatemur et al., 2013). There is a dose response relationship, with a progressive decline in offspring cognition with increasing maternal pre-pregnancy BMI (Basatemur et al., 2013; Casas et al., 2013), although the relationship is not observed when BMI is categorised (Heikura et al., 2007; Neggers et al., 2003; Tanda et al., 2013).

Maternal pre-pregnancy obesity is not associated with decreased motor development in offspring (Casas et al., 2013; Hinkle et al., 2012; Neggers et al., 2003), unless maternal obesity is severe (Hinkle et al., 2013). Maternal obesity is associated with autism spectrum disorder, developmental delay (Krakowiak et al., 2012), and increased risk of ADHD symptoms, perhaps as a result of poorer executive functioning (Buss et al., 2012).

Various mechanisms have been proposed as mediators of the association between maternal overweight or obesity on offspring neurodevelopment with evidence of systemic inflammation in the mother (Hernández-Trejo et al., 2017; Monthé-Drèze, Rifas-Shiman, Gold, Oken, & Sen, 2019), and infant (Hernández-Trejo et al., 2017), and even intrauterine inflammation (Challier

et al., 2008) in pregnant mothers who are obese. Experimental models demonstrate altered immune response in the placenta and altered brain development in offspring following intrauterine inflammation, even without evidence of raised inflammatory markers in the mother. Inflammatory cytokines in the mother are associated with genetic changes in the infant (Lazarides et al., 2019) and obesity, with altered regulation of genes associated with mitochondrial and lipid metabolism (Costa et al., 2016). Other possible mediators are factors associated with obesity such as maternal IQ (Kanazawa, 2014) and socioeconomic influences (T. J. Kim & von dem Knesebeck, 2018).

1.4.4 Children born small for gestational age

Infants with a birthweight lower than the 10th percentile for their gestation are defined as SGA. Many of these infants are also born preterm making it difficult to determine if poor longer-term outcomes of these infants are due to being SGA or preterm.

SGA infants born at term have reduced neurodevelopmental scores from term corrected to 10 years of age, whether or not they had abnormal placental blood flow, assessed by umbilical vessel doppler studies (Arcangeli, Thilaganathan, Hooper, Khan, & Bhide, 2012; McCowan, Pryor, & Harding, 2002) and all domains, cognitive, language, motor, social-emotional and adaptive are affected (Savchev et al., 2013). However, infants born with abnormal placental histopathology (but normal doppler studies) indicating under perfusion are at higher risk of abnormal neurodevelopment two years of age than those with normal placental histology, with lower BSID 3rd edition cognitive (105.5 vs 96.3, p=0.03), language (98.6 vs 87.8, p<0.001) and motor scores (102.7 vs 94.5, p=0.007) after adjusting for socioeconomic status, sex, gestation, maternal smoking and breast feeding (Parra-Saavedra et al., 2014). No difference in neurodevelopment is found between those born with asymmetric versus symmetric growth restriction (Maciejewski, Hamon, Fresson, & Hascoet, 2016). However, SGA infants with a fat mass percentage less than the 10th centile demonstrate lower cognitive, language and motor scores compared to those born at an appropriate weight, and are reported to have higher attention deficit or hyperactivity scores, but no other identified behavioural problems at two years of age (O'Neill et al., 2017).

Children born SGA have lower body fat percentage and muscle mass at seven years of age compared to those born LGA or appropriate for gestational age (AGA) (Nordman et al., 2016).

Infants with asymmetric growth restriction (head circumference at birth in the normal range) are more likely to demonstrate catch up growth to nine months of age than those with symmetric growth restriction (Maciejewski et al., 2016).

Term SGA infants who demonstrate catch up growth up to 20 months are more likely to have better neurocognitive outcomes by adulthood than those without catch up growth of height, weight or head circumference (Horta, Sibbritt, Lima, & Victora, 2009; R. B. Jensen, Juul, Larsen, Mortensen, & Greisen, 2015; Lundgren, Cnattingius, Jonsson, & Tuvemo, 2001). Those SGA children who do not have any catch-up growth have poorer neurocognitive outcomes between ages seven years and 18 years (Castanys-Muñoz et al., 2017; Maciejewski et al., 2016).

Unfortunately, better neurocognitive outcomes associated with catch up growth, are counterbalanced by adverse metabolic consequences. Weight gain early in life is associated with higher BMI and increased fat mass (Taal, Vd Heijden, Steegers, Hofman, & Jaddoe, 2013) between one and 21 years of age, although whether or not fat percentage is affected is less certain (Kramer et al., 2014; Taal et al., 2013). Rate of weight gain over the lifetime is associated with increased insulin resistance in early childhood (Deng et al., 2011; Soto et al., 2003) and at 21 years of age (Leunissen et al., 2008). There is also a positive association between postnatal growth and blood pressure (Hemachandra, Howards, Furth, & Klebanoff, 2007). As many studies examine weight gain over variable periods from a few months to adulthood (Castanys-Muñoz et al., 2017), the period over which weight gain is most critical remains uncertain. By 11 years of age, children born SGA who are overweight have higher concentrations of very low density lipoprotein and triglycerides compared to children born SGA with normal weight or those who were born AGA or LGA and are also overweight (Mullett et al., 2014).

The developmental origins of health and disease were recognised and described more than 30 years ago with data from 5654 males demonstrating the inverse relationship between birthweight or weight at one year of age and death rates from ischaemic heart disease (Barker, Osmond, Winter, Margetts, & Simmonds, 1989). Further, the combination of lower birthweight and lower weight at one year of age were associated with the highest death rates from ischaemic heart disease regardless of social class, showing that mechanisms contributing to poor fetal growth and postnatal growth in early childhood influence cardiovascular outcomes in adult life.

1.4.5 Children born large for gestational age

LGA infants are usually defined as those born weighing more than the 90th percentile for gestational age and sex. There is a paucity of data regarding the long-term neurodevelopment of these children. There are conflicting results with LGA infants assessed at four to five years of age having no significant differences in neurodevelopmental outcomes compared to AGA infants (Frank, Speechley, Macnab, & Campbell, 2018; Paulson, Mehta, Sokol, & Chauhan, 2014), including verbal abilities (Frank et al., 2018). Indeed, term LGA infants even have lower rates of adverse neurodevelopmental outcomes and better reading scores in 49,439 LGA infants compared to 400,418 AGA infants (Khambalia, Algert, Bowen, Collie, & Roberts, 2017). However, despite similar Denver developmental scale scores and child behaviour checklist scores at four years of age in 75 children born LGA, up to 30% had abnormal neurodevelopmental findings whether or not the infants had developed hypoglycaemia, (Brand, Molenaar, Kaaijk, & Wierenga, 2005).

The long-term outcomes of infants born LGA include an increased risk of being overweight or obese by early childhood (P. Kaul et al., 2019). LGA infants have higher rates of adult obesity (Mullett et al., 2014) but no difference in rates of dyslipidaemia or hypertension (Johnsson, Haglund, Ahlsson, & Gustafsson, 2015) than those born AGA. Childhood catch down growth ameliorates these risks to a certain degree (Renom Espineira et al., 2011). The risk of type 2 diabetes in men is increased, but women have a reduced risk if their birthweight was 2 to 3 SD above the population normal, and no significant increase in risk with birthweight greater than 3 SD above the normal (Johnsson et al., 2015).

1.4.6 Children born preterm

Lower gestational age at birth is not only associated with an increase in mortality and cerebral palsy (Pierrat et al., 2017), but also with an increased risk of later neurodevelopmental impairment (Pierrat et al., 2017; Roberts et al., 2010). The greatest risk is for babies born extremely preterm (< 28 weeks), but babies born very (28 - 31+6 weeks), moderate (32 - 34+6 weeks) and late preterm (35 - 36+5 weeks) are also at increased risk compared to babies born at term (Cheong, Doyle, et al., 2017; Hirvonen et al., 2017). Altered brain white matter microstructure can be seen on MRI in moderate and late preterm infants compared with those born at term (Kelly et al., 2016) and cerebellar volume at term corrected age is associated with

better neurodevelopment in these preterm born infants (Cheong et al., 2016). The increased risk in neurodevelopmental impairment in babies born preterm persists throughout childhood (Cheong, Anderson, et al., 2017) with some evidence that girls have better outcomes than boys (Romeo et al., 2016). Neurodevelopmental impairment in babies born preterm affects both cognitive function at two years of age and early school performance (Richards, Drews-Botsch, Sales, Flanders, & Kramer, 2016). Language delay is also more common in preterm children, (Rabie, Bird, Magann, Hall, & McKelvey, 2015; Stene-Larsen et al., 2014) and persists over time (Putnick et al., 2017). For children born preterm, school performance at seven years of age is still associated with the degree of prematurity, after adjusting for important confounders including socioeconomic status (Chan & Quigley, 2014). Poorer working memory performance is seen at 11 years of age in children born moderately preterm compared to term (Fitzpatrick, Carter, & Quigley, 2016). In addition, neurobehavioral disorders such as autism spectrum disorder and attention deficit hyperactivity disorder occur more frequently in preterm rather than term born children (Schieve et al., 2016).

Faster fetal and postnatal growth is associated with better neurodevelopment in children born preterm, with weight gain and BMI gain in the period up to term corrected age and weight gain and linear growth from term to 4 months associated with improved neurodevelopment (Belfort et al., 2011). However, when the effect of sex is examined, girls are less sensitive than boys to the beneficial association of growth with neurodevelopment (Frondas-Chauty et al., 2014). By contrast, poor postnatal weight gain, length and head growth to term are associated with delayed microstructural development in the cortical grey matter (Vinall et al., 2013). Nutrition of the preterm infant, its interaction with the gut microbiome, and the interaction of the gut microbiome with the brain may mediate part of this association between growth and neurodevelopment (Blakstad et al., 2019; Keunen, van Elburg, van Bel, & Benders, 2015; Younge et al., 2019).

In the short term, preterm born infants have higher rates of hospitalisation in the first year of life (McLaurin, Hall, Jackson, Owens, & Mahadevia, 2009). Longer term, both males and females born preterm have increased insulin resistance and systolic blood pressure by age 30 (Dalziel, Parag, Rodgers, & Harding, 2007; Haikerwal et al., 2019) and adult males born preterm have increased adiposity compared to preterm born females (Mathai et al., 2013). Preterm infants who are also SGA have similar measures of insulin resistance and adiposity

compared to preterm AGA, if they are fed breast milk alone (Visuthranukul, Abrams, Hawthorne, Hagan, & Hair, 2019).

1.5 Collating evidence from multiple sources

1.5.1 Systematic reviews

The need for critical summaries of all relevant randomised controlled trials was voiced by Dr Archie Cochrane in 1979 (Cochrane, 1979) since which time several databases of systematic reviews have been developed, including the leading Cochrane database of systematic reviews. High quality systematic reviews are important sources of information that give a summary and grading of the available evidence with a clear question on a specific topic to support decision making (Chandler et al., 2020). Meta-analyses of the pooled data from all relevant studies provide an overall direction of effect in regard to risk or benefit. In doing so, systematic reviews may be able to provide answers not possible at the individual trial level due to the power limitations of smaller numbers in individual trials. A key component of systematic reviews is assessing the risk of bias in the collated evidence in order to grade the quality of the evidence and provide a rationale for inclusion or exclusion of trial data in the synthesis of the evidence and support any conclusions. The Cochrane database of systematic reviews now requires authors of reviews to use Grading of Recommendations Assessment, Development, and Evaluation (GRADE), for the purpose of evaluating quality of evidence and risk of bias in a way that is reproducible and has acceptable interrater reliability (Mustafa et al., 2013). Non-Cochrane systematic reviews vary in structure and degree of evaluation of individual study methodology. The scope of content, sensitivity and precision of searching in different databases varies so comprehensive searches for systematic reviews should include more than one database (Rathbone, Carter, Hoffmann, & Glasziou, 2016).

1.5.2 Overviews

With the large number of systematic reviews now published on different but related topics, the additional step has been taken of collecting and evaluating these related reviews in one place, to provide researchers, healthcare professionals, guideline developers, policy makers and healthcare users with a document to support decision making. Broader summaries of the evidence relating to multiple questions within a specific topic are achieved through the use of overviews, also known as umbrella reviews (Hartling, Chisholm, Thomson, & Dryden, 2012).

The intention of overviews is to create an easily accessible and useable document for end users that brings together in one place the relevant evidence pertaining to a topic (Chandler et al., 2020). Overviews do not necessarily seek to compare interventions, but rather to synthesise the evidence from systematic reviews providing a supported judgement on the effectiveness of different interventions Pollock *et al.*, 2020). Published overviews have become increasingly common over the last 20 years and methods have been variably reported with little reporting of the quality of the evidence in earlier publications (Hartling et al., 2012). An assessment should be made of the methodological quality and risk of bias in the systematic reviews using tools such as ROBIS (Whiting et al., 2016) or AMSTAR (Shea et al., 2007, 2017) with similar results achieved using either ROBIS or AMSTAR 2 for assessment (Pieper, Puljak, González-Lorenzo, & Minozzi, 2019). Cochrane systematic reviews typically have higher scores with good interrater reliability than non-Cochrane reviews using the AMSTAR tool (Pollock, Fernandes, & Hartling, 2017), which may reflect the clear guidelines for writing Cochrane systematic reviews. In recent Cochrane overviews, prior assessment of the risk of bias of outcomes from contributing trials in the systematic reviews was used (Pollock, Fernandes, Becker, Pieper, & Hartling, 2020) but older reviews may not have assessed the risk of bias for the outcomes of interest.

The methodology of overviews is evolving (Lunny, Brennan, McDonald, & McKenzie, 2017). There are important considerations in the process of carrying out an overview to create a meaningful piece of work and checklists have been suggested to ensure balanced reporting of harm and benefit, transparent assessment of bias including the common issue of co-authorship of reviews included in the overview (Büchter & Pieper, 2016), dealing with overlapping data (Lunny, Brennan, Reid, McDonald, & McKenzie, 2020) and ensuring that included reviews are up to date (Pieper, Antoine, Neugebauer, & Eikermann, 2014). The preferred reporting items for systematic reviews and meta-analysis (PRISMA) (Moher, Liberati, Tetzlaff, Altman, & PRISMA Group, 2009), and PRISMA harms checklist (Zorzela et al., 2016) form the foundation for the checklist (Bougioukas, Liakos, Tsapas, Ntzani, & Haidich, 2018).

1.5.3 Impact and effectiveness of systematic reviews and overviews

How effective systematic reviews or overviews are in terms of influencing guidelines, clinical practice or decision-making is difficult to define, but an evaluation of Cochrane systematic reviews found 483 out of 3187 (15%) reviews have been cited in 247 guidance documents. An

analysis to determine the impact and use of systematic reviews with or without meta-analysis and overviews published in clinical practice guidelines is underway (Lunny, Ramasubbu, et al., 2020). The design process of new randomised trials must review what evidence is already available on the subject to avoid unnecessarily duplicating trials on subjects when there is already sufficient data to support an answer or change in practice. This was highlighted by the ongoing trials of the administration of antenatal corticosteroids at women at risk of giving birth prematurely, despite clearly reduced neonatal mortality in meta-analyses (Sinclair, 1995). However, there has continued to be low use of available systematic reviews by researchers to guide study design (Cooper, Jones, & Sutton, 2005). The discrepancy in scope between reviews and guidelines, reviews being out of date and lack of communication between clinical review groups and guideline developers are barriers to effective use of reviews (Bunn et al., 2015). Further, priority setting in research needs to address the mismatch of questions in clinical practice or the needs of users and those addressed by researchers to avoid wasting effort and funding resources (Chalmers et al., 2014; Liberati, 2011)

1.6 Aims

With increasing worldwide prevalence of diabetes in pregnancy, the number of children born to mothers with diabetes has risen. The reported outcomes of children born to mothers with diabetes conflict, and there are limited data on any association with neonatal hypoglycaemia, a known risk factor of adverse neurodevelopmental outcomes, with adverse later outcomes. Further, many studies that reported longer term outcomes of children born to mothers with diabetes were carried out when management of diabetes and neonatal care was very different to current practices and involved small numbers of participants.

These studies investigated if there were effective antenatal interventions to reduce the incidence of GDM, if glycaemic control in pregnancy is associated with improved neurodevelopmental outcomes and if prophylactic oral dextrose gel given to babies with risk factors for neonatal hypoglycaemia including babies born to diabetic mothers alters neurodevelopmental outcomes.

The aim of the Cochrane overview, described in chapter 3 was to identify effective interventions for the prevention of GDM from all relevant Cochrane systemic reviews related to this topic.

The aim of the CHYLD sub-study, described in chapter 4, was to determine whether maternal glycaemic control during pregnancy and during labour or just prior to delivery was associated with the 2 and 4.5 year neurodevelopmental outcomes of children born to mothers with diabetes.

Oral dextrose gel is an effective treatment for neonatal hypoglycaemia and is being investigated as a prophylactic treatment for newborn infants identified as at risk of hypoglycaemia, with any effect on later neurodevelopmental outcomes to be determined. The aim of the pre-hPOD two year follow-up study described in chapter 5, was to determine if prophylactic oral dextrose gel altered neurodevelopment, health and growth at two years' corrected age in children who were at risk of neonatal hypoglycaemia. The aim of the sub-study of the hPOD two year follow-up study described in chapter 6, was to determine in infants of mothers with diabetes, whether the neurodevelopment, health and growth at two years' corrected age differed between those who received dextrose or placebo gel.

These data will help inform preventative or treatment strategies to improve the neurodevelopmental outcomes of children born to mothers with diabetes.

2 Methods

The first section of this chapter supplements the methods described in the Cochrane overview of interventions to prevent GDM. The following sections detail the methods of three prospective follow-up studies of children born at risk of neonatal hypoglycaemia assessed between two and four and a half years of age. The Children with Hypoglycaemia and their Later Development (CHYLD) sub-study reports outcomes of children born to diabetic mothers. The pre-hPOD follow-up study reports outcomes of children who were randomised to receive different doses of prophylactic dextrose or placebo gel in a randomised controlled trial which aimed to prevent neonatal hypoglycaemia. The hPOD sub-study reports the outcomes of children who were randomised to receive prophylactic dextrose or placebo gel to prevent neonatal hypoglycaemia in a randomised controlled trial which aimed to reduce admission to neonatal intensive care and were born to diabetic mothers.

2.1 Interventions to prevent women developing gestational diabetes: An overview of Cochrane reviews

A Cochrane overview is a summary of the evidence from Cochrane systematic reviews relating to a particular topic. The aim of such overviews is to link together in one place reviews about different but related interventions in order to create a resource for healthcare providers, guideline developers, researchers and, in the case of this overview, women and their families. The aim of this overview was to identify interventions that are effective in reducing the risk of GDM, in order to improve health outcomes for mothers and babies and to identify areas requiring further priority research.

We revised a previous published version of the Cochrane interventions to prevent women developing gestational diabetes overview protocol (R. L. Lawrence et al., 2016). The revised protocol focused on the single outcome, GDM, removing the multiple outcomes many of which were related to complications of GDM, including Caesarean section, LGA, and neonatal hypoglycaemia. Maternal metabolism in normal pregnancy and GDM was described and the potential interventions were updated after reviewing the literature.

The overview was written using guidelines from the Cochrane Handbook for Systematic Reviews, version 5.1 (J. P. Higgins & Green, 2011). Standard Cochrane methodology was used including using two authors to search for relevant reviews, extract and collate data. Further

details on the methods are presented in section 3.4. A system of using graphic icons, also used in other overviews (Medley, Vogel, Care, & Alfirevic, 2018) was adapted and used in this overview in order to provide a quick visual cue as to the effectiveness of each intervention.
Two tools were used to assess the quality of evidence at the level of the reviews or trials, Risk of Bias In Systematic Reviews (ROBIS) and Grades of Recommendation, Assessment, Development and Evaluation (GRADE).

2.1.1 ROBIS: Risk of Bias In Systematic Reviews

ROBIS is a tool designed to provide structured guidance for assessment of the quality of systemic reviews (Whiting et al., 2016). It is intended for use by overview authors as well as guideline developers for assessing the quality of the methodology of reviews about interventions, diagnosis, prognosis, and aetiology. ROBIS was used to assess each systematic review included in the overview. We used phase 2, 'Identifying concerns with the review process', and phase 3, 'Judging risk of bias', but chose not to use the optional phase 1, 'Assessing relevance', as we had already determined inclusion or exclusion of reviews based on our predefined criteria. Phase 2 used 21 questions across 4 domains of the review process, 'study eligibility', 'identification and selection of studies', 'data collection and study appraisal' and 'synthesis and findings' to identify potential areas of bias. A judgement of low/high/unclear level of concern regarding the methods in each domain was made. In phase 3, an overall judgement was made of whether the systematic review is at low/high/unclear risk of bias. Phase 2 and 3 were performed by two authors independently then compared. We resolved any disagreements by consensus.

2.1.2 GRADE: Grades of Recommendation, Assessment, Development and Evaluation

GRADE (Guyatt, Oxman, Akl, et al., 2011) is now used in all Cochrane systematic reviews to assess the quality of evidence of trials within the reviews, but older reviews have not always used GRADE. We used the review authors' GRADE assessment for the outcome GDM when available, and to made our own assessment when this wasn't available. This was carried out by two authors and any disagreements resolved following discussion. When multiple outcomes are included in a review, a selected number of key outcomes are assigned a GRADE evidence profile. The quality of evidence is evaluated for each outcome of interest with consideration of the study design, risk of bias, indirectness of evidence, inconsistency of evidence, imprecision of the estimated effect, likelihood of publication bias, and other points such as the magnitude

of the effect, any dose response effect, or residual confounding. Randomised controlled trials are considered high quality and observational studies low quality and additional downgrading or upgrading is based on the assessment of quality in each of the areas listed. An overall rating is then assigned to each chosen outcome of high-, moderate-, low- or very low quality of evidence.

2.2 Follow-up studies summary

The CHYLD sub-study reports on the association of maternal metabolic markers during pregnancy and labour and later childhood outcomes at age four or a half and two years. The pre-hPOD and hPOD sub-study report on childhood outcomes at age two years. The assessments performed in each study were similar and are summarised in Table 2.1.

Table 2.1 Summary of Assessments for the CHYLD and hPOD Studies

Study name	**Children with Hypoglycaemia and their Later Development (CHYLD) study 2-year follow-up study**	**CHYLD 4.5-year follow-up study**	**Pre-hPOD 2-year follow-up study**	**hPOD 2-year follow-up sub-study in IDM**
Study design	Cohort observational study		Follow-up of randomised controlled trials	
Research Question/s:	How does maternal glycaemic control during pregnancy and labour in diabetic pregnancy affect later development, learning-related skills and academic achievements? Is there any effect of neonatal hypoglycaemia on these outcomes?		Does prevention of neonatal hypoglycaemia with different doses of oral dextrose gel improve later neurodevelopmental outcomes?	Does prevention of neonatal hypoglycaemia with oral dextrose gel improve later neurodevelopmental outcomes in IDM?
Aims	To determine in children at four and half years' of age (or two years' corrected age if later data not available): 1. The effect of maternal HbA1c or polycose results during pregnancy on offspring neurodevelopment 2. The effect of maternal glucose concentrations during labour on offspring neurodevelopment 3. Any effect of fetal sex or neonatal hypoglycaemia on these outcomes		To determine in children at two years' corrected age: 1. The effect of different doses of dextrose gel prophylaxis on neurodevelopment, growth and physical health. 2. Whether these relationships differ in children with different neonatal risk factors.	To determine in children at two years' corrected age: 1. The effect of dextrose gel prophylaxis on neurodevelopment, growth and physical health. 2. The relationship between neonatal glycaemia (hypoglycaemia, hyperglycaemia, blood glucose stability) and neurodevelopment.
Participants				
Cohort	Infants recruited to 1 of 2 studies (Babies and Blood Sugar's Influence on EEG Study [BABIES] and the Sugar Babies Study), conducted from December 2006 to November 2010.		Children who were recruited at birth to the hypoglycaemia Prevention in newborns with Oral Dextrose: randomised controlled dosage trial (pre-hPOD) between August 2013 and November 2014.	Children who were recruited at birth to the hypoglycaemia Prevention in newborns with Oral Dextrose (hPOD) randomised controlled trial between February 2015 and May 2019.
Site(s)	Waikato Hospital, Hamilton, New Zealand		Waitemata and Auckland hospitals	Multicentre across New Zealand and Australia
Inclusion criteria	At risk of neonatal hypoglycaemia: diabetic mother, preterm (<37 weeks), small (<10th centile or <2500g), large (>90th centile or >4500g)			

	or acute illness AND ≥ 35 weeks' gestation	or acute illness AND ≥ 32 weeks' gestation	AND unlikely to require NICU admission for other reasons AND ≥ 35 weeks' gestation, birth-weight ≥ 2.2 kg, < 1 h old AND mother intending to breast-feed.	
Age at assessment	Two years, corrected age	Four and a half years, corrected age	Two years, corrected age	
Consent	Written informed consent was obtained at study entry and at follow-up.			
Ethical approval	Approval by Northern Y Ethics Committee. NTY/10/03/021		13/NTA/8 New Zealand	13/NTA/8 New Zealand HRECR/16/WCHN/86 Australia
Exclusion criteria for follow up study	Children with a brain injury due to an accident or serious illness			
Assessments				
Venue of assessments	Braemar Hospital or Kahikatea Research House in Hamilton, in suitable local clinics or in the child's own home.		Clinical Research Unit, or Well Child Clinic, University of Auckland, Auckland in suitable local clinics or in the child's own home.	
Neurodevelopmental assessments	Bayley Scales of Infant Development, 3rd edition	Wechsler Preschool and Primary Scale of Intelligence, Third edition Movement Assessment Battery for Children-2 Beery-Buktenica Developmental Test of Visual Motor Integration, Sixth Edition Auditory processing by auditory subscale of Phelps Kindergarten Readiness Scale	Bayley Scales of Infant Development, 3rd edition	
Executive Function	Executive function: four graded tasks of inhibition (Snack delay; Fruit stroop), attention (Fruit stroop), working memory and cognitive flexibility (Ducks and buckets; Multisearch multilocation.	Executive function: five graded tasks of working memory (Digit Span), flexibility and attention (Dimensional Change Card Sort), delay inhibition (Gift Wrap Delay), and complex or conflict inhibition (Bear and Dragon and Day and Night Stroop).	Executive function: four graded tasks of inhibition (Snack delay; Fruit stroop), attention (Fruit stroop), working memory and cognitive flexibility (Ducks and buckets; Multisearch multilocation).	

Neurological examination	Neurological examination of gait, coordination, tone, reflexes			
Anthropometric assessments	Weight, height, BMI, head circumference, mid-arm circumference			
			AND Waist circumference, triceps and subscapular skinfold thickness, total bod fat mass and fat free mass (percentage)	
Questionnaires	2y: Behaviour Rating Inventory of Executive Function- preschool version (BRIEF-P) Parental questionnaire: details of family environment, socioeconomic status, and medical history.	4.5y: BRIEF-P Strengths and Difficulties Questionnaire (SDQ), Child Behavior Checklist, Social Communication Questionnaire (SComQ) lifetime form Parental questionnaire: details of family environment, socioeconomic status, and medical history.	BRIEF-P Parental questionnaire: details of family environment, socioeconomic status, and medical history.	
Other	Visual acuity, stereopsis, ocular health, alignment and motility, and noncycloplegic refractive error and retinoscopy Motion coherence threshold (RDK)			
		B4 school check		

2.3 Children with Hypoglycaemia and their Later Development (CHYLD) study

The prospective cohort observational CHYLD study assessed children who had been enrolled before or shortly after birth in one of two parallel studies: the Babies and Blood Sugar's Influence on EEG Study (BABIES, Dec 2006 - Feb 2009) (Harris et al., 2011) and the dextrose gel for neonatal hypoglycaemia (Sugar Babies Study, Dec 2008 – Nov 2010), conducted from 2006 to 2010 at Waikato Hospital, Hamilton, New Zealand (Harris et al., 2012, 2013). The BABIES study enrolled 102 infants and investigated the relationship between electroencephalography patterns and neonatal hypoglycaemia and assessed whether non-glucose cerebral fuels altered these patterns. Hypoglycaemia was not associated with cot-side amplitude integrated electroencephalography and plasma concentrations of lactate, beta-hydroxybutyrate and glycerol did not alter during hypoglycaemia (Harris et al., 2011). The Sugar Babies Study enrolled 514 infants and was a randomised controlled trial which compared the effectiveness of 40% dextrose gel versus feeding alone for treatment of hypoglycaemia in late preterm and term babies. The primary outcome was treatment failure, defined as continued hypoglycaemia following two doses of gel (Australian New Zealand Clinical Trials Registry – ACTRN 12608000623392). The use of dextrose gel to treat hypoglycaemia was associated with a reduced risk of treatment failure compared with placebo in 242 infants (Harris et al., 2013).

The aim of the CHYLD study was to investigate the relationship between the duration, frequency, and severity of neonatal hypoglycaemia and later neuropsychological development. Eligible infants were at risk of neonatal hypoglycaemia (maternal diabetes, preterm birth between 32 and < 37 weeks, birthweight less than 10^{th} centile or less than 2500g (small) or birthweight greater than 90^{th} centile, or greater than 4500g (large). Children with a brain injury due to an accident or serious illness were excluded from follow-up. Children born at ≥ 35 weeks' gestation were eligible for assessment at 2 years' corrected age and all were eligible for assessment at 4.5 years of age. At age 2 and 4.5 years corrected age, neonatal hypoglycaemia was not associated with adverse neurodevelopment (McKinlay et al., 2015, 2017). However, at age 4.5 years, those children who were exposed to hypoglycaemia had a higher risk of a low executive function score, with children who had developed severe neonatal hypoglycaemia being at most risk (McKinlay et al., 2017). Children who had the higher BGC compared to the middle quintile for group were more likely to have neurosensory impairment. In children who did become hypoglycaemic, a more rapid rise in BGC was associated with increased risk of neurosensory impairment (McKinlay et al., 2015).

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

We carried out a sub-analysis of children within the CHYLD cohort who were born to mothers with diabetes to assess how maternal glycaemic control was associated with the risk of neonatal hypoglycaemia and offspring neurodevelopment. The overall aim of this study was to relate markers of glycaemic control during pregnancy and labour in women with pre-gestational or gestational diabetes with offspring neuropsychological developmental outcomes at age 2 and 4.5 years of age. We included children in the CHYLD study born to mothers with pre-existing and gestational diabetes.

Specific aims of the sub-group analysis were to determine at 4.5 years corrected age (or 2 years corrected age when no data was available for 4.5 years):

- The relationship between maternal diabetes type and offspring neurodevelopment.
- The relationship between maternal HbA1c during pregnancy on offspring neurodevelopment.
- The relationship between polycose 1 hour result after a 50g carbohydrate drink and offspring neurodevelopment.
- The effect of intrapartum BGC on the risk of neonatal hypoglycaemia (BGC < 2.6 mmol/L) and association with offspring neurodevelopment.

Outcomes

The primary outcome was neurosensory impairment, defined as any of the following at 4.5 years of age: visual impairment (visual acuity > 0.5 logMAR, (Snellen ≥20/63) in the better eye), deafness (requiring hearing aids), cerebral palsy, full-scale IQ or visual motor integration score more than 1 standard deviation below the test mean, MABC-2 total score less than 15th centile, or motion coherence threshold or executive function score worse than 1.5 standard deviation from the cohort mean. If the child had not been seen at 4.5 years of age, we used neurosensory impairment at 2 years corrected age, defined as any of the following: developmental delay (BSID-III cognitive or language composite score of <85), motor impairment (BSID-III motor composite score of <85), cerebral palsy, hearing impairment (requiring hearing aids), or blindness (≥1.4 logMAR in both eyes).

Ethics and Consent

The regional ethics committee approved the neonatal (NTY/08/03/025) and follow-up (NTY/10/03/021) studies. Ethics application for the 2 year follow up study was approved by the Northern Y Health and Disability Ethics Committee on 4 June 2010. An amendment to include the 4.5 year follow-up was

approved on 24 June 2011. Parents or caregivers who agreed to their child being in the follow-up study were given an information pack, an explanation of the components of assessment, and the opportunity to ask questions. Written informed consent was obtained from a parent or guardian at study entry and at follow-up. Parents and caregivers had the right to withdraw their child from the study at any time without giving a reason

Contact tracing

Contact tracing was by using records obtained during the neonatal period. If information was incorrect or not available, tracing was via their primary health provider, midwife or other family members. A check was made of NHI numbers to ensure not contacting families whose babies had died. Invitations to participate in the CHYLD follow-up study were sent to families when the child was nearing 2 years' and 4.5 years' age

Maternal data

Information about maternal BMI (calculated from recorded booking height and weight) and diabetes type was taken from clinical records. Both electronic laboratory results and paper records were retrieved and reviewed for maternal HbA1c, polycose and BGC results.

Diagnosis of gestational diabetes

At the time this study was performed, women with previous GDM, LGA baby, previous stillbirth, high risk ethnicity (such as Māori, Pacific Islander, Indian) or a family history of diabetes were screened for gestational diabetes. Testing was generally advised at 28 weeks' gestation using a polycose test, then oral glucose tolerance test if the polycose was positive. However, practice varied across practitioners caring for women during pregnancy. Gestational diabetes was diagnosed by a fasting BGC of $\geq$ 5.5 mmol/L or 1-hour BGC of > 11 mmol/L after 50 g carbohydrate load ("polycose") administered between 20 and 32 weeks' gestation.

Intrapartum monitoring

There was no national guideline on the frequency of maternal BGC measurements during labour at the time of this study. We included blood glucose measurements in the 6 hours prior to birth as we considered this period more likely to influence neonatal glycaemic control in the first few hours after birth.

Infant data

Details of gestational age at birth, birth weight, height and head circumference were recorded at the time of enrolment. Infant BGC 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, BGC were measured 4 hourly for 12 hours, and then as clinically indicated.

Assessment format at 2 years' corrected age

The assessment was conducted by a research nurse, paediatrician and optometrist, who were unaware of the child's neonatal course and randomisation group. Psychological and visual assessment were carried out first in the session. Assessors were trained to 98% agreement on observational measures, Bayley Scales of Infant Development, 3rd edition (BSID) and executive function (EF). Children were assessed as close as possible to 2 years' corrected age. Visual assessments at age 2 years' corrected age were by a single assessor. Assessments were carried out during a single session in a health clinic or if preferred, at home.

Bayley Scales of Infant Development, 3rd edition (Bayley, 2006b): Composite scores on these scales have a mean score of 100 and SD of 15. Higher scores indicate better performance. Children who were unable to complete the Cognitive, Language or Motor Scales of the BSID-III because of severe delay in these domains were assigned scores of 49.

Executive function: Four graded tasks administered in a standard order: snack delay (inhibition), fruit stroop (attention, inhibition), reverse categorisation of ducks (working memory, cognitive flexibility), multisearch multilocation (working memory, cognitive flexibility) (Ansell et al., 2017). The BRIEF-P (Gioia et al., 2002) rating scale was completed by the parent or caregiver as a complementary assessment of executive function as observed in everyday living. The five domains (Inhibit, Shift, Emotional Control, Working Memory, and Plan/ Organize) are summarised in three overlapping indexes: Inhibitory Self-Control (Inhibit and Emotional Control), Flexibility (Shift and Emotional Control), and Emergent Metacognition (Working Memory and Plan/Organize).

Neurology exam: Cerebral palsy was categorised according to the Gross Motor Function Classification System (Palisano et al., 1997). A paediatric neurological examination was conducted including assessment of tone, reflexes, gait, balance and coordination.

Vision screening: Children received an optometric examination as posterior white matter changes and restricted diffusion have been associated with hypoglycaemia (Burns et al., 2008; Tam et al., 2008).

Motion coherence threshold: Children were seated 50 cm to 70 cm from the computer screen. MATLAB® software (MathWorks, Natick, MA) was used to present random dot kinematograms (RDKs) with coherence levels of 100%, 84%, 68%, 52%, 36%, 20% in random order across consecutive trials and the sequence was repeated until the child could no longer be encouraged to look at the monitor. During each trial, the RDK stimulus was presented for 8 seconds at a fixed level of coherence. The video footage was reviewed by assessors trained to detect ocular movements. Visible slow tracking eye movement, fast saccades, or a combination of slow tracking and fast saccades were used to determine the presence and direction of the OKN. Only datasets with a minimum of 3 per level of coherence for a minimum of 5 levels of coherence were analysed (T.-Y. Y. Yu et al., 2013).

Home environment and general health were assessed using a questionnaire.

Assessment format at 4.5 years' corrected age

The assessment was conducted by a paediatrician, psychologist and optometrist, who were unaware of the child's neonatal course and randomisation group. Assessors were trained and overseen by one psychologist. Children were assessed as close as possible to 4.5 years' corrected age.

Cognitive ability: Wechsler Preschool and Primary Scale of Intelligence, Third edition (Wechsler, 2002)
Executive function: 5 graded tasks of working memory (digit span), flexibility and attention (dimensional change card sort), delay inhibition (gift wrap delay), complex or conflict inhibition (bear and dragon and day and night stroop). Successful completion of the practice trials of a task scored one point, completion of lower levels of a task scored two points, and completion of more complex levels of a task scored three points. 6 points could be scored for each task, and the executive function score was the sum of the individual task scores, out of a maximum of 30 points. Further details for scoring can be found below (McKinlay et al., 2017). The BRIEF-P rating scale was completed by the parent or caregiver.

Table 2.2 Executive function tasks administered at 4.5 years' age

Task	Successfully completed practice trials	Success at level 1	Success at higher level
Score for each task at this level	1	2	3
Gift Wrap Delay	Latency to first peek ≥10 seconds	Peek resistance score ≤1	No peeking
Bear / Dragon - Inhibition	≥3 out of 6 correct (non-consecutive, bear or dragon)	Dragon trials only: ≥12 out of 18 correct	Dragon trials: all 18 correct
Dimensional Change Card Sort	≥5 out of 6 on pre- switch trials	All 6 of the post- switch trials correct	≥9 out of 12 of border trials correct
Day / Night Stroop	At least 1 day and 1 night trial correct in the 6 practices or first 6 trials	≥16 out of 32 correct for total trials score	≥30 out of 32 correct for total trials score
Digit Span	≥3 out of 4 correct (sequence A or sequence B)	≥4 out of 14 trials correct on sequence A or B	≥6 out of 14 trials correct on sequence A or B
Maximum score for this level	5	10	15

Movement Assessment Battery for Children-2 (Henderson, Sugden, & Barnett, 2007) to identify motor impairment.

Vision assessment: Optometry examination and global motion coherence MATLAB (MathWorks, Natick, MA). Beery-Buktenica Developmental Test of Visual Motor Integration, Sixth Edition (Beery, Buktenica, & Beery, 2010) to identify deficits in coordination of motor and visual skills.

Auditory processing was assessed using auditory subscale of Phelps Kindergarten Readiness Scale (*Phelps Kindergarten Readiness Scale Manual.*, 2003).

Neurology exam: A paediatric neurological examination was conducted including assessment of tone, reflexes, gait, balance and coordination. Cerebral palsy was categorised according to the Gross Motor Function Classification System (Palisano et al., 1997).

Behavioural and emotional difficulties were screened for using the Strengths and Difficulties Questionnaire (SDQ) (Goodman, 1997), Child Behavior Checklist (Achenbach & Rescorla, 2000) and Social Communication Questionnaire (SCQ) lifetime form (Rutter, Bailey, & Lord, 2003).

Home environment and general health were assessed using a questionnaire.

Statistical analysis for the CHYLD study

Study data were stored and maintained using an SQL database. All quality checks were performed using and statistical analyses performed using JMP 12.1 (SAS Institute Inc., Cary, NC) software.
We pre-specified statistical analysis plans, agreed upon by all co-authors before undertaking data analysis.

Standard descriptive statistics were presented as measures of central tendency and spread or numbers and frequency. Odds ratios with 95% confidence intervals were estimated using nominal logistic regression, adjusted for New Zealand Deprivation Index (NZDPI) (model 1); New Zealand Deprivation Index, gestation, birthweight z-score (model 2); NZDPI, maternal BMI category at booking (model 3); NZDPI, maternal BMI category at booking, gestation, birthweight z-score (model 4). These potential confounders were pre-specified based on knowledge of their association with neurodevelopmental outcomes. All statistical tests were 2-sided with a p value of 5%. Ethnicity was prioritised in the order Māori, Pacific, Asian, New Zealand European, other.

Similar comparisons were made for secondary outcomes, with estimation of relative risks or mean differences with 95% confidence intervals nominal logistic regression, adjusting for above factors. A significance level of 5% was used for each secondary outcome.

Since the number of pairs of twins in the study was small, analyses were not adjusted for the clustering effect of children from multiple pregnancy. Because any missing data were not likely to be missing at random, imputation methods were not used.

2.4 Long term effects of dextrose gel prophylaxis for neonatal hypoglycaemia

2.4.1 Outcome at two years after dextrose gel prophylaxis for neonatal hypoglycaemia: Follow up of the pre-hPOD randomised trial

Prophylactic oral dextrose gel for newborn babies at risk of neonatal hypoglycaemia: randomised controlled dose-finding trial (the pre-hPOD study)

The pre-hPOD dosage study was a randomised controlled trial to determine a dose of 40% oral dextrose gel that would prevent neonatal hypoglycaemia in newborn babies at risk (Harding, Crowther, et al., 2015). The trial was undertaken between August 2013 and November 2014 by researchers from the

University of Auckland, at Auckland City Hospital and Waitakere Hospital (Australian New Zealand Clinical Trials Registry – ACTRN 12613000322730).

Eligibility criteria.

Inclusion criteria:
Babies at risk of hypoglycaemia: IDM (any type of diabetes), preterm (<37 weeks), small (< 2.5 kg or < 10th centile on population or customised birthweight chart) or large (> 4.5 kg or > 90th centile on population or customised birthweight chart)
AND ≥ 35 weeks' gestation, birthweight ≥ 2.2 kg, < 1 hour old
AND no apparent indication for NICU admission at time of randomisation)
AND mother intending to breast-feed.

Exclusion criteria:
Major congenital abnormality, previous formula feed or intravenous fluids, previous diagnosis of hypoglycaemia, admitted to NICU or imminent admission to NICU.

A total of 416 infants were recruited to this study (1 incorrectly after the trial had finished) and randomised to one of eight arms of the trial: four oral 40% dextrose dose regimes, with four equal volume placebo (2% hydroxymethylcellulose) arms for comparison:

1. Single-dose oral dextrose gel 0.5 ml/kg (200 mg/kg)
2. Single-dose placebo gel 0.5 ml/kg
3. Single-dose oral dextrose gel 1 ml/kg (400 mg/kg)
4. Single-dose placebo gel 1 ml/kg
5. One initial dose of oral dextrose gel 0.5 ml/kg followed by three subsequent pre-feed doses of oral dextrose 0.5 ml/kg
6. One initial dose placebo gel 0.5 ml/kg followed by three subsequent pre-feed doses of placebo gel 0.5 ml/kg
7. One initial dose of oral dextrose gel 1 ml/kg followed by three subsequent pre-feed doses of oral dextrose 0.5 ml/kg
8. One initial dose placebo gel 1 ml/kg followed by three subsequent pre-feed doses of placebo gel 0.5 ml/kg.

Study gel was massaged into the buccal mucosa once 1 hour after birth or additionally on three further occasions before feeds, 2 - 4 hourly, in the first 12 hours after birth. BGC were measured at 2 hours of

age and subsequently according to hospital guidelines. BGC were analysed by the gold standard glucose oxidase method with a portable blood glucose analyser (iSTAT, Abbott Laboratories, Abbott Park, IL USA) or a combined metabolite/blood gas analyser (ABL 700, Radiometer Ltd, Copenhagen, Denmark). Hypoglycaemia was defined as a BGC of < 2.6 mmol/L. The primary outcome of the trial was hypoglycaemia, defined as any BGC < 2.6 mmol/L.

Results

Any dose of dextrose gel reduced the risk of the infant developing hypoglycaemia (RR 0.79, 95% CI 0.64, 0.98, p = 0.03; number needed to treat=10, 95% CI 5-115) after adjusting for sex, gestational age and mode of birth. The risk in different dextrose gel dosage groups were: 0.5 ml/kg: RR 0.68 (95% CI 0.47 – 0.99), p=0.04; 1 ml/kg: RR 0.84 (95% CI 0.61 – 1.15), p=0.28; 0.5 ml/kg four doses: RR 0.85 (95% CI 0.58 – 1.23), p=0.39; 1 ml/kg then 0.5 ml/kg three doses: RR 0.79 (95% CI 0.54 – 1.17), p=0.24. Dextrose and placebo groups were similar for secondary outcomes: admission to a NICU (RR 0.64; 95% CI 0.33–1.25, p= 0.19), and breastfeeding at discharge and at 6 wk. However, admission for hypoglycaemia was less common in infants who received dextrose gel (RR 0.46; 95% CI 0.21–1.01, p= 0.05) (Hegarty et al., 2016). Follow-up of this cohort was planned to determine if there were clinically important benefits in the longer term.

Two year follow-up of the pre-hPOD randomised trial

The overall aim of our study was to determine if prophylactic oral dextrose altered development, health and growth at two years' corrected age.

Specific aims were to determine in pre-hPOD participants at two years' corrected age:

1. The effect of dextrose gel prophylaxis compared with placebo on neurodevelopment, growth and physical health.
2. Whether the effect of dextrose gel on these outcomes was influenced by the dose of dextrose gel
3. The relationship between neonatal glycaemia (hypoglycaemia, hyperglycaemia, blood glucose stability) and neurodevelopment
4. Whether these relationships differed in children with different neonatal risk factors.

Eligible participants were children who had participated in the pre-hPOD trial, who were alive at age two years and whose parents had given consent for follow-up at the time of enrolment.

Ethics and Consent

Consent to contact families of babies for later childhood follow up was sought at the time of recruitment to the neonatal trial. All parents or caregivers of the children who participated in the pre-hPOD dosage trial and who consented to further contact were invited to join this follow-up study. Parents and caregivers could withdraw their child from the study at any time without needing to provide a reason. Ethics approval was obtained from the Health and Disability Ethics Committees of New Zealand (trial: 13/NTA/8) (follow-up study: 15/STH/97) and caregivers gave written informed consent at the time of assessment.

Tracing

The hPOD Study Group maintained contact with participants' families, sending a first birthday card to the participating child and, for families who registered to receive them, monthly newsletters. A check was made using the child's NHI number to avoid contacting families whose child had died, before sending an invitation to participate in the hPOD 2 year follow-up study when the child was approaching two years' corrected age. When contact information was not available or out of date, families were traced via hospital records, their primary health care provider or other family members. An invitation and information sheet was sent via email. If there was no response, this was followed up by phone call or text then home visit. An information sheet was provided to ensure families had adequate information before making a decision about participation. Children were assessed as close as possible to 24 months' corrected age. Assessments were carried out in clinic or if preferred at home.

Assessment format

The assessment was conducted by a paediatrician, research nurse or research assistant (overseas trained doctor), who were unaware of the child's neonatal course and randomisation group. Assessors were trained and overseen by one psychologist. Assessments performed in clinic were videoed with parental consent and a copy given to families. A random selection of 10% of the videos were reviewed by the psychologist to ensure interrater reliability and accuracy of administration.

The session took between 1.5 and 2.5 hours with breaks as needed to maintain the child's interest and compliance with assessment tasks. The BSID cognitive, language and fine motor domains were assessed first, then executive function. These were followed by motion coherence threshold testing, BSID gross motor domain and paediatric assessment. During the assessment, the parent or caregiver completed questionnaires. When these were not able to be completed, a postage paid addressed envelope was provided for return of completed questionnaires. A short written summary of findings was sent to the

parent or guardian and to the child's General practitioner (GP) with parental consent. If there were concerns about a child's development, referral to the appropriate health agency via the GP was made with the consent of the parents. Parents, caregivers or healthcare providers could request a more detailed report of the assessment if required.

Developmental testing

The psychological assessment included the Cognitive, Language (receptive and expressive), Motor (gross and fine motor), Social-Emotional and Adaptive Behaviour scales of the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) (Bayley, 2006b). Composite scores on these scales have a mean (SD) score of 100 (15) and are corrected for prematurity (<37 weeks). Higher scores indicate better performance. Children unable to complete the Cognitive, Language or Motor Scales of the BSID-III because of severe delay in any of these domains were assigned scores of 49.

Developmental delay was defined as:

Mild: Cognitive or Language composite scores >1 to 2 SD below the mean.

Moderate: Cognitive or Language composite scores >2 to 3 SD below the mean.

Severe: Cognitive or Language composite scores more than 3 SD below the mean.

Neurosensory Disability was defined as:

Mild: Mild cerebral palsy (the child is able to walk by 2 years of age) or Motor composite score >1 to 2 SD below the mean or mild developmental delay.

Moderate: Moderate cerebral palsy (the child is non-ambulant at 2 years of age but is likely to walk) or Motor composite score >2 to 3 SD below the mean or moderate developmental delay or deafness.

Severe: Severe cerebral palsy (the child is considered permanently non-ambulant) or Motor composite score below 3 SD below the mean or severe developmental delay or blindness.

Executive function tasks

Four graded tasks were administered to test inhibitory control and attentional flexibility. Simple inhibitory control was tested with the Snack Delay, and more complex inhibitory control with the Shape Stroop (Kochanska et al., 2000) and Reverse Categorisation (Ducks and Buckets) tasks (Carlson et al., 2004). Attentional flexibility was tested with the Multi-search Multi-location Task (MSML) (Zelazo et al., 1998). Each task included practice trials to ensure the child understood the instructions and could complete the task. If a child could not be tested (did not succeed with practice or any trials), assessors recorded whether this was due to difficulties with language (didn't understand the task) or behaviour

(refused to do the task). Scores were allocated as below. A total score up to a maximum of 24, was calculated even if data were missing for some tasks.

Table 2.2 Scoring of the executive function test battery

Task	**Can Do (Completed practice trials)**	**Did Do (Success at level 1)**	**Did Advanced (Success at higher level)**
Score for each task at this level	1	2	3
MSML	1-3 trials	3 consecutive pre-switch	2 consecutive post-switch
Fruit Stroop	1-3 trials	1 correct	2-3 correct
Snack Delay	1-2 trials	Score 1 (5 second delay)	Score 2-4 (15 to 45 second delay)
Ducks & Buckets	1-2 trials	5 out of 6 categorised	>3 reverse categorised
Maximum score for this level	**4**	**8**	**12**

Paediatric assessment:

A health questionnaire was completed, which included past medical history, atopic disease and allergies, immunisation history, infections.

Neurological examination

The child's gait when walking and running, their balance and manoeuvrability were observed. The tone and reflexes in both upper and lower limbs were examined.

Anthropometry

Children were weighed to the nearest 100g, without shoes and with minimal clothing, using digital scales. The height was measured to the nearest completed millimetre using a calibrated stadiometer. Head circumference was measured to the nearest completed millimetre three times, using a non-stretch tape measure, around the longest occipito-frontal circumference and the greatest measurement recorded. Abdominal circumference and mid-arm circumference measured to the nearest completed millimetre, using a non-stretch tape measure.

Skin-fold thickness at triceps and subscapular sites was measured to the nearest 0.2 cm using a Harpenden calliper (Baty International, Burgess Hill, UK. Two measurements were taken at each site and an average calculated. If the two measurements were discrepant by > 0.6 cm, a third measure was obtained and the median calculated.

Corrected age and sex-specific z-scores were calculated using WHO growth standards. Specifically, we used the SAS igrowup software (World Health Organisation, 2010), developed by the WHO, which calculates z-scores for seven anthropometric indicators, as below.

1. Weight-for-age and sex z-score
2. Height-for-age z-score
3. Weight for height
4. Head circumference-for-age z-score
5. Arm circumference-for-age z-score
6. Triceps skin fold thickness
7. Subscapular skinfold thickness

Body composition

Three measurements of total body fat mass and fat free mass were estimated using multifrequency bioimpedance analysis (Imp SFB7, ImpediMed, Carlbad, USA) and software provided by the manufacturer. Latex free gel electrodes were applied to landmarks: above the wrist between the styloid processes of the radius and ulna and back of the hand over distal third metacarpal and anterior ankle between the medial and lateral malleoli and over the central second metatarsal.

Parental questionnaires

Parents or caregivers were asked to complete 3 questionnaires: the home and family questionnaire family (included contact details, demographics, income, education, languages spoken at home, health information, maternal health, breast feeding, household alcohol and drug use); Behavior Rating Inventory of Executive Function-Preschool Version (BRIEF-P) (Gioia et al., 2002) and Bayley III Social-Emotional and Adaptive Behavior.

Outcomes

Primary outcomes

We defined two co-primary outcomes: neurosensory impairment (legal blindness; sensorineural deafness requiring hearing aids; cerebral palsy; Bayley Scales of Infant Development 3rd edition [BSID-III] cognitive, language or motor score more than one standard deviation below the mean) and executive function z-score <-1.5.

Secondary outcomes

1. Bayley Scale of Infant Development Version III composite cognitive score and proportion with score more than one standard deviation below the mean.
2. Bayley Scale of Infant Development Version III composite and scaled (expressive and receptive) language scores and proportion with scores more than one standard deviation below the mean.
3. Bayley Scale of Infant Development Version III composite and scaled (fine motor and gross motor) motor scores and proportion with scores more than one standard deviation below the mean.
4. Bayley Scale of Infant Development Version III Social Emotional score.
5. Bayley Scale of Infant Development Version III General Adaptive score.
6. Legal blindness (Yes/No), low vision (Yes/No), other visual problems (Yes/No)
7. Sensorineural deafness requiring hearing aids (Yes/No), other hearing problems (Yes/No)
8. Cerebral palsy (Yes/No) and severity (Mild, Moderate, Severe)
9. Abnormalities of tone and coordination (gait, balance, tone and reflexes) (Yes/ No)
10. Executive function score and proportion with z-score <-1.5
11. Brief-P Summary Indexes and Composite score, and proportion with a global T score ≥ 65
    - Inhibitory Self-Control Index (ISCI)
    - Flexibility Index (FI)
    - Emergent Metacognition Index (EMI)
    - Global Executive Composite (GEC)
12. Anthropometry by UK-WHO (World Health Organisation, 2010).
    - Height for age and sex z-score
    - Weight for age and sex z-score
    - Head circumference for age and sex z-score
    - Weight for height and sex z-score
    - Skinfold thickness (triceps and subscapular) for age and sex z-score
    - Mid-arm circumference for age and sex z-score
13. Total body fat mass and fat free mass adjusted for height
14. Abdominal circumference adjusted for height
15. Seizures (afebrile/febrile/none)
16. Asthma: Doctor diagnosed (Yes/No), hospitalisation for wheeze / asthma (Yes/No), use of inhaler for wheeze / asthma in past 12 months (Yes/No)
17. Eczema: Doctor diagnosed (Yes/No), Itchy rash coming and going for ≥6 months (Yes/No), Use of medications or ointments / creams for itchy rash in past 12 months, current eczema (Yes/No) and severity (assessed using the Severity Scoring of Atopic Dermatitis: SCORAD index)

18. Any allergic disease (doctor diagnosed) (Yes/No)
19. Healthcare utilisation: Bacterial infections requiring antibiotics (Yes/No), viral infections requiring visit to doctor (Yes/No), hospitalisation for infectious disease (Yes/No)

Analyses

If there were no differences in primary outcomes between different placebo groups, we planned to combine these into a single placebo group for analyses.

For the primary outcomes, the proportions of children with neurosensory disability or processing difficulty was compared between those randomised to: 1) increasing total dextrose dose (200 mg, 400 mg, 800 mg or 1 g) vs. placebo; 2) single vs. multiple dextrose gel doses; 3) any dextrose dose vs. any placebo dose. These multiple analyses were undertaken because this was the first available data on later outcomes of prophylactic dextrose gel and was therefore being examined for information about safety.

We calculated the interaction between the effect of any dextrose gel versus placebo on primary outcomes and their components and:

1. Reason for risk of hypoglycaemia (IDM versus other)
2. Gestational age (preterm 35-36 weeks versus term 37-41 weeks)

We also conducted exploratory analyses of:

1. The effect of hypoglycaemia on the primary outcome and its components.
2. The effect of dextrose versus placebo on outcomes in those who became hypoglycaemic.

In a sub-group analysis, the proportions of children with the primary outcomes were compared specifically between those who received any single dose of placebo and those who received a single 200mg/kg dose of dextrose gel, since this was the dose selected for use in the main hPOD study.

Statistical methods

Study data were stored and maintained centrally using an SQL database. All data quality checks and statistical analyses were performed using SAS version 9.4 (SAS Institute Inc. Cary NC).

We prespecified statistical analysis plans, agreed upon by all members of the steering group committees, including a statistician, before undertaking data analysis.

Standard descriptive summary statistics were presented as measures of central tendency and spread, or numbers and frequency. Relative risks with 95% confidence intervals were estimated using generalised

linear models (log-binomial for categorical variables; identity-normal for continuous variables), adjusted for recruitment centre, socioeconomic status New Zealand Deprivation Index (NZDep) at birth, gestational age and sex. These potential confounders were pre-specified with knowledge of their association with neurodevelopmental outcomes. All statistical tests were two-sided with a p value set at 5%. For the co-primary outcomes, alpha error was maintained at 5% by dividing the p value evenly between the two outcomes. All analyses were performed on an intention to treat basis. We used orthogonal contrasts for linear trend analysis over increasing total dextrose dose and Dunnett's test for multiple comparisons. Ethnicity was prioritised in the order Māori, Pacific Island, Asian (Indian or Chinese), New Zealand European, other.

Similar comparisons were made for secondary outcomes, with estimation of relative risks or mean differences with 95% confidence intervals using generalised linear models (log-binomial for categorical variables; identity-normal for continuous variables), adjusting for above factors. A significance level of 5% was used for each secondary outcome with no adjustment for multiple comparisons.

Since the number of pairs of twins in the study was small, analyses were not adjusted for the clustering effect of children from multiple pregnancy. Because any missing data were not likely to be missing at random, imputation methods were not used.

2.4.2 Outcome at two years of children born to diabetic mothers after dextrose gel prophylaxis for neonatal hypoglycaemia: a sub-study of follow up of the hPOD randomised trial.

Neonatal hypoglycaemia prevention with oral dextrose gel (hPOD): A multicentre, double blind, randomised controlled trial.

The hypoglycaemia prevention in newborns with oral dextrose trial was a multicentre, randomised, placebo-controlled, double blind trial to investigate the effect of 40% dextrose gel on the risk of hypoglycaemia and admission to NICU in the first 48 hours after birth (Harding, Hegarty, et al., 2015). The trial was undertaken between Jan 2015 and May 2019 in 18 hospitals in New Zealand and Australia (Australian New Zealand Clinical Trials Registry - ACTRN 12614001263684).

Eligibility criteria were the same as for the pre-hPOD trial (see 2.4.1).

A total of 2149 infants were recruited to the trial and randomised to 0.5 ml/kg (200mg/kg) of 40% dextrose or placebo. Study gel was massaged into the buccal mucosa 1 hour after birth. The primary

outcome was admission to neonatal intensive care. Follow-up of the cohort was planned to determine if prophylactic dextrose gel improves development, health and growth at two years' corrected age.

Two year follow-up study

Analysis of the two year outcome data of a subgroup of IDM, collected by the end of February 2020, was blinded to group allocation (dextrose or placebo gel), since the follow-up study is ongoing. Unblinded data management staff, who are not involved in any other aspects of the study or the data analysis extracted data and allocated the two randomisation groups (dextrose gel or placebo) as A or B. All other research team members remained blinded to the group allocation.

Study objectives

The overall aim was to determine if IDM who received prophylactic gel A differed from those who received gel B in development, health and growth at two years' corrected age.

Specific aims were to determine in hPOD IDM participants at two years' corrected age:

1. The effect of gel A versus gel B on neurodevelopment, growth and physical health
2. The relationship between neonatal glycaemia (hypoglycaemia, hyperglycaemia, blood glucose stability) and neurodevelopment
3. Whether these relationships differed in children with different types of maternal diabetes.
4. Whether these relationships differed in children with additional risk factors (preterm, small, large)

Eligible participants were children of diabetic mothers who had participated in the hPOD trial, who were alive at age two years and whose parents had given consent for follow-up at the time of enrolment.

Ethics and Consent

Consent to contact families of babies for later childhood follow up was sought at the time of recruitment to the neonatal trial. All parents or caregivers of the children who participated in the hPOD dosage trial and who consented to further contact were invited to join this follow-up study. Parents and caregivers could withdraw their child from the study at any time without needing to provide a reason. Ethics approval was obtained from the Health and Disability Ethics Committees of New Zealand (trial: 13/NTA/8), (follow-up study: (15/STH/97) and caregivers gave written informed consent at the time of assessment.

Tracing

As per pre-hPOD methods, section 2.4.1

Assessment format

As per pre-hPOD methods, section 2.4.1

Analyses

The primary outcome was Neurosensory impairment at 2 years' corrected age defined as any of:
legal blindness; sensorineural deafness requiring hearing aids; cerebral palsy; Bayley Scale of Infant Development Version III (Bayley, 2006b) cognitive, language or motor score more than one standard deviation below the mean or Executive Function composite z-score <-1.5 (derived from standardisation within the pre-hPOD cohort (Hegarty et al., 2016).

Secondary outcomes were:

1. Severity of neurosensory impairment (Mild, Moderate, Severe)
2. Developmental delay (Yes/No) and severity (Mild, Moderate, Severe)
3. Bayley Scale of Infant Development Version III composite cognitive score and proportion with score more than one standard deviation below the mean.
4. Bayley Scale of Infant Development Version III composite language score and proportion with score more than one standard deviation below the mean.
5. Bayley Scale of Infant Development Version III composite motor score and proportion with scores more than one standard deviation below the mean.
6. Bayley Scale of Infant Development Version III Social Emotional score.
7. Bayley Scale of Infant Development Version III General Adaptive score.
8. Legal blindness (Yes/No)
9. Sensorineural deafness requiring hearing aids (Yes/No)
10. Cerebral palsy (Yes/No) and severity (Mild, Moderate, Severe)
11. Abnormalities of tone and coordination (gait, balance, tone and reflexes) (Yes/ No)
12. Executive function composite score and composite z-score <-1.5 (defined from standardisation within the pre-hPOD 2 year follow-up cohort)
13. BRIEF-P (Gioia et al., 2000) summary indexes and global T score, and proportion with a global T score ≥ 65
    - Inhibitory Self-Control Index (ISCI)
    - Flexibility Index (FI)

- Emergent Metacognition Index (EMI)
- Global Executive Composite (GEC)

14. Anthropometry by WHO (World Health Organisation, 2010).
    - Height for age and sex z-score
    - Weight for age and sex z-score
    - Head circumference for age and sex z-score
    - Weight for height and sex z-score
    - Skinfold thickness (triceps and subscapular) for age and sex z-score
    - Mid-arm circumference for age and sex z-score
15. Total body fat mass and fat free mass adjusted for height
16. Abdominal circumference adjusted for height
17. Seizures (afebrile/febrile/none)
18. Asthma: Doctor diagnosed (Yes/No), hospitalisation for wheeze / asthma (Yes/No), use of inhaler for wheeze / asthma in past 12 months (Yes/No)
19. Eczema: Doctor diagnosed (Yes/No), Itchy rash coming and going for ≥6 months (Yes/No), Use of medications or ointments / creams for itchy rash in past 12 months, current eczema (Yes/No) and severity (SCORAD ("Severity Scoring of Atopic Dermatitis: The SCORAD Index. Consensus Report of the European Task Force on Atopic Dermatitis.," 1993))
20. Any allergic disease (doctor diagnosed) (Yes/No)
21. Healthcare utilisation: Suspected infections treated with antibiotics (Yes/No), suspected infections requiring visit to doctor (Yes/No), hospitalisation for presumed infectious disease (Yes/No)

Primary analyses

For the primary and secondary outcomes, the proportions of children with neurosensory impairment were compared between those randomised to gel A vs gel B.

Secondary Exploratory Analyses

Secondary analyses looked for any interaction between the effect of gel A vs gel B on the primary outcomes and its components and:

1. Type of maternal diabetes (gestational, type 1 or type 2)
2. Gestational age (preterm (35-36 weeks) vs term (37-41 weeks))

We conducted exploratory analyses within this cohort to investigate the association between the following exposures and the primary outcome and its components, for the IDM cohort, of:

1. Hypoglycaemia (a hypoglycaemic episode was defined as one or more consecutive measurements of BGC < 2.6mmol/L): i) none vs. any hypoglycaemia, ii) none vs. severe hypoglycaemia (BGC <2.0mmol/L) iii) none vs recurrent (≥ 3 episodes) hypoglycaemia, in the first 48 hours after birth.
2. Hyperglycaemia (any BGC >8mmol/L) in the first 48 hours after birth.
3. Blood glucose stability, defined as % of results, in quintiles (Q1-5), outside the central referent range (Q3) in the first 48 hours after birth.
4. Additional risk factors: preterm, LGA, or SGA (present / not present).

Subgroup analysis

Subgroup analysis used logistic regression to determine the effect of gel A vs gel B in those who became hypoglycaemic on the primary outcome.

Sensitivity analyses

We performed a sensitivity analysis excluding children in whom events or diagnoses are likely to have affected the outcome independent of the study intervention.

- Children who experienced a post-neonatal illness or injury or have a post-neonatal diagnosis of a congenital anomaly that might have influenced neurodevelopmental outcome were reviewed by a panel of the clinician members of the Steering Group. They identified children in whom these events or diagnoses were likely to have affected the outcome independent of the study intervention.

We also performed a sensitivity analysis excluding children who were assessed outside of the intended age window (24 months' corrected age +/- 1 month).

Statistical methods

Study data were stored and maintained centrally using an SQL database. All data quality checks and statistical analyses were performed using JMP 15 (SAS Institute Inc., Cary, NC, 1989-2019).

We prespecified statistical analysis plans, agreed upon by all members of the steering group committees, including a statistician, before undertaking data analysis.

Standard descriptive summary statistics were presented as measures of central tendency and spread, or numbers and frequency. Odds ratios with 95% confidence intervals were estimated using nominal logistic

regression, adjusted for recruitment centre, socioeconomic status (New Zealand Deprivation Index (NZDep) or Australian Index of Deprivation, socio-economic indexes for areas (SEIFA)) at birth, gestational age and sex. These potential confounders were pre-specified with knowledge of their association with neurodevelopmental outcomes. All statistical tests were two-sided with a p value set at 5%. All analyses were performed on an intention to treat basis. Ethnicity was prioritised in the order Māori, Aboriginal or Torres Strait Islander, Pacific Island, Asian (Indian or Chinese), Australian or New Zealand European, other.

Similar comparisons were made for secondary outcomes, with estimation of odds ratios or mean differences with 95% confidence intervals using nominal logistic regression models, adjusting for above factors. We used nominal logistic regression models, excluding gestational age in the adjusted model, for secondary analysis 2. A significance level of 5% was used for each secondary outcome with no adjustment for multiple comparisons.

Since the number of pairs of twins in the study was small, analyses were not adjusted for the clustering effect of children from multiple pregnancy. Because any missing data were not likely to be missing at random, imputation methods were not used.

3 Interventions to prevent women developing gestational diabetes: An overview of Cochrane reviews

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3.1 Abstract

Background

The prevalence of gestational diabetes mellitus (GDM) is increasing, with approximately 15% of pregnant women affected worldwide, varying by country, ethnicity and diagnostic thresholds. There are associated short- and long-term health risks for women and their babies.

Objectives

We aimed to summarise the evidence from Cochrane systematic reviews on the effects of interventions for preventing GDM.

Methods

We searched the Cochrane Database of Systematic Reviews (6 August 2019) with key words 'gestational diabetes' OR 'GDM' to identify reviews pre-specifying GDM as an outcome. We included reviews of interventions in women who were pregnant or planning a pregnancy, irrespective of their GDM risk status. Two overview authors independently assessed eligibility, extracted data and assessed quality of evidence using ROBIS and GRADE tools. We assigned interventions to categories with graphic icons to classify the effectiveness of interventions as: clear evidence of benefit or harm (GRADE moderate- or high-quality evidence with a confidence interval (CI) that did not cross the line of no effect); clear evidence of no effect or equivalence (GRADE moderate- or high-quality evidence with a narrow CI crossing the line of no effect); possible benefit or harm (low-quality evidence with a CI that did not cross the line of no effect or GRADE moderate- or high-quality evidence with a wide CI); or unknown benefit or harm (GRADE low-quality evidence with a wide CI or very low- quality evidence).

Main results

We included 11 Cochrane Reviews (71 trials, 23,154 women) with data on GDM. Nine additional reviews pre-specified GDM as an outcome, but did not identify GDM data in included trials. Ten of the 11 reviews were judged to be at low risk of bias and one review at unclear risk of bias. Interventions assessed included diet, exercise, a combination of diet and exercise, dietary supplements, pharmaceuticals, and management of other health problems in pregnancy. The quality of evidence ranged from high to very low.

Diet

Unknown benefit or harm: there was unknown benefit or harm of dietary advice versus standard care, on the risk of GDM: risk ratio (RR) 0.60, 95% CI 0.35 to 1.04; 5 trials; 1279 women; very low-quality evidence. There was unknown benefit or harm of a low glycaemic index diet versus a moderate-high

glycaemic index diet on the risk of GDM: RR 0.91, 95% CI 0.63 to 1.31; 4 trials; 912 women; low-quality evidence.

Exercise

Unknown benefit or harm: there was unknown benefit or harm for exercise interventions versus standard antenatal care on the risk of GDM: RR 1.10, 95% CI 0.66 to 1.84; 3 trials; 826 women; low-quality evidence.

Diet and exercise combined

Possible benefit: combined diet and exercise interventions during pregnancy versus standard care possibly reduced the risk of GDM: RR 0.85, 95% CI 0.71 to 1.01; 19 trials; 6633 women; moderate-quality evidence.

Dietary supplements

Clear evidence of no effect: omega-3 fatty acid supplementation versus none in pregnancy had no effect on the risk of GDM: RR 1.02, 95% CI 0.83 to 1.26; 12 trials; 5235 women; high-quality evidence.

Possible benefit: myo-inositol supplementation during pregnancy versus control possibly reduced the risk of GDM: RR 0.43, 95% CI 0.29 to 0.64; 3 trials; 502 women; low-quality evidence.

Possible benefit: vitamin D supplementation versus placebo or control in pregnancy possibly reduced the risk of GDM: RR 0.51, 95% CI 0.27 to 0.97; 4 trials; 446 women; low-quality evidence.

Unknown benefit or harm: there was unknown benefit or harm of probiotic with dietary intervention versus placebo with dietary intervention (RR 0.37, 95% CI 0.15 to 0.89; 1 trial; 114 women; very low-quality evidence), or probiotic with dietary intervention versus control (RR 0.38, 95% CI 0.16 to 0.92; 1 trial; 111 women; very low-quality evidence) on the risk of GDM. There was unknown benefit or harm of vitamin D + calcium supplementation versus placebo (RR 0.33, 95% CI 0.01 to 7.84; 1 trial; 54 women; very low-quality evidence) or vitamin D + calcium + other minerals versus calcium + other minerals (RR 0.42, 95% CI 0.10 to 1.73; 1 trial; 1298 women; very low-quality evidence) on the risk of GDM.

Pharmaceutical

Possible benefit: metformin versus placebo given to obese pregnant women possibly reduced the risk of GDM: RR 0.85, 95% CI 0.61 to 1.19; 3 trials; 892 women; moderate-quality evidence.

Unknown benefit or harm: eight small trials with low- to very low-quality evidence showed unknown benefit or harm for heparin, aspirin, leukocyte immunisation or IgG given to women with a previous stillbirth on the risk of GDM.

Management of other health issues

Clear evidence of no effect: universal versus risk based screening of pregnant women for thyroid dysfunction had no effect on the risk of GDM: RR 0.93, 95% CI 0.70 to 1.25; 1 trial; 4516 women; moderate-quality evidence.

Unknown benefit or harm: there was unknown benefit or harm of using fractional exhaled nitrogen oxide versus a clinical algorithm to adjust asthma therapy on the risk of GDM: RR 0.74, 95% CI 0.31 to 1.77; 1 trial; 210 women; low-quality evidence. There was unknown benefit or harm of pharmacist led multidisciplinary approach to management of maternal asthma versus standard care on the risk of GDM: RR 5.00, 95% CI 0.25 to 99.82; 1 trial; 58 women; low-quality evidence.

Authors' conclusions

No interventions to prevent GDM in 11 systematic reviews were of clear benefit or harm. A combination of exercise and diet, supplementation with myo-inositol, supplementation with vitamin D and metformin were of possible benefit in reducing the risk of GDM, but further high-quality evidence is needed. Omega-3-fatty acid supplementation and universal screening for thyroid dysfunction did not alter the risk of GDM. There was insufficient high-quality evidence to establish the effect on the risk of GDM of diet or exercise alone, probiotics, vitamin D with calcium or other vitamins and minerals, interventions in pregnancy after a previous stillbirth, and different asthma management strategies in pregnancy. There is a lack of trials investigating the effect of interventions prior to or between pregnancies on risk of GDM.

3.2 Plain language summary

Interventions to prevent women from developing diabetes during pregnancy: an overview of Cochrane systematic reviews.

What is the issue?

Gestational diabetes mellitus (GDM) is defined as high blood glucose levels (hyperglycaemia) first detected during pregnancy. GDM can affect the health of women and their babies.

During pregnancy a woman’s body changes how it processes the nutrients from her food, to ensure that the baby is well nourished. In the first three months the mother has increased sensitivity to insulin. In the second and third trimesters her insulin sensitivity is reduced. Women with GDM have less of an initial increase in sensitivity and their insulin sensitivity is reduced beyond normal later in pregnancy, resulting

in the mother developing high blood glucose levels. Her blood levels of fats are also higher than normal, which may contribute to the risk of the baby becoming large for its gestational age.

Why is this important?

Women with GDM are more likely to develop complications in pregnancy including high blood pressure and need labour to be induced. They are at increased risk later of developing type 2 diabetes. Babies born to women with GDM are more likely to be born large, and therefore to experience birth injuries. Once born, the babies are at higher risk of experiencing difficulties in breathing, jaundice and reduced blood sugar levels, and later obesity and diabetes.

There are many risk factors for GDM, making it likely that interventions before/during pregnancy could reduce the risk of women developing GDM. This overview summarises evidence from Cochrane Reviews of randomised controlled trials on interventions that might prevent GDM.

What evidence did we find?

We searched the Cochrane Library (August 2019) and identified 11 Cochrane Reviews that assessed interventions during pregnancy and reported on GDM. The reviews had findings from 71 randomised controlled trials involving 23,154 pregnant women. Interventions included diet, exercise, a combination of diet and exercise, dietary supplements, medications, and management of other health problems. The evidence from the trials ranged from very low to high quality. We identified a further 10 reviews that may provide more information on this topic in the future.

Diet and exercise

Diet and exercise together possibly reduced the risk of a woman developing GDM when compared to standard care (19 trials; 6633 women; moderate-quality evidence).

Dietary advice alone (5 trials; 1279 women; very low-quality evidence) and a low glycaemic index diet compared with a moderate to high glycaemic index diet (4 trials; 912 women; low-quality evidence) had an unclear effect on the risk of GDM. Exercise alone had an unclear effect on the risk of GDM (3 trials; 826 women; low-quality evidence).

Dietary supplements

Omega-3 fatty acid supplementation in pregnancy had no effect (12 trials; 5235 women; high-quality evidence).

Myo-inositol supplementation during pregnancy possibly reduced the risk of GDM (3 trials with 502 women; low-quality evidence).

Vitamin D supplementation in pregnancy had a possible benefit in reducing the risk of developing GDM (4 trials with 446 women; low- quality evidence). These trials were all from Asian countries and the women's vitamin D levels before supplementation were mostly unknown.

Vitamin D given with calcium supplementation, or with calcium plus other minerals had an unclear effect.

Probiotic with dietary intervention had an unclear effect on the risk of developing GDM.

Medications

The drug metformin had a possible benefit in reducing the risk of developing GDM when given to obese pregnant women (3 trials; 892 women; moderate-quality evidence).

Low- to very low-quality evidence from eight small trials showed unclear effect on GDM risk for heparin, aspirin, leukocyte immunisation or immunoglobulin (IgG) given to women who had previously experienced a stillbirth.

Management of other health issues

Universal versus risk-based screening for thyroid problems had no effect on the risk of GDM (1 trial; 4516 women; moderate-quality evidence). Two different approaches to management of the mothers' asthma had an unclear effect (low-quality evidence).

What does this mean?

A combination of exercise and diet, supplementation with myo-inositol and vitamin D supplementation were of possible benefit in reducing the risk of developing GDM. Further high-quality evidence from randomised controlled trials is needed to confirm these results, and to look further at the use of metformin. No trials assessed interventions before pregnancy.

3.3 Background

3.3.1 Description of the condition

Gestational diabetes mellitus (GDM) is glucose intolerance causing hyperglycaemia with onset during pregnancy. The optimal blood glucose concentration cut-off to diagnose GDM remains controversial (American College of Obstetricians and Gynaecologists, 2018; Coustan et al., 2010; Hadar & Hod, 2010; HAPO Study Cooperative Research Group, 2008; Ministry of Health, 2014; National Institute for Health and Care Excellence, 2015; Wah Cheung & Moses, 2018). Lower blood glucose concentration thresholds for diagnosis have resulted in more women being diagnosed with GDM (Hadar & Hod, 2010; Nankervis et al., 2014; World Health Organisation, 2013a). The prevalence of GDM varies internationally with approximately 15% of pregnant women affected (Bottalico, 2007; Egan et al., 2017; Ferrara, 2007; Guariguata, Linnenkamp, Beagley, Whiting, & Cho, 2014; McIntyre et al., 2018; Melchior, Kurch-Bek, & Mund, 2017; National Institute for Health and Care Excellence, 2015). Prevalence varies by country, ethnicity and the diagnostic thresholds (Farrar et al., 2016; HAPO Study Cooperative Research Group, 2008; Pu et al., 2015).

Normal pregnancy is characterised by changes in the metabolism of carbohydrate, amino acids and lipids. The result of these combined changes is a switch to maternal use of lipids as a source of energy, sparing glucose and amino acids for the fetus.

In the first trimester of pregnancy there is increased insulin sensitivity (Catalano et al., 1991, 1993, 1992) as a result of adaptation of the pancreatic ß-cells (Van Assche et al., 1978), increased insulin synthesis (Weinhaus et al., 1996) and secretion (Sorenson et al., 1993), leading to improved utilisation and oxidation of glucose. By 14 weeks' gestation, the first phase of insulin secretion in response to a glucose load has increased by approximately 120% (Bowes et al., 1996; Catalano et al., 1993), resulting in a reduced plasma glucose concentration (Catalano et al., 1992). In the second and third trimesters, insulin sensitivity reduces (Catalano et al., 1991, 1993, 1992; Ryan et al., 1985), and hepatic gluconeogenesis increases (T. Nelson et al., 1994).

In women with GDM, the increase in first phase insulin secretion in response to a glucose load is reduced (Catalano et al., 1993), with inadequate adaptation of ß-cells leading to impaired glucose homeostasis (Buchanan, 2001). In the second and third trimesters the insulin sensitivity is further reduced (Catalano et al., 1998) with resultant maternal hyperglycaemia, elevated glycated haemoglobin (HbA1c) concentrations and increased transport of glucose across the placenta to the developing fetus (Setji, Brown, & Feinglos, 2005).

During normal pregnancy, changes in adipocytes result in more fat stores being laid down with increased synthesis and reduction in clearance of triglycerides (Ginci et al., 1997), resulting in an increase in all plasma lipid components (Butte, 2000). Women with GDM have hyperlipidaemia (raised levels of lipids in the blood) beyond that seen in normal pregnancy (Koukkou et al., 1996) due to increased synthesis in the liver and reduced activity of lipoprotein lipase and hepatic lipase (Ginci et al., 1997; Sattar et al., 1997). Higher concentrations of free fatty acids cross the placenta than in normal pregnancy, which may contribute to the risk of macrosomia (large baby) (Knopp, Magee, Walden, Bonet, & Benedetti, 1992).

There are multiple risk factors for GDM (Berkowitz, Lapinski, Wein, & Lee, 1992; Chu et al., 2007; Khan, Ali, & Khan, 2013; Pu et al., 2015; Solomon et al., 1997; Theriault, Forest, Masse, & Giguere, 2014; Xiong, Saunders, Wang, & Demianczuk, 2001). These include advanced maternal age, maternal high or low birthweight, high parity (Petry, 2010), polycystic ovarian syndrome (Toulis et al., 2009), a past history of GDM (C. Kim et al., 2007), family history of first-degree relatives with GDM or type 2 diabetes (Petry, 2010), maternal overweight or obesity (Morisset et al., 2010; Torloni et al., 2009), physical inactivity before or in early pregnancy (Dempsey et al., 2004; Tobias et al., 2011; Zhang et al., 2014), gestational weight gain (Morisset et al., 2010), and a past history of a macrosomic baby or a stillbirth (Petry, 2010). Impaired glucose tolerance is common to many of these risk factors, but the exact mechanisms by which each contributes to the development of GDM are uncertain. Some of these risk factors are potentially modifiable through preventive interventions.

Women with GDM have a higher risk of pre-eclampsia and need for induction of labour (Dodd et al., 2007). Women with a history of GDM have a greater than seven-fold increased risk of developing type 2 diabetes later, with more than half these women developing type 2 diabetes within 10 years after giving birth (Bellamy et al., 2009; C. Kim, Newton, & Knopp, 2002). Infants born to mothers with GDM are at increased risk of being born large-for-gestational age (Sacks et al., 2015), and are therefore more likely to experience birth injuries such as nerve palsy, bone fracture and shoulder dystocia. In the neonatal period, they are at higher risk of respiratory distress syndrome, jaundice and hypoglycaemia (reduced levels of blood sugar) (Adams, Li, Nelson, Ogburn, & Danilenko-Dixon, 1998; Crowther et al., 2005; González-Quintero et al., 2007; He et al., 2015; Landon et al., 2009; Langer, Yogev, Most, & Xenakis, 2005). Longer-term health consequences into childhood and adulthood include obesity, diabetes, the metabolic syndrome (Boney et al., 2005; Cho, Silverman, Rizzo, & Metzger, 2000), and adverse neurodevelopmental outcomes (Chatzi et al., 2014; A. Fraser et al., 2012; C. A. Nelson et al., 2000; Torres-Espínola et al., 2015).

3.3.2 Description of the interventions

Interventions to prevent GDM have been used preconception, during pregnancy and inter-conception (between pregnancies). Preconception and inter-conception interventions have been used, particularly in women at high risk of GDM, such as those who are overweight or obese (Yeung et al., 2010), or with a history of GDM (Khan et al., 2013; Shyam et al., 2013). The opportunity exists to intervene with health promotion strategies prior to and between pregnancies for women identified with risk factors for GDM (Hanson et al., 2015; Jack & Culpepper, 1990).

Interventions directed at preventing GDM include dietary or exercise interventions, or a combination of these, dietary supplement interventions and pharmaceutical interventions.

The focus of some dietary advice interventions for GDM prevention have been specific, such as increasing fibre intake (R. B. Fraser, Ford, & Lawrence, 1988; R. B. Fraser, Ford, & Milner, 1983) or aiming for a low glycaemic index diet (Kizirian et al., 2017; Markovic et al., 2015). Others have included broader advice regarding "healthy eating" as part of more comprehensive lifestyle interventions (Quinlivan, Lam, & Fisher, 2011).

Exercise or physical activity interventions for preventing GDM have varied from general advice to specific individualised programs using a range of different activities, such as aerobic activities, stationary cycling or yoga (Barakat, Cordero, Coteron, Luaces, & Montejo, 2012; Guelfi et al., 2016; Ong et al., 2009; Rakhshani et al., 2012; Stafne et al., 2012). These have been employed in isolation (Barakat et al., 2012; S. G. da Silva et al., 2017; Goodarzi-Khoigani et al., 2017; Guelfi et al., 2016; Ong et al., 2009; Stafne et al., 2012), or in combination with dietary interventions (Dodd et al., 2014; Harrison, Lombard, Strauss, & Teede, 2013; Koivusalo et al., 2016; Riitta Luoto et al., 2011; Petrella et al., 2014; Poston et al., 2015; Simmons et al., 2015).

Dietary supplement interventions such as probiotics (Lindsay et al., 2014; Raakel Luoto, Laitinen, Nermes, & Isolauri, 2010; Wickens et al., 2017), myo-inositol (D'Anna et al., 2013; Farren et al., 2017; Santamaria et al., 2016), vitamin D (Bao et al., 2017; Soheilykhah, Mojibian, Moghadam, & Shojaoddiny-Ardekani, 2013), and fish oils have been investigated for GDM prevention (Zhou et al., 2012).

Pharmaceutical therapies, which may have a role in GDM prevention, include sulphonylureas, biguanides, thiazolidinediones, alpha-glucosidase inhibitors, meglitinides and peptide analogues. Metformin or glibenclamide (also known as glyburide) are the only oral hypoglycaemics recommended

in clinical practice guidelines for use in pregnancy (American College of Obstetricians and Gynaecologists, 2018; National Institute for Health and Care Excellence, 2015). However, there is a paucity of data regarding the safety of many of these in pregnancy (Holt & Lambert, 2014; Kavitha, De, & Kanagasabai, 2013; Slocum & Sosa, 2002). Where safety data are available, this has often been limited to short- term health outcomes. The Metformin in Gestational diabetes (MiG) trial investigated the use of metformin for women with GDM, and demonstrated metformin was safe in the offspring, at least up to nine years of age (Rowan et al., 2018).

3.3.3 How the intervention might work

Dietary interventions

Different dietary components have direct and indirect effects on glycaemic profile. Interventions that alter these could be utilised to reduce GDM risk (Ley et al., 2011; Rogozińska et al., 2015; Zhang, Liu, Solomon, & Hu, 2006). Insulin sensitivity and secretion are reduced in association with high simple sugar intake (Davis et al., 2005; Reiser et al., 1979). With ongoing high sugar intake, pancreatic exhaustion may ensue with impaired glucose tolerance (Ludwig, 2002). Less insulin resistance is seen with a high-fibre and low-glycaemic index diet. Fibre slows digestion (Burton-Freeman, 2000; Jenkins et al., 2000; Vahouny et al., 1988) and rate of glucose absorption, thus altering the blood glucose concentration and insulin response (Jenkins et al., 2000; Liese et al., 2005; Mcintosh & Miller, 2001). Increasing dietary fibre intake may reduce appetite and hence insulin resistance associated with adiposity (Burton-Freeman, 2000). Intake of protein and fats may also reduce appetite (Tannous dit El Khoury, Obeid, Azar, & Hwalla, 2006) with similar effect (Kantartzis, Totsikas, Haring, & Stefan, 2009; Kohrt et al., 1993; Pan & Storlien, 1993), and through protection of ß-cells from oxidative injury (W. Cai et al., 2012; Lin, Zhang, & Su, 2012). A general reduction in calorie intake with resultant weight loss and reduced adiposity improves insulin sensitivity and glycaemic profile (Knopp, Magee, Raisys, & Benedetti, 1991; Larson-Meyer et al., 2006). This needs to be balanced against potential risks of weight loss during pregnancy such as ketonaemia associated with marked calorie restriction (Churchill, Berendes, & Nemore, 1969; Magee, Knopp, & Benedetti, 1990; Metzger et al., 2007; Ornoy et al., 1998; Rizzo et al., 1991). Due to these concerns, international guidelines do not recommend hypocaloric diets during pregnancy (Canadian Diabetes Association Clinical Practice Guidelines Expert Committee et al., 2013; Health Service Executive, 2010; National Institute for Health and Care Excellence, 2010). There is ongoing debate as to whether calorie restriction might be appropriate in overweight and obese pregnant women (Knopp et al., 1991; Procter & Campbell, 2014). Interventions to aid with weight loss in overweight or obese women preconception or inter-conception may reduce the risk of GDM in any future pregnancy (Pole & Dodds, 1999).

Exercise interventions

The risk of developing GDM is inversely associated with the amount of regular physical activity before or during pregnancy (Dempsey et al., 2004; Zhang et al., 2014). There is increased energy expenditure and hence glucose consumption during exercise; blood flow through muscle mass and capillary surface area for glucose exchange increases (Rose & Richter, 2005; Sjøberg, Rattigan, Hiscock, Richter, & Kiens, 2011). During muscle contraction, there is translocation of the glucose transporter type 4 (GLUT-4) from within skeletal muscle cells to the surface (Jessen & Goodyear, 2005; Kennedy et al., 1999; Rose & Richter, 2005) with resultant increased glucose uptake. The increase in insulin sensitivity continues beyond the exercise period (T. E. Jensen & Richter, 2012; Perseghin et al., 1996). Muscle mass increases with regular physical activity, and thus glucose tolerance and insulin sensitivity are likely to improve (Yki-Jarvinen & Koivisto, 1983).

Diet and exercise interventions combined

Combined interventions targeting more than one of the multiple risk factors for GDM could be synergistic. Prevention of type 2 diabetes has been demonstrated using combined dietary, exercise and weight loss interventions (Haw et al., 2017; Knowler et al., 2002; Tuomilehto et al., 2001). These might be expected to have a similar effect in prevention of GDM.

Dietary supplement interventions

Probiotics

Probiotic use can change the microbiome of the gut, which may reduce insulin resistance (Hill et al., 2014; Kondo et al., 2010; World Health Organization & Food and Agriculture Organization of the United Nations, 2006), through decreasing inflammatory signalling (Ma, Hua, & Li, 2008), and upregulating genes involved in fat metabolism and insulin sensitivity (Kondo et al., 2010).

Myo-inositol

Myo-inositol, a polyol with insulin-mimetic properties (Croze & Soulage, 2013; Saltiel, 1990) involved in insulin transduction signalling (Baillargeon, Iuorno, Apridonidze, & Nestler, 2010), increases GLUT-4 translocation to the cell membrane in skeletal muscle (Dang et al., 2010), thus improving insulin sensitivity (Corrado et al., 2011). Supplementary use in polycystic ovarian syndrome results in reduced fasting insulin concentrations (Unfer, Facchinetti, Orrù, Giordani, & Nestler, 2017). Myo- inositol is present in the diet in some seeds, grains, nuts, beans, vegetables and fruit (Clements Jr & Darnell, 1980).

Vitamin D

Vitamin D deficiency is associated with insulin resistance (Esteghamati et al., 2014) and poor pancreatic β-cell function (Chiu, Chu, Go, & Saad, 2004). Vitamin D may affect insulin secretion by binding to vitamin D receptors in the pancreas and regulating the balance between the extracellular and intracellular calcium pools (Sooy et al., 1999). Vitamin D deficiency may reduce pancreatic insulin secretion (Bourlon, Billaudel, & Faure-Dussert, 1999; Norman, Frankel, Heldt, & Grodsky, 1980), while supplementation with vitamin D may influence the expression of insulin-sensitive genes (Alkharfy et al., 2013), thus reducing inflammatory markers and improving glucose uptake (Marcotorchino et al., 2012).

Fish oil

The circulating concentrations of several long-chain polyunsaturated fatty acids are altered in GDM (Wijendran et al., 1999). Omega-3 fatty acids have several anti-inflammatory effects (Calder, 2006). The predominant sources of the omega-3 fatty acids, eicosapentaenoic acid and docosahexaenoic acid, are fish and fish oils (Kris-Etherton, Grieger, & Etherton, 2009; Kris-Etherton et al., 2000). The lipid composition of cell membranes is altered with changes to dietary fatty acid composition (Calder, 2006; Lardinois, 1987), which affects insulin binding and sensitivity. Increased insulin secretion and sensitivity may result from omega-3 or fish oil supplementation (Baynes, Mideksa, & Ambachew, 2018). Increased inflammation can result in insulin resistance, while omega-3 fatty acids inhibit TLR-2 and TLR-4 receptors for inflammatory cytokines (J. Y. Lee et al., 2004).

Pharmaceutical interventions

Metformin, a biguanide, crosses the placenta with similar concentrations found in maternal and fetal circulations (Vanky, Zahlsen, Spigset, & Carlsen, 2005). Metformin reduces hepatic gluconeogenesis (Stumvoll, Nurjhan, Perriello, Dailey, & Gerich, 1995; Wollen & Bailey, 1988), and enhances peripheral glucose uptake and utilisation (Viollet et al., 2012), improving insulin sensitivity and reducing hyperglycaemia (Jackson et al., 1987). Metformin may enhance insulin sensitivity and preserve pancreatic β-cell capacity in women with polycystic ovarian syndrome (Ainuddin, Kazi, Aftab, & Kamran, 2015). Glibenclamide crosses the placenta with fetal blood concentrations approximately 70% of maternal blood concentrations (Hebert et al., 2009). Glibenclamide stimulates insulin secretion, but has been associated with an increased risk of macrosomia, neonatal hypoglycaemia and higher maternal weight gain in comparison to metformin (Liang, Ma, Xiao, & Tan, 2017).

3.3.4 Why it is important to do this overview

A number of risk factors for GDM, such as physical inactivity, being overweight or obese prior to pregnancy, and having a poor diet are potentially modifiable. While different strategies have shown

promise in the prevention of GDM, it is currently unclear which strategies are most effective. Primary prevention of GDM rather than treatment would lead to economic (Danyliv et al., 2015) and health benefits.

This overview provides an important resource for all healthcare professionals caring for pregnant women, guideline developers, policy makers, researchers, and pregnant women at risk of developing GDM, and their families.

Use of the overview to identify and target effective preventive interventions may contribute to reducing the increase in rates of GDM seen globally, thus reducing the significant short- and long- term health risks for the mothers and their infants. Further, this overview identifies priority areas requiring further research.

3.4 Objectives

We aimed to summarise the evidence from Cochrane systematic reviews on the effects of interventions for preventing gestational diabetes mellitus (GDM).

3.5 Methods

Criteria for considering reviews for inclusion

In this overview of systematic reviews, we included only Cochrane systematic reviews, that assessed interventions that may prevent gestational diabetes mellitus (GDM), reporting GDM as a primary or secondary outcome of the review. We identified Cochrane protocols and titles for potential future inclusion in an update of the overview, and classified them as 'ongoing reviews' (in Appendix 8.1).

When reviews were identified for inclusion that were more than two years out of date, we contacted the Cochrane Pregnancy and Childbirth Editorial Base to identify whether an update was in progress. We did not contact individual review authors, but noted the publications and search dates of the reviews. When a review was out of date and would not be updated in time to be included in the overview, we included the last published version and acknowledged this as a potential limitation.

Participants

We included women planning a pregnancy, between pregnancies, or pregnant women. We excluded women with pre-existing type 1 or type 2 diabetes.

Interventions

We included interventions prior to pregnancy (preconception), between pregnancies (inter-conception), or implemented prior to GDM screening in pregnancy, and for each of these time periods these included:

- dietary interventions;
- exercise interventions;
- dietary and exercise interventions combined;
- dietary supplement interventions (e.g. probiotics, myo-inositol, vitamin D and omega-3 fatty acids);
- pharmaceutical interventions (e.g. oral anti-diabetic pharmaceutical therapies);
- interventions for the management of other health problems during pregnancy.

We included reviews comparing the above interventions with standard care or no intervention (or a placebo), as well as those comparing different interventions.

Outcome

GDM (defined by review authors and trialists).

Search methods for identification of reviews

We searched the Cochrane Database of Systematic Reviews (6 August 2019) using key words 'gestational diabetes' OR 'GDM'. We used the search terms to search 'all text', and did not limit to 'title, abstract, or keywords'. We did not apply any language or date restrictions. The review group was contacted to identify titles for future inclusion and no additional titles were identified.

Data collection and analysis

We based the methodology for data collection and synthesis on Chapter 22, 'Overviews of Reviews' in the Cochrane Handbook of Systematic Reviews of Interventions (J. P. Higgins & Green, 2011).

Selection of reviews

Two overview authors independently assessed for potential inclusion all Cochrane systematic reviews we identified that evaluated the effects of the aforementioned interventions and reported on the incidence of GDM. We then assessed the methods section of reviews and protocols to ensure those with the appropriate population and pre-specified outcome were selected for inclusion. We resolved any disagreement through discussion or consultation with a third overview author.

Data extraction and management

Two of the overview authors independently extracted data from each systematic review, using an electronic form which we designed and piloted. We resolved disagreements by consensus or by discussion with a third overview author. When information from the review was missing, we accessed the published papers of the individual study and contacted the systematic review authors for further details. We extracted and tabulated information for the following.

Review characteristics

- Review title and authors.
- Search date: date of search conducted by review (we considered less than two years ago to be current).
- The number of trials in the review, number of women and their infants, and their characteristics.
- Risk of bias of the included trials (as reported by the review authors; see 'Risk of bias of included studies within reviews' below, under Assessment of methodological quality of included reviews).
- Interventions and comparisons relevant to this overview.
- The prespecified outcome (GDM) relevant to this overview.
- Any other characteristics required to assess and report on review quality (see 'Quality of included reviews' under Assessment of methodological quality of included reviews).

Statistical summaries

- The summary intervention effects, including the pooled effects (e.g. risk ratios (RRs), odds ratios (ORs), mean differences (MDs), 95% confidence intervals (CIs)), and numbers of studies and participants contributing data to each pooled effect from comparisons and for the outcome relevant to this overview.
- Results of any subgroup or sensitivity analyses conducted by the authors for overview outcome.
- Information required to assess and report on the quality of the evidence for the intervention effects extracted above (see 'Quality of evidence in included reviews' under Assessment of methodological quality of included reviews).
- All reviews performed meta-analyses for GDM, the outcome for our overview

Assessment of methodological quality of included reviews

Quality of included reviews

Two overview authors assessed for relevance, by checking that the population, intervention, comparator and outcomes aligned between the review and overview, and independently assessed the methodological quality of the included systematic reviews using the Risk of Bias in Systematic Reviews (ROBIS) tool

(Whiting et al., 2016). We resolved differences through discussion and, when needed, through discussion with a third overview author.

The ROBIS tool assesses risk of bias across four domains.

- Study eligibility criteria.
- Identification and selection of studies.
- Data collection and study appraisal.
- Synthesis and findings.

ROBIS uses signalling questions to assess specific concerns about potential biases within the review, and the ratings from these questions are used to judge overall risk of bias. The signalling questions were answered as 'yes', 'probably yes', 'probably no', 'no' or 'no information'. Each of these four domains were then designated as low, high or unclear risk of bias. If the answers to all signalling questions for a domain were 'yes' or 'probably yes', the level of concern could be judged as low. If any signalling question was answered 'no' or 'probably no', the potential for concern about bias exists. Finally, a summary judgement based on any concerns, assessment of methods and bias was made of low, high or unclear overall risk of bias for the systematic review.

Quality of evidence in the included reviews

We assessed the quality of the evidence for GDM using GRADE (Grades of Recommendation, Assessment, Development and Evaluation). When available, we used the GRADE assessments from the included Cochrane systematic reviews. When this was not available, we used the GRADE system to review pooled summary statistics and risk of bias of included trials. The GRADE system assesses the following features for the evidence found for selected outcomes.

- Risk of bias: internal validity of the evidence.
- Inconsistency: heterogeneity or variability in the estimates of effect across studies.
- Indirectness: degree of differences between population, intervention and outcome of interest.
- Imprecision (random error):extent to which confidence in the effect estimate is adequate to support a particular decision.
- Risk of publication bias: degree of selective publication of studies.

The GRADE system rates the quality of the evidence as:

- high (further research is very unlikely to change confidence in the estimate of the effect);
- moderate (further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate);
- low (further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate);
- very low (any estimate of effect is very uncertain).

We summarised the evidence in 'Summary of findings' tables which we populated with the summary risk estimates and 95% CIs, number of participants, and the quality of the review for each intervention and whether GDM was a primary or secondary review outcome. We planned to include timing of intervention (preconception, inter-conception and during pregnancy), but all interventions within our included reviews were during pregnancy.

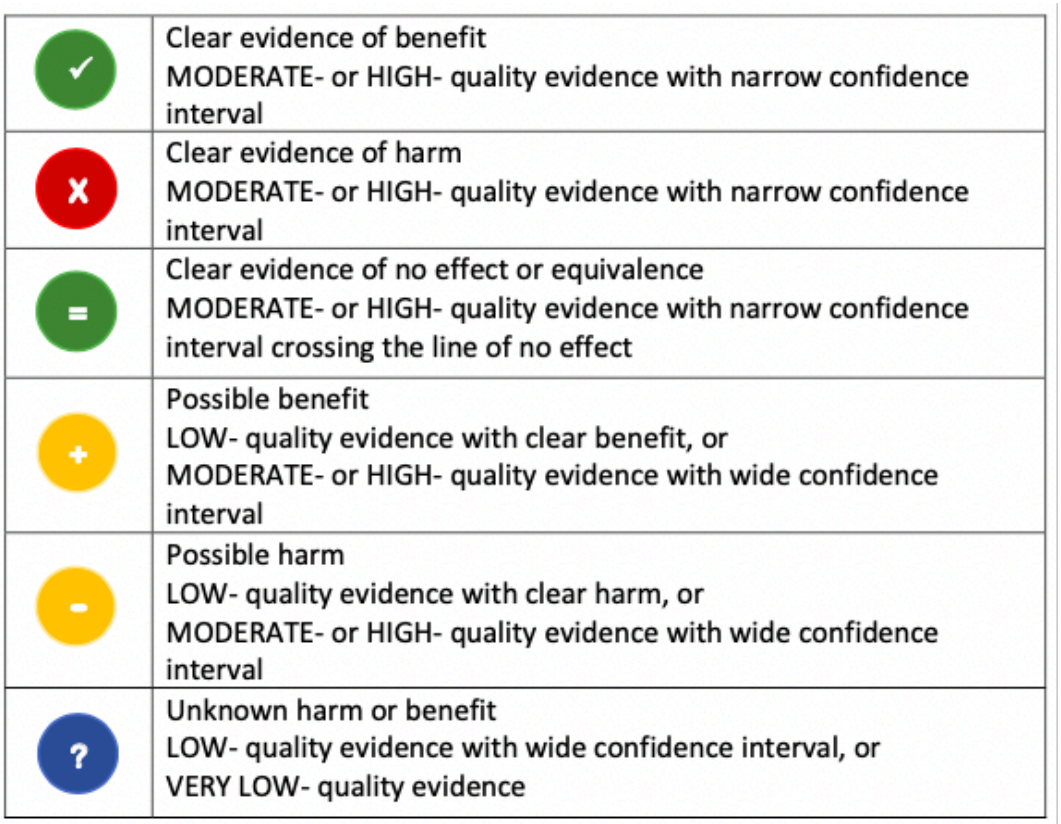
Risk of bias of included studies within reviews

We did not reassess the risk of bias of included studies within reviews, but instead reported study risk of bias according to the review authors' assessment. In the case that individual studies were included in two or more Cochrane Reviews, we report this, and any variation regarding review authors' assessments of study risk of bias. We collected this information during the data extraction process.

Data synthesis

We undertook a narrative description of the included Cochrane systematic reviews. We did not examine indirect comparisons or conduct network meta-analyses. We summarised the main results of the included reviews by categorising their findings in the following framework, and by intervention focus/topic. We planned to organise by timing of intervention (preconception, inter-conception and during pregnancy), but no preconception or inter-conception interventions were identified. We assigned graphic icons to communicate the direction of review effect estimates and our confidence in the available data. This is the framework adopted by Medley and colleagues in their overview on 'Interventions during pregnancy to prevent preterm birth: an overview of Cochrane systematic reviews' (Medley et al., 2018), and was based on graphics produced by the World Health Organization to escribe different types of workers and their roles in maternal and newborn care (World Health Organisation, 2013b). We used graphic icons to indicate mutually exclusive assessment categories (see Figure 3.1).

Figure 3.1 Overview icon key



- Clear evidence of benefit (moderate- or high-quality evidence with CIs not crossing line of no effect).
- Clear evidence of harm (moderate- or high-quality evidence with CIs not crossing line of no effect).
- Clear evidence of no effect or equivalence (moderate- or high-quality evidence with narrow CIs crossing the line of no effect).
- Possible benefit (low- quality evidence with clear benefit, or moderate- or high-quality evidence with wide CIs crossing the line of no effect).
- Possible harm (low-quality evidence with clear harm, or moderate- or high-quality evidence with wide CIs crossing the line of no effect).
- Unknown benefit or harm (low-quality evidence with wide CIs crossing the line of no effect or very low-quality evidence).

The choice of category reflected the information synthesised from the included reviews for the overview outcome (GDM). We used separate assessments for different comparisons when required (e.g. where one intervention was compared with both placebo (or no treatment) and with an alternative intervention). This approach to summarising the evidence is based on an earlier overview 'Antenatal and intrapartum interventions for preventing cerebral palsy: an overview of Cochrane systematic reviews' (E. Shepherd, Gomersall, et al., 2017).

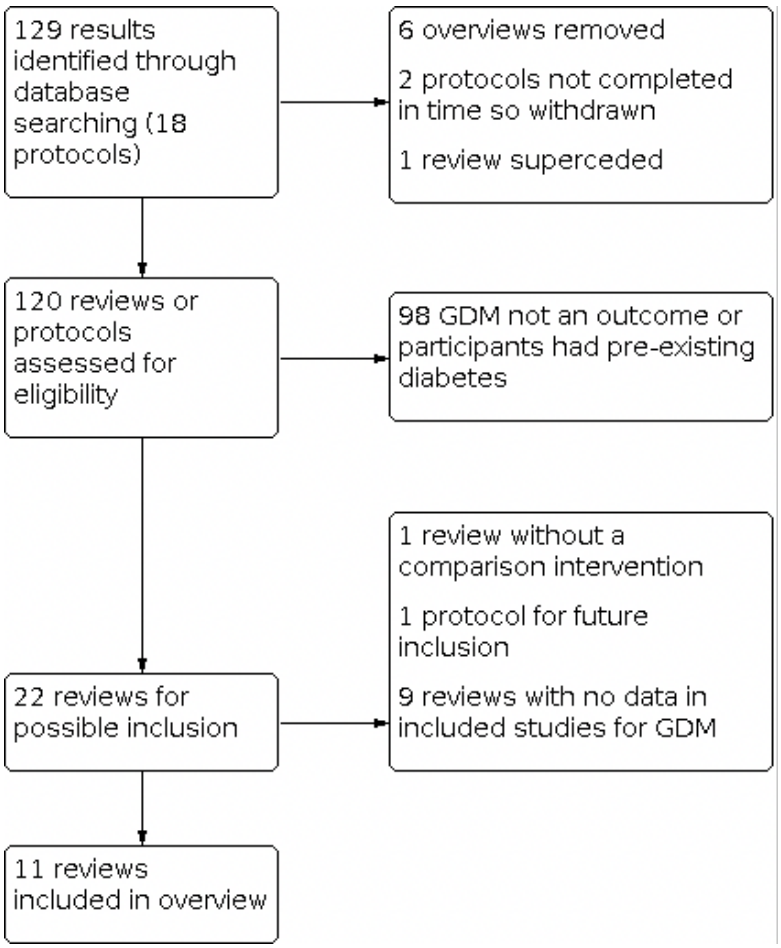
We conducted a sensitivity analysis excluding Cochrane systematic reviews with a ROBIS (Risk of Bias in Systematic Reviews) review rating that was of high concern for risk of bias in any domain.

3.6 Results

Our search of the Cochrane Database of Systematic Reviews identified 129 results. After excluding six overviews, two protocols which had been withdrawn, and one review which had been superceded, we searched the text of 120 protocols and completed systematic reviews for the outcome, GDM. We assessed the full text of those protocols and reviews which pre-specified GDM as an outcome. No overview author assessed their own systematic review (several eligible reviews were authored by members of the overview team).

We included 11 reviews in this overview. We excluded 98 reviews that included participants with pre-existing diabetes or did not pre- specify GDM as a review outcome and one review (Crowe et al., 2019) for which there was no comparison group (see Figure 3.2).

Figure 3.2 Cochrane Review flow diagram



We listed 10 protocols and reviews, that may provide data in future updates of this overview, in the appendices.

- Appendix 8.1, Ongoing reviews, cites one Cochrane protocol that pre-specifies GDM as a secondary outcome, and will be considered for inclusion in future updates of this overview when it is published as a full review.
- Appendix 8.2, Reviews awaiting further classification, summarises nine Cochrane Reviews that pre-specified GDM as a primary or secondary outcome, but the included trials had no data reported for this outcome. These reviews will be considered again for inclusion in future updates of this overview.

Description of included reviews

The 11 included systematic reviews all involved pregnant women. They included 71 trials of 23,154 women. There was one review for each of the following:

- Dietary advice versus standard care or different dietary advice (Tieu, Shepherd, Middleton, & Crowther, 2017);
- any type of exercise regimen versus standard care or another type of exercise regimen (Han, Middleton, & Crowther, 2012);
- any combined dietary and exercise combination versus standard care or a different dietary and exercise combination (E. Shepherd, Gomersall, et al., 2017);
- omega-3 fatty acid supplementation (supplement or food) versus placebo or no omega-3 (Middleton et al., 2018);
- myo-inositol versus control or placebo (Crawford, Crowther, Alsweiler, & Brown, 2015);
- vitamin D (alone or in combination with other micronutrients) versus other micronutrients or control (Palacios, Kostiuk, & Peña-Rosas, 2019);
- probiotics versus "any type" of comparison intervention (Barrett, Dekker Nitert, Conwell, & Callaway, 2014);
- metformin (alone or in combination) versus placebo or control in overweight or obese women (Dodd, Grivell, Deussen, & Hague, 2018);
- any single intervention, combination of interventions or tailored model of care/algorithm/guideline/protocol for improving health outcomes in subsequent pregnancies following stillbirth versus no intervention or standard care (Wojcieszek et al., 2018);
- screening for thyroid dysfunction versus no screening or an alternative screening method for improving maternal and infant health (Spencer, Bubner, Bain, & Middleton, 2015);

- interventions for managing asthma in pregnancy versus alternative interventions, or placebo or control (Bain et al., 2014).

All the included reviews reported interventions during pregnancy. No reviews reported interventions prior to, or between pregnancies. The number of randomised trials that reported data on GDM in the included systematic reviews ranged from one to 19. The number of pregnant women in the included reviews ranged from 217 (Wojcieszek et al., 2018) to 6633 (Spencer et al., 2015). Only one review included trials from low-income countries (Palacios et al., 2019). Six reviews were published more than two years ago (Bain et al., 2014; Barrett et al., 2014; Crawford et al., 2015; Han et al., 2012; Spencer et al., 2015; Tieu et al., 2017). One review (E. Shepherd, Gomersall, et al., 2017), though published within the last two years had conducted the search more than two years ago. Four reviews (Dodd et al., 2018; Middleton et al., 2018; Palacios et al., 2019; Wojcieszek et al., 2018) had conducted searches in the last two years and were considered up to date. Han 2012 (Han et al., 2012) is undergoing an update. There are no known active updates in progress for the remaining reviews.

Further details of the included reviews can be found in Table 3.1 'Characteristics of included reviews'. Details of the 'Risk of bias' assessments included in each review can be found in Table 3.2.

Table 3.1 Characteristics of included reviews

Review ID	Date of search; date assessed as up-to-date	No. included trials; years of publication and countries	No. participants in included trials	No. participants and trials with data on GDM	Inclusion criteria for "Types of participants"	Relevant comparison interventions (no. trials and participants)	GDM primary or secondary outcome in review
Bain 2014	Search June 2014; Up-to-date October 2014	8 RCTs published in 1996, 1998, 2004, 2005, 2006, 2011, 2012 (2) in Brazil, USA (2), Egypt, Australia, Germany and multi country	1181	268 (2)	Pregnant women with current asthma (with a health professional's diagnosis), regardless of age, parity, plurality, and severity of asthma	Any intervention to manage asthma (pharmacological/non-pharmacological) versus placebo/no intervention/alternative intervention	Secondary
Barrett 2014	Search August 2013; Up-to-date February 2014	1 RCT in 2008 in Finland	256	256 (1)	Pregnant women including those with previous GDM	Probiotic in combination with diet vs diet with placebo or placebo alone	Primary
Crawford 2015	Search November 2015; Up-to-date December 2015	4 RCTs in 2013 (2), 2014, 2015 in Italy	567	502 (3)	Pregnant women	Any doses of myo-inositol in pregnancy, alone or in a combination preparation versus no treatment or placebo or another intervention	Primary
Dodd 2018	Search October 2017; Up-to-date July 2018	3 RCTs in 2015 (2), 2016 in Egypt and UK (2)	1099 (data for 1034)	892 (3)	Pregnant women with obesity or who are overweight, defined as women with booking or early pregnancy or pre-pregnancy body mass index (BMI) ≥ 25.0 kg/m2	Metformin versus placebo or no metformin	Secondary

Han 2012	Search April 2012; Up-to-date July 2012	5 RCTs in 2009, 2010 (2), 2011, 2012 in Australia, (2), Norway, Spain, New Zealand	1115 (data for 922)	826 (3)	Pregnant women of any age, gestation, parity or plurality	Any types of exercise and lifestyle management versus standard care or different frequencies of same intervention or different interventions	Primary
Middleton 2018	Search 16 August 2018; up to date 14 November 2018	70 RCTs. 1989-2018. Multiple countries including Bangladesh, Mexico, Venezuela	19,927	5235 (12)	Pregnant women, regardless of their risk for pre-eclampsia, preterm birth or intrauterine growth restriction.	Omega-3 fatty acids (usually fish or algal oils) compared with placebo or no omega-3 fatty acids. Trials that assessed omega-3 fatty acid co-interventions (e.g. omega-3 with another agent) Studies or study arms that compared omega-3 doses or types of omega-3 (e.g. DHA versus EPA) directly	Secondary
Palacios 2019	Search July 2018; Up-to-date July 2019	30 RCTs in 1980 (1), 1986 (2), 1987 (1), 1988 (1), 1991 (1), 2000 (1), 2002 (1), 2008 (1), 2009 (1), 2010 (1), 2011 (1), 2012 (3), 2013 (6), 2014 (1), 2015 (2), 2016 (4), 2017 (2) in Australia (1), Bangladesh (2), Brazil (1), China (1), France (2), India (5), Iran (12), New Zealand (1), Pakistan (1), Russia (1) and the UK (3)	7033	446 (1)	Pregnant women any gestation or chronological age, parity, number of fetuses	Vitamin D (any dose, duration, time of commencement) during pregnancy (alone or in combination with other micronutrients) versus placebo/no intervention/other vitamins or minerals	Primary
Shepherd 2017	Search November 2016; Up-to-date November 2017	23 RCTs (2 cluster and 21 individually randomised) in 2002, 2009, 2011 (4), 2012, 2013 (5), 2014 (3), 2015 (3), 2016 (4), 2017 in Australia (2), Brazil, Canada (2), China (2), Denmark, Egypt, Finland (3), Germany, Italy (2), Norway, UK (2), USA (5)	8918	6633 (19)	Pregnant women regardless of age, gestation, parity or plurality	Any type of diet intervention with any type of exercise intervention versus no intervention or a different diet and exercise intervention	Primary

Spencer 2015	Search July 2015; Up-to-date September 2015	2 RCTs in 2010, 2012 in Italy, UK	26,408	4516 (1)	Women, either pre-pregnancy or during pregnancy, including both singleton and multiple pregnancies	Any screening method (e.g. tool, program, guideline or protocol) for detecting thyroid dysfunction pre-pregnancy or during pregnancy versus no screening	Secondary
Tieu 2017	Search January 2016; Up-to-date January 2017	11 RCTs (1 quasi randomised) in 1983, 1998, 2006, 2008, 2009 (2), 2011 (2), 2012, 2014, 2016 in Australia (4), Brazil, Denmark, Ireland, Finland, UK, USA (2)	2786	2191 (9)	Pregnant women of any age gestation, parity or plurality	Dietary advice before testing for GDM versus no advice or different types of advice	Primary
Wojcieszek 2018	Search June 2018; Up-to-date December 2018	9 RCTs and 1 quasi randomised in 1964, 1994, 1995, 2002, 2004, 2009, 2012, 2014, 2015, 2016 in Canada (2), Denmark (3), France, Israel, Italy, and Pakistan. One trial was undertaken across both Austria and Germany	222	210 (8)	"Parents" who had experienced a stillbirth of 20 weeks' gestation or more who were pregnant or considering a subsequent pregnancy.	Any single intervention, combination of interventions or tailored model of care/algorithm/guideline/protocol for improving health outcomes in subsequent pregnancies following stillbirth	Secondary

GDM: gestational diabetes mellitus

RCT: randomised controlled trial

DHA: docosahexaenoic acid

EPA: eicosapentaenoic acid

Table 3.2 Risk of bias of trials in included reviews

Review ID	Summary of trial limitations (risk of bias)
Bain 2014	Sequence generation: 5 low, 3 unclear Allocation concealment: 4 low, 4 unclear Blinding (participants and personnel): 3 low, 3 unclear, 2 high Blinding (outcome assessors): 5 low, 3 unclear Incomplete outcome data: 4 low, 4 unclear Selective reporting: 2 low, 5 unclear, 1 high Other: 3 low, 5 unclear Overall: "Overall we judged two trials to be at a low risk of bias, two trials to be at an unclear risk of bias, and the other four trials to be at a moderate risk of bias."
Barrett 2014	Sequence generation: 1 low Allocation concealment: 1 low Blinding (participants and personnel): 1 low Blinding (outcome assessors): 1 low Incomplete outcome data: 1 low Selective reporting: 1 low Other: 1 low Overall: "The included study was assessed to be at low risk of bias across all domains."
Crawford 2015	Sequence generation: 3 low, 1 unclear Allocation concealment: 2 low, 2 unclear Blinding (participants and personnel): 2 unclear, 2 high Blinding (outcome assessors): 1 low, 3 unclear Incomplete outcome data: 2 low, 1 unclear, 1 high Selective reporting: 2 low, 1 unclear, 1 high Other: 2 low, 1 unclear, 1 high Overall: "Overall, there was unclear risk of bias due to insufficient information provided to enable a judgement of risk, particularly with regard to allocation concealment and blinding of outcome assessment."
Palacios 2019	Sequence generation: 21 low 8 unclear 1 high Allocation concealment: 13 low 16 unclear 1 high Blinding (participants and personnel): 15 low 1 unclear 14 high Blinding (outcome assessors): 10 low 18 unclear 2 high Incomplete outcome data: 16 low 4 unclear 10 high Selective reporting: 29 unclear 1 high Other: 14 low 2 unclear 4 high Overall: "The risk of bias was high for allocation and/or blinding in 14 trials and for attrition in 10 trials."
Dodd 2018	Sequence generation: 2 low, 1 unclear Allocation concealment: 2 low, 1 unclear Blinding (participants and personnel): 2 low, 1 unclear Blinding (outcome assessors): 2 low, 1 unclear Incomplete outcome data: 3 low Selective reporting: 2 low, 1 high Other: 2 low, 1 unclear Overall risk of bias reported: no comment in main text
Han 2012	Sequence generation: 2 low, 3 unclear Allocation concealment: 2 low, 3 unclear Blinding (participants and personnel): 5 high Blinding (outcome assessors): 5 unclear Incomplete outcome data: 2 low, 3 high Selective reporting: 3 low, 2 high Other: 3 low, 2 high Overall: "Overall, the risk of bias was judged to be moderate."

Middleton 2018	Sequence generation: 37 low, 32 unclear, 1 high Allocation concealment: 29 low, 40 unclear, 1 high Blinding (participants and personnel): 52 low, 15 unclear, 3 high Blinding (outcome assessors): 39 low, 41 unclear Incomplete outcome data: 13 low, 30 unclear, 27 high Selective reporting: 13 low, 45 unclear, 12 high Other: 34 low, 34 unclear, 2 high Overall: “Overall study-level risk of bias was mixed, with selection and performance bias mostly at low risk, but there was high risk of attrition bias in some trials.”
Shepherd 2017	Sequence generation: 17 low, 6 unclear Allocation concealment: 13 low, 10 unclear Blinding (participants and personnel): 23 high Blinding (outcome assessors): 8 low, 15 unclear Incomplete outcome data: 12 low, 7 unclear, 4 high Selective reporting: 3 low, 15 unclear, 5 high Other: 16 low, 6 unclear, 1 high Overall: "Primarily due to lack of reporting, the overall risk of bias was judged to be unclear."
Spencer 2015	Sequence generation: 2 low Allocation concealment: 2 low Blinding (participants and personnel): 1 low, 1 unclear Blinding (outcome assessors): 2 low Incomplete outcome data: 1 low, 1 unclear Selective reporting: 2 unclear Other: 2 low Overall: "Overall, the two trials were judged to be of low risk of bias."
Tieu 2017	Sequence generation: 7 low, 2 unclear, 1 high Allocation concealment: 4 low, 6 unclear, 1 high Blinding (participants and personnel): 11 high Blinding (outcome assessors): 2 low, 9 unclear Incomplete outcome data: 5 low, 5 unclear, 1 high Selective reporting: 2 low, 8 unclear, 1 high Other: 6 low, 5 unclear Overall: "Overall, the risk of bias was judged to be unclear to moderate."
Wojcieszek 2018	Sequence generation: 9 low, 1 high Allocation concealment: 8 low, 1 unclear, 1 high Blinding (participants and personnel): 4 low, 1 unclear, 5 high Blinding (outcome assessors): 10 low Incomplete outcome data: 7 low, 1 unclear, 2 high Selective reporting: 1 low, 9 unclear Other: 7 low, 3 unclear Overall: "We judged the risk of bias in the trials for methodology and reporting to be low to moderate."

Methodological quality of included reviews

When assessed against the ROBIS domains, 10 reviews (Bain et al., 2014; Crawford et al., 2015; Dodd et al., 2018; Han et al., 2012; Middleton et al., 2018; Palacios et al., 2019; E. Shepherd, Gomersall, et al., 2017; Spencer et al., 2015; Tieu et al., 2017; Wojcieszek et al., 2018) were considered at low risk of bias across all domains, 'Study eligibility criteria', 'Identification and selection of studies', 'Data collection and study appraisal' and 'Synthesis and findings'. One review (Barrett et al., 2014) was assessed as being at unclear risk of bias in the domains 'Data collection and study appraisal' and 'Synthesis and findings'. This review included six papers relating to one trial that was considered to have some design flaws. Only 45%

of women, who were considered "high risk" for GDM were tested for GDM. The intervention group (probiotic with dietary intervention) numbers were halved in the Barrett 2014 review analyses as they performed two comparisons: "probiotics versus placebo" and "probiotics versus diet". The review comparison labelled "probiotics vs diet" refers to comparison of probiotic with dietary intervention versus placebo with dietary intervention with both these groups receiving dietary intervention. The review comparison labelled "probiotics versus placebo" refers to probiotics with dietary intervention versus placebo with no dietary intervention. As the GRADE approach was not used in the review to assess the quality of the evidence, we reviewed original trial reports in order assess their risk of bias and quality of evidence using GRADE. The trial included in Barrett 2014 was also in Tieu 2017, but the 'Risk of bias' assessment differed, which could be because different groups in the trial were being compared in these reviews. Barrett 2014 assessed the trial as low risk of bias across all domains. Tieu 2017 assessed risk of bias for the same trial as follows. Sequence generation: low; Allocation concealment: low; Blinding (participants and personnel): high, Blinding (outcome assessors): unclear; Incomplete outcome data: low; Selective reporting: unclear; Other: low.

Details of the ROBIS assessments we made can be found in Table 3.3.

Table 3.3 ROBIS assessments for included reviews

Review ID	ROBIS Domains				Overall risk of bias
	Study eligibility criteria	**Identification and selection of studies**	**Data collection and study appraisal**	**Synthesis and findings**	
Bain 2014	Low risk	Low risk	Low risk	Low risk	LOW RISK
Barrett 2014	Low risk	Low risk	Unclear risk	Unclear risk	UNCLEAR RISK
Crawford 2015	Low risk	Low risk	Low risk	Low risk	LOW RISK
Palacios 2019	Low risk	Low risk	Low risk	Low risk	LOW RISK
Dodd 2018	Low risk	Low risk	Low risk	Low risk	LOW RISK
Han 2012	Low risk	Low risk	Low risk	Low risk	LOW RISK
Middleton 2018	Low risk	Low risk	Low risk	Low risk	LOW RISK
Shepherd 2017	Low risk	Low risk	Low risk	Low risk	LOW RISK
Spencer 2015	Low risk	Low risk	Low risk	Low risk	LOW RISK
Tieu 2017	Low risk	Low risk	Low risk	Low risk	LOW RISK
Wojcieszek 2018	Low risk	Low risk	Low risk	Low risk	LOW RISK

Effect of interventions

We have summarised the main results below. The outcome, GDM is presented for the different intervention types and categorised according to the framework described under 'Data synthesis': clear evidence of benefit; clear evidence of harm; clear evidence of no effect or equivalence; possible benefit; possible harm; or unknown benefit or harm. The first three categories represent GRADE moderate- or high-quality evidence for which we found either clear benefit, clear harm or clear evidence of no effect (i.e. equivalence with a comparator). These categories are identified by a green tick, a red-cross and a

green equal-sign icon, respectively (see Figure 3.1). For 'clear' benefit or harm, the confidence interval (CI) associated with the effect size did not cross the line of no effect. For 'clear evidence of no effect or equivalence' we considered a CI approximating the range of risk ratio (RR) 0.75 to 1.25 as sufficiently narrow to indicate a minimal effect relative to the comparator; these are thresholds recommended by GRADE (Guyatt, Oxman, Kunz, et al., 2011). Please refer to Figure 3.3 for a summary of all assessments.

Figure 3.3 Summary of the effect of interventions on the risk of women developing gestational diabetes mellitus

Intervention	Comparison	Participants	No. of participants (No. trials)	RR (95% CI)	GRADE	Effect on GDM
Dietary interventions						
Dietary advice	Standard care	Pregnant women	1279 (5)	0.60 (0.35 to1.04)	Very low	?
Low glycaemic index diet	Moderate to high glycaemic index diet	Pregnant women	912 (4)	0.91 (0.63 to1.31)	Low	?
Exercise interventions						
Exercise	Standard care	Pregnant women	826 (3)	1.10 (0.66 to1.84)	Low	?
Combined diet and exercise interventions						
Combined diet and exercise interventions	Standard care or minimal additional information	Pregnant women	6633 (19)	0.85 (0.71 to 1.01)	Moderate	+
Dietary supplement interventions						
Omega-3 fatty acid supplementation	Placebo or no omega-3	Pregnant women	5235 (12)	1.02 (0.83 to 1.26)	High	=
Vitamin D	Placebo or no intervention	Pregnant women	446 (4)	0.51 (0.27 to 0.97)	Low	+
Myo-inositol +folic acid	Placebo or folic acid	Pregnant women	502 (3)	0.43 (0.29 to 0.64)	Low	+
Probiotic + diet	Placebo + diet	Pregnant women	114 (1)	0.37 (0.15 to 0.89)	Very low	?
Probiotic + diet	Placebo	Pregnant women	111 (1)	0.38 (0.16 to 0.92)	Very low	?
Vitamin D + calcium	Placebo or no intervention	Pregnant women	54 (1)	0.33 (0.01 to 7.84)	Very low	?
Vitamin D + calcium +other vitamins and minerals	Placebo + calcium + other vitamins and minerals	Pregnant women	1298 (1)	0.42 (0.10 to 1.73)	Very low	?

Intervention	Comparison	Participants	No. of participants (No. trials)	RR (95% CI)	GRADE	Effect on GDM
Pharmaceutical interventions						
Metformin	Placebo	Obese pregnant women	892 (3)	0.85 (0.61 to 1.19)	Moderate	+
Low molecular weight heparin	Standard care	Pregnant women who had experienced a stillbirth of 20 weeks' gestation or more	85 (2)	1.28 (0.50 to 3.25)	Low	?
Low dose aspirin	Placebo	Pregnant women who had experienced a stillbirth of 20 weeks' gestation or more	24 (1)	0.42 (0.04 to 4.06)	Very low	?
Low dose aspirin + Low molecular weight heparin	Low dose aspirin	Pregnant women who had experienced a stillbirth of 20 weeks' gestation or more	29 (1)	0.27 (0.01 to 6.23)	Very low	?
Low dose aspirin + Low molecular weight heparin	Placebo	Pregnant women who had experienced a stillbirth of 20 weeks' gestation or more	27 (1)	0.14 (0.01 to 2.68)	Very low	?
Low molecular weight heparin	Low dose aspirin	Pregnant women who had experienced a stillbirth of 20 weeks' gestation or more	22 (1)	no events	Very low	?
Low molecular weight heparin (dose adjusted according to anti-factor Xa levels)	Low molecular weight heparin (fixed dose)	Pregnant women who had experienced a stillbirth of 20 weeks' gestation or more	13 (1)	0.38 (0.02 to 7.93)	Very low	?
Leukocyte immunisation	Placebo	Pregnant women who had experienced a stillbirth of 20 weeks' gestation or more	4 (1)	no events	Very low	?
Intravenous IgG	Placebo	Pregnant women who had experienced a stillbirth of 20 weeks' gestation or more	7 (2)	no events	Very low	?
Management of other health issues in pregnancy						
Universal screening and treatment for thyroid dysfunction	Risk based screening	Pregnant women	4516 (1)	0.93 (0.70 to 1.25)	Moderate	=
Fractional exhaled nitrogen oxide to adjust asthma therapy	Clinical algorithm to adjust asthma therapy	Pregnant women with asthma	210 (1)	0.74 (0.31 to 1.77)	Low	?
Pharmacist led multidisciplinary management of maternal asthma	Standard care	Pregnant women with asthma	58 (1)	5.00 (0.25 to 99.82)	Low	?

Additional details can also be found in the 'Summary of findings' for each intervention type: Table 3.4; Table 3.5; Table 3.6; Table 3.7; Table 3.8; Table 3.9.

Interventions for prevention of GDM

Dietary interventions

Unknown benefit or harm. Low- or very low-quality evidence with wide CIs

- Dietary advice: very low-quality evidence in Tieu 2017 showed unknown benefit or harm of dietary advice (most focused on giving general guidelines for healthy eating in pregnancy, with a dietician involved in four trials) compared with standard care on the risk of GDM (RR 0.60, 95% CI 0.35 to 1.04; 5 trials; 1279 women). Low-quality evidence showed unknown benefit or harm on of a low glycaemic index diet versus a moderate-high glycaemic index diet on the risk of GDM (RR 0.91, 95% CI 0.63 to 1.31; 4 trials; 912 women), Table 3.4.

Exercise interventions

Unknown benefit or harm. Low-quality evidence with wide CIs or very low-quality evidence

- Exercise: low-quality evidence in Han 2012 showed unknown benefit or harm of exercise interventions (individualised plans or a combination of various supervised and unsupervised sessions at least three times a week, starting between 12 and 24 weeks' gestation) on the risk of GDM compared with standard antenatal care (RR 1.10, 95% CI 0.66 to 1.84; 3 trials; 826 women), Table 3.5.

Combined dietary and exercise interventions

Possible benefit. Low-quality evidence with clear benefit (CI does not cross the line of no effect), or moderate- or high-quality evidence with wide CI

- Diet and exercise combined: moderate-quality evidence in Shepherd 2017 indicated a possible benefit with reduction in the risk of GDM with combined diet and exercise interventions during pregnancy compared with standard care (RR 0.85, 95% CI 0.71 to 1.01; 19 trials; 6633 women), Table 3.6. There were no clear subgroup differences for GDM by trial design ($Chi^2 = 0.22$, df = 1 (P = 0.64), $I^2 = 0.0\%$), maternal body mass index (BMI) ($Chi^2 = 1.73$, df = 3 (P = 0.63), $I^2 = 0.0\%$), or ethnicity ($Chi^2 = 0.22$, df = 3 (P = 0.97), $I^2 = 0.0\%$) (Table 3.10). Sensitivity analysis including only those trials considered at low risk of selection bias (Table 3.10) did not affect results (RR 0.86; 95% CI 0.68 to 1.09; 11 trials; 5019 women).

Dietary supplement interventions

Clear evidence of no effect. Moderate- or high-quality evidence with narrow CI crossing the line of no effect

- Omega-3 fatty acid: high-quality evidence in Middleton 2018 showed no effect of omega-3 fatty acid supplementation in pregnancy (doses between 0.22 g and 2.8 g per day, starting between 12 and 24 weeks' gestation) on the risk of GDM (RR 1.02, 95% CI 0.83 to 1.26; 12 trials; 5235 women), Table 3.7.

Possible benefit. Low-quality evidence with clear benefit (CI does not cross the line of no effect), or moderate- or high-quality evidence with wide CI

- Myo-inositol: low-quality evidence in Crawford 2015 showed a possible benefit with a reduction in the risk of GDM with 2 g to 4 g of myo-inositol per day during pregnancy compared with control (RR 0.43, 95% CI 0.29 to 0.64; 3 trials; 502 women), Table 3.7.

- Vitamin D: low-quality evidence in Palacios 2019 showed benefit of vitamin D supplementation in pregnancy (varying dose regimens with a weekly total of between 1400 IU and 30,000 IU, starting before 25 weeks' gestation, duration of treatment from a single dose to the remainder of the pregnancy), with a reduction in risk of GDM (RR 0.51, 95% CI 0.27 to 0.97; 4 trials; 446 women), Table 3.7. These trials were all from Asian countries and the women's vitamin D levels before supplementation were mostly unknown. One study was from India and three from Iran. One study identified whether women in the intervention group were vitamin D deficient prior to supplementation, and gave different vitamin D doses according to serum vitamin D concentrations. There were no subgroup differences for GDM by gestation at start of supplementation (Chi^2 = 2.15, df = 2 (P = 0.34), I^2 = 7%), maternal pre-gestational BMI (Chi^2 = 2.08, df = 1 (P = 0.15), I^2 = 52%), supplementation regimen (Chi^2 = 2.20, df = 2 (P = 0.33), I^2 = 9%), or season at start of supplementation (Chi^2 = 2.09, df = 2 (P = 0.35), I^2 = 4%) (Table 3.10).

Unknown benefit or harm. Low-quality evidence with wide CIs or very low- quality evidence

- Probiotics: very low-quality evidence in Barrett 2014 from one trial showed a reduction in the risk of GDM with probiotic and diet intervention combined versus placebo and diet intervention combined (RR 0.37, 95% CI 0.15 to 0.89; 114 women), or probiotic and diet intervention combined versus control (RR 0.38, 95% CI 0.16 to 0.92; 111 women), Table 3.7.

- Vitamin D with calcium: very low-quality evidence in Palacios 2019 showed unknown benefit or harm of vitamin D with calcium supplementation (RR 0.33, 95% CI 0.01 to 7.84; 1 trial; 54 women) and unknown benefit or harm of vitamin D supplementation + calcium + other vitamins and minerals versus calcium + other vitamins and minerals (RR 0.42, 95% CI 0.10 to 1.73; 1 trial; 1298 women) on the risk of GDM, Table 3.7.

Pharmaceutical interventions

Possible benefit. Low-quality evidence with clear benefit (CI does not cross the line of no effect), or moderate- or high-quality evidence with wide CI

- Metformin: moderate-quality evidence in Dodd 2018 showed a possible benefit of 1 g to 3 g per day of metformin compared with placebo on the risk of GDM in obese pregnant women (RR 0.85, 95% CI 0.61 to 1.19; 3 trials; 892 women), Table 3.8.

Unknown benefit or harm. Low- quality evidence with wide CIs or very low-quality evidence

- Care prior to and during subsequent pregnancies following stillbirth: evidence in Wojcieszek 2018 showed unknown benefit or harm of several medications on the incidence of GDM: low-quality evidence for low molecular weight heparin versus no/standard care (RR 1.28, 95% CI 0.50 to 3.25; 2 trials; 85 women); very low-quality evidence for low-dose aspirin versus placebo (RR 0.42, 95% CI 0.04 to 4.06; 1 trial; 24 women); very low-quality evidence for low-dose aspirin and low molecular weight heparin versus low-dose aspirin alone (RR 0.27, 95% CI 0.01 to 6.23; 1 trial; 29 women); very low-quality evidence for low-dose aspirin and low molecular weight heparin versus placebo (RR 0.14, 95% CI 0.01 to 2.68; 1 trial; 27 women); very low-quality evidence for low molecular weight heparin versus low-dose aspirin (no events; one trial; 22 women); very low- quality evidence for low molecular weight heparin (adjusted dose) versus low molecular weight heparin (fixed dose) (RR 0.38, 95% CI 0.02 to 7.93; 1 trial; 13 women); very low-quality evidence for leukocyte immunisation versus placebo (no events; one trial; four women); very low-quality evidence for intravenous IgG versus placebo (no events); two trials; seven women), Table 3.8.

Management of other health issues

Clear evidence of no effect. Moderate- or high-quality evidence with narrow CI crossing the line of no effect

- Universal screening for thyroid dysfunction vs risk based screening: moderate-quality evidence in Spencer 2015 showed no effect on the risk of GDM with universal screening of pregnant women for thyroid dysfunction compared with risk based screening (RR 0.93, 95% CI 0.70 to 1.25; 1 trial; 4516 women), Table 3.9.

Unknown benefit or harm. Low-quality evidence with wide CIs or very low-quality evidence

- Asthma management: low-quality evidence in Bain 2014 showed unknown benefit or harm of using fractional exhaled nitrogen oxide versus a clinical algorithm to adjust asthma therapy on the incidence of GDM (RR 0.74, 95% CI 0.31 to 1.77; 1 trial; 210 women). Low-quality evidence in Bain 2014 showed unknown benefit or harm of a pharmacist led multidisciplinary approach to management of maternal asthma versus standard care on the incidence of GDM (RR 5.00, 95% CI 0.25 to 99.82; 1 trial; 58 women), Table 3.9.

Sensitivity analysis

No sensitivity analysis was required as no reviews were assessed as being of high concern for risk of bias using ROBIS.

3.7 Discussion

We have summarised the evidence from relevant Cochrane Reviews on the effectiveness of interventions to prevent gestational diabetes mellitus (GDM), and have assigned interventions to six mutually exclusive categories with graphic icons to provide a quick visual prompt for readers as to the effectiveness or otherwise of these interventions: clear evidence of benefit; clear evidence of harm; clear evidence of no effect or equivalence; possible benefit; possible harm; or unknown benefit or harm.

Summary of main results

This overview, evaluating interventions with GDM as a primary or secondary outcome, included 11 Cochrane Reviews, involving 71 randomised controlled trials and 23,154 women. Five reviews evaluated interventions directed at preventing GDM, and a further six reviews included interventions in pregnant women that may improve maternal or infant health, with GDM as a primary or secondary outcome for the review. All the trials in the 11 systematic reviews included pregnant women; no trials assessed interventions prior to pregnancy or between pregnancies.

Four reviews reported interventions of possible benefit to pregnant women, with a reduction in the risk of GDM: combined diet and exercise (E. Shepherd, Gomersall, et al., 2017), myo-inositol (Crawford et al., 2015), vitamin D supplementation (Palacios et al., 2019), or metformin (Dodd et al., 2018). Two reviews reported no benefit to pregnant women with universal screening and treatment for thyroid dysfunction (Spencer et al., 2015); nor to pregnant women using omega-3 fatty acid supplements (Middleton et al., 2018) for reducing the risk of GDM. The evidence was insufficient to assign a level of effectiveness in interventions in seven reviews (Bain et al., 2014; Barrett et al., 2014; Dodd et al., 2018; Han et al., 2012; Palacios et al., 2019; Tieu et al., 2017; Wojcieszek et al., 2018). Importantly, no reviews demonstrated evidence of harm (defined as a clear increase in the risk of GDM).

Overall completeness and applicability of evidence

Our aim was to summarise the evidence relating to strategies that may prevent GDM. However, six reviews were published more than two years ago (Bain et al., 2014; Barrett et al., 2014; Crawford et al., 2015; Han et al., 2012; Spencer et al., 2015; Tieu et al., 2017). There may be trials now published that might alter the results of the reviews, in particular those relating to probiotics and exercise. Exercise interventions used in trials have been widely differing in level of activity, intensity and details of other activity not related to the study, making comparisons between different exercise interventions and pooling results difficult to interpret.

Palacios 2019 reported a possible benefit of vitamin D supplementation in pregnancy with a reduction in the risk of GDM. It is worth noting that this evidence came from four small trials of only 446 women and all trials were conducted in Asian countries. The effect may differ for other ethnicities or geographical locations. Vitamin D concentrations prior to supplementation were determined in two of six trials and it may be that women with vitamin D deficiency are more likely to benefit than those with normal concentrations. The review authors concluded vitamin D supplementation possibly reduces the risk of GDM.

A clear research gap in the published literature is that no randomised trials of interventions in women preconception or inter-conception for prevention of GDM in a subsequent pregnancy were identified, an important time for intervention. We only included Cochrane systematic reviews in this overview and there are published non-Cochrane systematic reviews.

Quality of the evidence

We used ROBIS in our evaluation of risks of bias in the included systematic reviews. Cochrane Review methodology includes assessment of risk of bias of included trials. We did not plan to reassess the quality

of the included trials in the reviews, though in order to apply GRADE to the outcome pre-specified in our overview, details of original trial papers were reviewed from Bain 2014, Barrett 2014, Han 2012, Middleton 2018, Spencer 2015 and Wojcieszek 2018. Barrett 2014, suggested a reduction in GDM with the use of probiotics. However, the trial design had a significant limitation with only 45% of women tested for GDM.

Potential biases in the overview process

We were aware that there were risks of introducing bias at all stages of the overview process, and took a number of steps to minimise this. We published a protocol for our overview. At least two overview authors independently assessed reviews as to eligibility for inclusion, carried out data extraction and quality assessment, and assessed the quality of the evidence using the GRADE approach. A potential source of bias relates to authors of this overview being authors for some of the included reviews. As pre-specified in our protocol, data extraction and quality assessment for such reviews were carried out by two overview authors who were not authors of the individual reviews. We undertook a comprehensive search of the Cochrane Database of Systematic Reviews without language or date restrictions, and identified published reviews, as well as planned and ongoing reviews (protocols).

Agreements and disagreements with other studies or reviews

We found no published overviews of interventions for preventing GDM in women. One review article was identified that included several different types of intervention for preventing GDM: Agha-Jaffar 2016 reviewed trials investigating, exercise, diet, metformin, myo-inositol and fish oil as interventions for prevention of GDM (Agha-Jaffar, Oliver, Johnston, & Robinson, 2016). Probiotics and myo-inositol were possibly effective in reducing the incidence of GDM in women at high risk. Dietary intervention was effective in reducing GDM in obese women. Otherwise, the combination of diet and exercise or exercise alone did not show a clear benefit in reducing the incidence of GDM, and fish oil was of no benefit. Metformin did not reduce the incidence of GDM in women with obesity or polycystic ovarian syndrome. No meta-analysis was included in this review, but the conclusions were similar to those of this overview. The authors of the review were unable to identify randomised trials with strategies implemented before conception.

Guo 2018 published a systematic review that demonstrated a reduction in the incidence of GDM with dietary intervention (RR 0.75, 95% CI 0.59 to 0.95; 11 trials; 2838 women)(Guo et al., 2018). This review included five additional trials to Tieu 2017 where data had been published more recently, but also did not include five trials that Tieu 2017 included, likely as result of different search strategies and inclusion criteria. Guo 2018 excluded trials with "severely unbalanced risk factors or dropout rates" between

groups. Bennett 2018 systematic review found a reduction in risk of GDM with dietary interventions (RR 0.56, 95% CI 0.36 to 0.86; 9 trials) (Bennett et al., 2018). Song 2016 reported a meta-analysis of studies in English or Chinese and found no significant effect on risk of GDM with dietary interventions (RR 0.80, CI 0.58 to 1.10; 5 trials; 1279 women) (Song, Li, Leng, Ma, & Yang, 2016).

Song 2016 meta-analysis did not find a significant reduction in the risk of GDM with exercise interventions (RR 0.77, 95% CI 0.54 to 1.09; 10 trials; 4161 women). However, exercise alone was found to be of benefit in reducing the risk of GDM in several other systematic reviews: Bennett 2018 (RR 0.62, 95% CI 0.50 to 0.78; 10 trials; 2981; women) (Bennett et al., 2018), Yu 2018 (odds ratio (OR) 0.59, 95% CI 0.39 to 0.88; 5 trials; 1370 women) (Ying Yu, Xie, Shen, & Shu, 2018), Davenport 2018 (OR 0.62, 95% CI 0.52 to 0.75; 26 trials; 6934 women) (Davenport et al., 2018), Guo 2018 (RR 0.70, 95% CI 0.59 to 0.84; 19 trials; 5883 women) (Guo et al., 2018), Sanabria-Martínez 2015 (RR 0.69, 95% CI 0.52 to 0.91; 8 trials; 2501 women) (Sanabria-Martínez et al., 2015) and Zheng 2017 (OR 0.62, 95% CI 0.43 to 0.89; 5 trials; 1872 women) (Zheng, Wang, & Ren, 2017). There may be a threshold for frequency and intensity of exercise above which a benefit is seen. In addition, the earlier in pregnancy the intervention was initiated, the more benefit was seen (Guo et al., 2018). A meta-analysis by Sanabria-Martínez 2015 indicated a reduction in GDM when an exercise programme was undertaken by pregnant women with previously low levels of activity (Sanabria-Martínez et al., 2015). All these reviews were published more recently than Han 2012.

A combined diet and exercise intervention did not clearly reduce the risk of GDM in systematic reviews by Bennett 2018 (RR 0.90, 95% CI 0.77 to 1.05; 19 trials; 7274 women) and Guo 2018 (RR 0.86, 95% CI 0.71 to 1.04; 18 trials; 7024 women). The authors of Bennett 2018 suggested the reason for this was that changing both diet and exercise simultaneously was too difficult. Bennett 2018 included search results of Chinese databases and therefore included additional trials not included in the Cochrane systematic reviews. Guo 2018 suggested that the earlier the intervention, the more benefit there was in reduction of GDM risk. The Song 2016 meta-analysis of interventions included publications in English or Chinese and did not find a significant reduction in risk of GDM with combined exercise and dietary intervention (RR 0.85, 95% CI 0.70 to 1.03; 14 trials; 6047 women).

The Vitagliano 2019 systematic review included an additional trial to Crawford 2015 and also demonstrated a possible reduction in the risk of GDM with myo-inositol supplementation in pregnancy, though the quality of the evidence was assessed as very low, using GRADE criteria, (OR 0.49, 95% CI 0.24 to1.03; 4 trials; 848 women) (Vitagliano et al., 2019). Subgroup analysis including the two trials

with the higher dose of 4 g my-inositol per day was advantageous over the lower dose of 1.1 g with OR 0.34, 95% CI 0.21 to 0.53; 3 trials; 608 women.

The Jarde 2018 systematic review, including two studies of 355 women, showed unclear benefit or harm of probiotics in the prevention of GDM (RR 1.25, 95% CI 0.61 to 2.56) (Jarde et al., 2018). The PiP study (Wickens et al., 2017), published since the Jarde review, demonstrated no significant effect on GDM risk when using probiotics compared with placebo, using the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) criteria for diagnosis (RR 0.59, 95% CI 0.32 to 1.08; 373 women), but a reduction was evident when the New Zealand criteria were used for diagnosis (RR 0.32, 95% CI 0.11 to 0.96; 383 women). The recent SPRING trial (Callaway et al., 2019) demonstrated no difference in the rates of GDM in overweight or obese women who received probiotic compared to placebo (OR 1.62, 95% CI 0.91 to 2.89; 411 women).

No other systematic reviews of randomised controlled trials that examined the effect of vitamin D supplementation on risk of GDM were found.

No other systematic reviews of randomised controlled trials that examined the effect of metformin on risk of GDM were found.

Population data from Canada demonstrated no effect of asthma treatment nor asthma severity on the risk of GDM in pregnant asthmatics (Baribeau, Beauchesne, Rey, Forget, & Blais, 2016; Blais, Kettani, & Forget, 2014).

3.8 Authors' Conclusions

Our overview included 11 systematic reviews with 71 trials involving 23,154 women. No interventions to prevent GDM in 11 systematic reviews were of clear benefit or harm. Myo-inositol, metformin, combined exercise and dietary intervention, and vitamin D supplementation in pregnancy, were identified as having a possible benefit in reducing the incidence of GDM. There remains a need for further high-quality evidence investigating the effect of myo-inositol, vitamin D, probiotics, metformin, exercise and dietary interventions alone or in combination. There is a lack of trials investigating interventions prior to or between pregnancies for the prevention of GDM.

Implications for practice

The aim of this overview was to summarise the evidence on the topic of interventions that may prevent GDM, not to provide practice recommendations. Evidence shows a combination of exercise and diet,

supplementation with myo-inositol, vitamin D supplementation in pregnancy and metformin are of possible benefit in reducing the risk of GDM. There is evidence that omega-3- fatty acid supplements and universal screening for thyroid dysfunction are of no benefit in pregnancy for preventing GDM, though this does not exclude benefit for other health outcomes. There is insufficient high-quality evidence to establish the effect on the risk of GDM of diet or exercise alone, probiotics, vitamin D with calcium or other vitamins and minerals, interventions in pregnancy after a previous stillbirth, and different strategies for managing asthma in pregnancy.

Implications for research

In randomised controlled trials investigating the effect of interventions for preventing GDM, all included participants should be tested for GDM.

Further high-quality research is needed to determine the possible benefit of a combination of diet and exercise, myo-inositol, vitamin D supplementation in different ethnic populations and metformin in preventing GDM. The dose of myo-inositol or metformin and timing of intervention may be important and it would be helpful if future studies were to replicate sound methodology of earlier trials where available, and be of adequate power.

For trials assessing exercise interventions, the intensity, duration, frequency and timing during pregnancy need to be clearly defined and compared as there is heterogeneity in these parameters between trials, making meaningful synthesis of results and meta- analysis challenging. Dietary interventions are heterogenous in type and timing, which may have an impact on the effect. It is important for trials to record not only allocation of intervention types, but also adherence to the treatment protocol participants are allocated to and other qualities such as pre-trial diet, activity level or use of additional exercise.
Where possible trials published in using non-Latin scripts should be included, for example, Chinese.

Table 3.4 Summary of findings: dietary interventions

Intervention and comparison	Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)
		Assumed risk with comparator	Corresponding risk with intervention			
Dietary advice vs standard care in pregnancy Tieu 2017	GDM	126 per 1000 82/651	76 per 1000 (44 to 131) 54/628	RR 0.60 (0.35, 1.04)	1279 (5)	Very low[a]
Low GI vs mod-high GI diet in pregnancy Tieu 2017	GDM	110 per 1000 49/444	100 per 1000 (70 to 145) 47/468	RR 0.91 (0.63, 1.31)	912 (4)	Low[b]

a Studies contributing data had design limitations; There was considerable variation in the size of the effect in different studies; Wide 95% confidence interval crossing the line of no effect.

b Studies contributing data had design limitations; Wide 95% confidence interval crossing the line of no effect.

Table 3.5 Summary of findings: exercise interventions

Intervention and comparison	Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)
		Assumed risk with comparator	Corresponding risk with intervention			
Any exercise vs routine care in pregnancy Han 2012	GDM	62 per 1000 24/389	68 per 1000 (41 to 114) 30/437	RR 1.10 (0.66, 1.84)	826 (3)	Low[a]

a Study design limitations; wide 95% confidence interval crossing the line of no effect.

Table 3.6 Summary of findings: combined diet and exercise interventions

Intervention and comparison	Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)
		Assumed risk with comparator	Corresponding risk with intervention			
Diet and exercise vs standard care in pregnancy Shepherd 2017	GDM	168 per 1000 551/3280	143 per 1000 (119 to 170) 525/3353	RR 0.85 (0.71, 1.01)	6633 (19)	Moderate[a]

a Study design limitations: 19 RCTs, intervention unable to be blinded (not downgraded for this as outcome is objective); some RCTS with potentially serious design limitations (unclear randomisation, attrition bias); Inconsistency: $I^2 = 42\%$, possibly largely due to one trial (Dodd 2014), not downgraded))

Table 3.7 Summary of findings: dietary supplement interventions

Intervention and comparison	Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)
		Assumed risk with comparator	Corresponding risk with intervention			
Omega-3 fatty acid supplementation in pregnancy vs none Middleton 2018	GDM	62 per 1000 158/2569	63 per 1000 (51 to 77) 167/2666	RR 1.02 (0.83, 1.26)	5235 (12)	High
Myo-inositol vs control in pregnancy Crawford 2015	GDM	283 per 1000 75/265	122 per 1000 (82 to 181) 27/237	RR 0.43 (0.29, 0.64)	502 (3)	Low[a]
Probiotics and diet vs placebo and diet in pregnancy Barrett 2014	GDM	333 per 1000 27/76	131 per 1000 (53 to 316) 5/38	RR 0.37 (0.15, 0.89)	114 (1)	Very low[b]
Probiotics and diet vs control in pregnancy Barrett 2014	GDM	342 per 1000 25/73	130 per 1000 (55 to 315) 5/38	RR 0.38 (0.16, 0.92)	111 (1)	Very low[b]
Vitamin D vs control/placebo in pregnancy Palacios 2019	GDM	127 per 1000 25/197	65 per 1000 (34 to 123) 13/249	RR 0.51 (0.27, 0.97)	446 (4)	Low[c]
Vitamin D+calcium vs control/placebo in pregnancy Palacios 2019	GDM	37 per 1000 1/27	12 per 1000 (0 to 290) 0/27	RR 0.33 (0.01, 7.84)	54 (1)	Very low[d]
Vitamin D+calcium+other vitamins or minerals vs calcium+other vitamins or minerals in pregnancy Palacios 2019	GDM	12 per 1000 3/259	5 per 1000 (1 to 20) 5/1039	RR 0.42 (0.10, 1.73)	1298 (1)	Very low[e]

a Unclear risk of bias for allocation concealment in two of the included trials (one trial did not provide sufficient detail to determine allocation concealment and one trial (reported as a conference abstract) had no details of random sequence generation, allocation concealment or blinding) and for high risk of performance bias for lack of blinding (two trials were open-label trials with no blinding of participants or researchers, however one trial explicitly described blinding of outcome assessors and was assessed as low risk of detection bias); Studies were conducted in Italy with Caucasian women and generalisability of findings is limited.

b Serious limitations in study design as not all women tested for GDM. Very serious imprecision with one small study and a wide 95% confidence interval crossing the line of no effect.

c Serious limitations in study design due to one study being assessed as high risk of bias for several domains. Serious limitations due to indirectness with studies performed only in Asian countries (this downgrading was added by overview authors).

d Serious limitations in study design due to one study being at high risk of performance and detection bias; Very serious limitations in imprecision due to one small study, with a single event and wide 95% confidence intervals crossing the line of no effect contributing data.

e Very serious limitations in imprecision with only one study, with few events, and wide 95% confidence intervals crossing the line of no effect; Serious indirectness as there were multiple nutrient interventions in addition to vitamin D.

Table 3.8 Summary of findings: pharmaceutical interventions

Intervention and comparison	Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)
		Assumed risk with comparator	Corresponding risk with intervention			
Metformin vs placebo in pregnancy Dodd 2018	GDM	143 per 1000 64/448	121 per 1000 (87 to 170) 53/444	0.85 (0.61, 1.19)	892 (3)	Moderate[a]
Care prior to and during subsequent pregnancies following stillbirth. Low molecular weight heparin versus no treatment/standard care. Wojcieszek 2018	GDM	125 per 1000 5/40	160 per 1000 (63 to 406) 8/45	1.28 (0.50, 3.25)	85 (2)	Low[b]
Care prior to and during subsequent pregnancies following stillbirth. Low-dose aspirin versus placebo. Wojcieszek 2018	GDM	182 per 1000 2/11	76 per 1000 (7 to 738) 1/13	RR 0.42 (0.04, 4.06)	24 (1)	Very low[c]
Care prior to and during subsequent pregnancies following stillbirth. Low-dose aspirin + low molecular weight heparin versus low-dose aspirin. Wojcieszek 2018	GDM	77 per 1000 1/13 (aspirin)	21 per 1000 (1 to 479) 0/16	0.27 (0.01, 6.23)	29 (1)	Very low[c]
Care prior to and during subsequent pregnancies following stillbirth. Low-dose aspirin + low molecular weight heparin versus placebo Wojcieszek 2018	GDM	182 per 1000 2/11	25 per 1000 (2 to 487) 0/16	0.14 (0.01, 2.68)	27 (1)	Very low[c]
Care prior to and during subsequent pregnancies following stillbirth. Low molecular weight heparin versus low-dose aspirin. Wojcieszek 2018	GDM	0 per 1000 0/12 (aspirin)	0 per 1000 (not estimable) 0/10	no events	22 (1)	Very low[d]
Care prior to and during subsequent pregnancies following stillbirth. Low molecular weight heparin (dose adjusted according to anti-factor Xa levels) versus low molecular weight heparin (fixed dose). Wojcieszek 2018	GDM	143 per 1000 1/7 (fixed dose)	54 per 1000 (3 to 1000) 0/6	0.38 (0.02, 7.93)	13 (1)	Very low[e]
Care prior to and during subsequent pregnancies following stillbirth. Leukocyte immunisation versus placebo. Wojcieszek 2018	GDM	0 per 1000 0/2	0 per 1000 (not estimable) 0/2	no events	4 (1)	Very low[f]
Care prior to and during subsequent pregnancies following stillbirth. Intravenous IgG versus placebo. Wojcieszek 2018	GDM	0 per 1000 0/4	0 per 1000 (not estimable) 0/3	no events	7 (2)	Very low[f]

a Study design limitations as one study of the three studies included has unclear risk of bias for random sequence generation, allocation concealment, performance bias, outcome assessor bias and selective reporting bias and reports a much greater effect than the other two studies.

b Limitations in study design; wide 95% confidence intervals crossing the line of no effect.

c Serious limitations in study design; very serious limitations in imprecision with only one study, with few events, and wide 95% confidence intervals crossing the line of no effect.

d Serious limitations in study design; very serious limitations in imprecision with only one study, with few events, and wide 95% confidence intervals crossing the line of no effect.

e Limitations due to indirectness as study population at increased risk of pregnancy loss and GDM not a predefined outcome; Very serious limitations in imprecision with only one study, with few events, and wide 95% confidence intervals crossing the line of no effect.

f Limitations due to indirectness as study population at increased risk of pregnancy loss and GDM not a predefined outcome; Very serious limitations in imprecision with only one study, with few events, and wide 95% confidence intervals crossing the line of no effect.

Table 3.9 Summary of findings: management of other health issues in pregnancy

Intervention and comparison	Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)
		Assumed risk with comparator	Corresponding risk with intervention			
Universal screening for thyroid dysfunction vs risk based screening in pregnancy Spencer 2015	GDM	40 per 1000 90/2257	37 per 1000 (28 to 50) 84/2259	RR 0.93 (0.70, 1.25)	4516 (1)	Moderate[a]
Fractional Exhaled Nitrogen Oxide algorithm vs clinical guideline algorithm to adjust asthma therapy in pregnancy Bain 2014	GDM	104 per 1000 11/106	77 per 1000 (32 to 184) 8/104	RR 0.74 (0.31, 1.77)	210 (1)	Low[b]
Pharmacist led multidisciplinary approach to management of maternal asthma vs standard care in pregnancy Bain 2014	GDM	69 per 1000 0/29	345 per 1000 (17 to 1000) 2/29	RR 5.00 (0.25, 99.82)	58 (1)	Low[b]

a Serious limitation in imprecision with a wide confidence interval crossing the line of no effect

b Very serious limitation in imprecision as a single study with a small sample and a wide 95% confidence interval crossing the line of no effect.

Table 3.10 Summary of findings: subgroup and sensitivity analyses for select comparisons for GDM

Intervention and comparison	Outcome	Subgroup or sensitivity analysis		Assumed risk with comparator	Corresponding risk with intervention	Relative effect (95% CI)	Number of participants (trials)	Test for subgroup differences
Combined diet and exercise vs standard care	GDM	Study design	Individually randomised	546/3222	515/3270	0.84 (0.70, 1.01)	6492 (17)	$Chi^2 = 0.22$, df = 1 (P = 0.64), I^2 = 0.0%
			Cluster randomised	7/58	10/83	1.05 (0.42, 2.60)	141 (2)	
		Maternal BMI at or before trial entry	Healthy (BMI < 25 kg/m^2)	8/150	8/150	0.91 (0.19, 4.24)	300 (3)	$Chi^2 = 1.73$, df = 3 (P = 0.63), I^2 = 0.0%
			Overweight or obese (BMI ≥ 25 kg/m^2)	206/1436	210/1465	0.77 (0.50, 1.2)	2901 (8)	
			Obese (BMI ≥ 30 kg/m^2)	204/880	191/858	0.96 (0.81, 1.13)	1738 (3)	
			Any	551/814	525/880	0.80 (0.63, 1.03)	1694 (8)	
		Ethnicity	Majority low-risk ethnicities	180/1494	196/1503	0.85 (0.50, 1.43)	2998 (5)	$Chi^2 = 0.22$, df = 3 (P = 0.97), I^2 = 0.0%
			Majority high-risk ethnicities	1/29	1/27	1.07 (0.07, 16.3)	56 (1)	
			Mixed ethnicities	242/1046	216/1077	0.89 (0.76, 1.05)	2123	
			Unclear	128/710	112/746	0.83 (0.61, 1.12)	1456	
		Sensitivity	Low risk of bias	418/2501	409/2518	0.86 (0.68, 1.09)	5019 (11)	Not applicable
Vitamin D versus no treatment/placebo	GDM	Gestation at start of supplementation	Less than 20 weeks of pregnancy	8/70	7/70	0.88 (0.34, 2.28)	140 (1)	$Chi^2 = 2.15$, df = 2 (P = 0.34), I^2 = 7%
			20 weeks of pregnancy or more	2/84	1/135	0.43 (0.05, 3.45)	219 (2)	
			Unknown/unreported/mixed	15/43	5/44	0.33 (0.13, 0.82)	87 (1)	
		Pre-gestational BMI	BMI 18.5-24.9	9/127	8/178	0.83 (0.33, 2.05)	305 (2)	$Chi^2 = 2.08$, df = 1 (P = 0.15), I^2 = 52%
			BMI 25 or higher	16/70	5/71	0.33 (0.13, 0.79)	141 (2)	
		Supplementation regimen	Single dose	1/57	1/108	0.53 (0.03, 8.28)	165 (1)	$Chi^2 = 2.20$, df = 2 (P = 0.33), I^2 = 9%
			Daily dose	16/70	5/71	0.33 (0.13, 0.79)	141 (2)	
			Weekly/monthly dose	8/70	7/70	0.88 (0.34, 2.28)	140 (1)	
		Season at start of supplementation	Summer	1/27	0/27	0.33 (0.01, 7.84)	54 (1)	$Chi^2 = 2.09$, df = 2 (P = 0.35), I^2 = 4%
			Winter	8/70	7/70	0.88 (0.34, 2.28)	140 (1)	
			Mixed/unknown	16/100	6/152	0.34 (0.14, 0.82)	252 (2)	

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

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4.1 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 (Sells et al., 1994; R. C. Temple et al., 2011; Y. Yamashita et al., 1996). Others found an adverse association between poor maternal glycemic control and intellect (Silverman et al., 1998, 1991), developmental quotient (Brinciotti et al., 2009), hand-eye coordination (Ornoy et al., 1998), motor test scores(Ornoy et al., 1998; Ratzon et al., 2000), school grades (Knorr et al., 2015) and cognitive scores in adult males (Nielsen et al., 2010). 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 (Coustan et al., 2010; Landon, Gabbe, & Sachs, 1990; Singh, Rahimpanah, & Barclay, 2015; Wah Cheung, 2009; World Health Organisation, 2013a). Furthermore, many studies did not adjust for confounding factors such as obesity, parental education or socioeconomic status (Brinciotti et al., 2009; Nielsen et al., 2007; Ornoy et al., 1998; Ratzon et al., 2000; R. C. Temple et al., 2011; Y. Yamashita et al., 1996) 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 (Clausen et al., 2013) and there is increasing evidence that maternal obesity has an adverse effect on their children's neurodevelopment (Basatemur et al., 2013; Bliddal et al., 2014; Casas et al., 2013; Gage et al., 2013; Helderman et al., 2012; Hinkle et al., 2012; Huang et al., 2014; Kerstjens et al., 2013; Krakowiak et al., 2012; Neggers et al., 2003). Obesity is associated with increased risk of diabetes in pregnancy (Shin & Song, 2015) and with poorer socioeconomic status (Mclaren, 2007; Y. Wang & Beydoun, 2007). 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 (Barrett et al., 2009; Njenga et al., 1992), 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 (Balsells et al., 2000; S. C. Brown et al., 1999; Flores-le Roux et al., 2012; Kline & Edwards, 2007; Taylor et al.,

2002). 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.

4.2 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 (McKinlay et al., 2015, 2017). 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 (McKinlay et al., 2015, 2017), 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 hypoglycemia 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 (Wechsler, 2002) (WPPSI-III) score < 85; Beery Visual-Motor Integration 6th edition (Beery et al., 2010) (Beery VMI) score more than 1 SD below the test mean; Movement Assessment Battery for Children-2nd Edition (MABC-2) (Henderson et al., 2007) total Score <15th centile; Motion coherence threshold (T.-Y. Y. Yu et al., 2013) 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 (Bayley, 2006b) 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.

4.2.1 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) (Salmond, Crampton, & Atkinson, 2007) 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 (McKinlay et al., 2015). 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.

4.3 Results

Primary outcome data were available for 196/229 (86%) eligible children (196/231, 85% of recruited children) (Figure 4.1). The majority of children (155/196, 79%) were born to mothers with gestational diabetes. As expected, diabetes management varied by diabetes type (Table 4.1). 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 4.2). 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 4.3, 4.4). 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 4.4).

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 (Table 4.5).

The secondary outcomes also did not vary by maternal diabetes type, HbA1c or polycose quartile, nor intrapartum blood glucose range (Tables 4.2, 4.3).

Figure 4.1 CHYLD participant flow to four-and-a-half-year follow-up

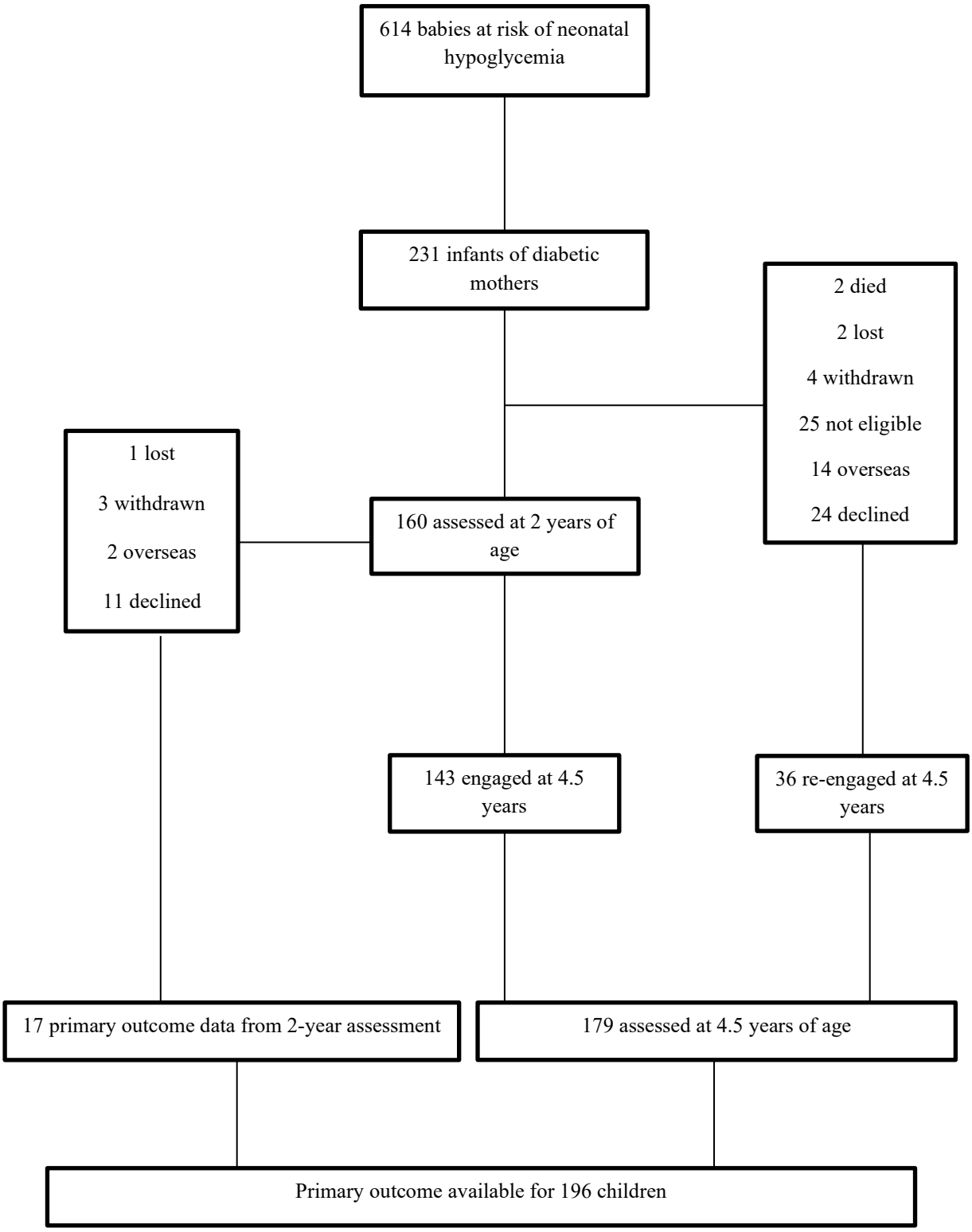

Table 4.1 Characteristics of mothers with different types of diabetes in pregnancy and their babies

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[1]
Booking BMI[a]	31.2 (7.8)	31.5 (7.9)	25.3 (4.0)	34.7 (5.9)	<0.01
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 Diet/lifestyle only Metformin Insulin	 58 (30) 24 (13) 110 (57)	 58 (38) 22 (14) 73 (48)	 0 (0) 0 (0) 20 (100)	 0 (0) 2 (11) 17 (89)	<0.01[2]
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] 1	 25 (12.8)	 18 (11.6)	 3 (15.0)	 4 (19.1)	0.70
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 Maori Pacific Asian NZ European	 73 (37.2) 7 (3.6) 15 (7.7) 101 (51.5)	 54 (34.8) 7 (4.5) 12 (7.7) 82 (52.9)	 8 (40.0) 0 (0) 1 (5) 11 (55.0)	 11 (52.4) 0 (0) 2 (9.5) 8 (33.1)	0.43
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 Small Large	 37 (19) 13 (7) 59 (30)	 21 (14) 7 (5) 44 (29)	 6 (30) 2 (10) 10 (50)	 10 (53) 4 (21) 5 (26)	 <0.01[2] 0.08 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 Chi-square.
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 4.2 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 4.3 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**	P value
Neurosensory impairment	10 (42) [24]	10 (36) [28] 0.78 (0.25-2.39), 0.66	10 (42) [24] 1 (0.31-3.15), 1	11 (44.0) [25] 1.1 (0.35-3.41), 0.89	0.94
Low IQ	3 (14) [22]	3 (11) [27] 0.79 (0.14-4.38), 0.79	3 (13) [23] 0.95 (0.17-5.30), 0.95	4 (18) [22] 1.41 (0.28-7.18), 0.68	0.92
Low Visual Motor Integration score	1 (5) [22]	2 (7) [27] 1.68 (0.14-19.85), 0.68	1 (4) [23] 0.95 (0.06-16.27), 0.97	0 (0) [21] Not calculable	0.50
Low Movement ABC score	5 (24) [21]	7 (28) [25] 1.24 (0.38-4.71), 0.74	6 (26) [23] 1.13 (0.29-4.44), 0.86	6 (30) [20] 1.37 (0.34-5.49), 0.66	0.97
Cerebral palsy	0 (0) [20]	0 (0) [27] Not calculable	0 (0) [19] Not calculable	0 (0) [21] Not calculable	
Executive function performance poor	1 (5) [20]	5 (20) [25] 2.38 (0.41-13.7), 0.33	2 (9) [23] 0.91 (0.12-7.07), 0.93	0 (0) [20] Not calculable	0.07
BRIEF P Executive function poor	3 (14) [21]	4 (15) [27] 0.79 (0.17-3.59), 0.76	2 (10) [21] 0.69 (0.13-3.43), 0.64	4 (19) [21] 1.85 (0.46-7.40), 0.39	0.85
Motion coherence threshold poor	0 [21]	2 (8) [25] Not calculable	2 (9) [22] Not calculable	1 (5) [22] Not calculable	0.37
Deaf	0 (0) [21]	1 (4) [27] Not calculable	0 (0) [23] Not calculable	0 (0) [22] Not calculable	0.48

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

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 4.4 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.

Table 4.5 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)

4.4 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 (Sells et al., 1994; Y. Yamashita et al., 1996), but are contrary to others, which found an association between HbA1c and offspring neurodevelopment between the ages of five and sixteen years (Knorr et al., 2015; Ratzon et al., 2000; Silverman et al., 1998). However, these studies included exclusively or a large proportion of mothers with pre-existing diabetes (Knorr et al., 2015; Ratzon et al., 2000; Silverman et al., 1998). Although pre-existing diabetes alters the intrauterine environment throughout pregnancy (Sturrock, Fay, Pound, Kirk, & Danks, 2001), whereas gestational diabetes, has its onset later pregnancy (Rizzo et al., 1990), 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 (A. Fraser et al., 2014).

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 (Clausen et al., 2013; Knorr et al., 2015; Nielsen et al., 2007; Ornoy et al., 1998; Ratzon et al., 2000; Sells et al., 1994; Silverman et al., 1998, 1991; Y. Yamashita et al., 1996). For example, there are new insulin formulations and metformin is now used in gestational diabetes (Landon et al., 1990; Singh et al., 2015; Wah Cheung, 2009). The definitions of abnormal glucose tolerance in pregnancy and recommended targets for glucose management (Coustan et al., 2010; World Health Organisation, 2013a) 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 (Derr, Garrett, Stacy, & Saudek, 2003; Kerssen, de Valk, & Visser, 2006). 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 (Clausen et al., 2013; Nielsen et al., 2010). Nevertheless, there is evidence from animal studies that intermittent maternal hyperglycemia results in a greater increase in fetal insulin secretion than constant stable hyperglycemia (Carver et al., 1996). 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 (National Institute for Health and Care Excellence, 2015). 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 (Flores-Le Roux et al., 2010), 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.

4.5 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.

5 Two-year outcomes after dextrose gel prophylaxis for neonatal hypoglycaemia.

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5.1 Abstract

Objective: To determine the effect of prophylactic dextrose gel for prevention of neonatal hypoglycaemia on neurodevelopment and executive function at two years' corrected age.

Design: Prospective follow-up of a randomised trial

Setting: New Zealand

Patients: Participants from the pre-hPOD trial randomised to one of four dose regimes of buccal 40% dextrose gel, or equivolume placebo.

Main outcome measures: Co-primary outcomes were neurosensory impairment and executive function. Secondary outcomes were components of the primary outcomes, neurology, anthropometry and health measures.

Results: We assessed 360 of 401 eligible children (90%) at two years' corrected age. There were no differences between dextrose gel dose groups, single or multiple dose groups, or any dextrose and any placebo groups in the risk of neurosensory impairment or low executive function (any dextrose vs any placebo neurosensory impairment relative risk [RR] 0.77, 95% confidence interval [CI] 0.50, 1.19 p=0.23; low executive function RR 0.50, 95% CI 0.24, 1.06, p=0.07). There were also no differences between groups in any secondary outcomes. There was no difference between children who did or did not develop neonatal hypoglycaemia in the risk of neurosensory impairment (RR 1.05, 95% CI 0.68, 1.64, p=0.81) or low executive function (RR 0.73, 95% CI 0.34, 1.59, p=0.43).

Conclusion: Prophylactic dextrose gel did not alter neurodevelopment or executive function and had no adverse effects to two years' corrected age, but this study was underpowered to detect potentially clinically important effects on neurosensory outcomes.

5.2 Introduction

Neonatal hypoglycaemia is common (Harris et al., 2012; Kaiser et al., 2015) and is associated with brain injury, seizures and poor neurodevelopmental outcomes (Burns et al., 2008; Lucas et al., 1988; McKinlay et al., 2017). Even transient and treated neonatal hypoglycaemia has been associated with adverse outcomes, particularly executive and visual-motor dysfunction (McKinlay et al., 2017) and poorer school performance (Kaiser et al., 2015).

Buccal 40% dextrose gel is an effective treatment for neonatal hypoglycaemia (Harris et al., 2013) with no adverse effects up to 2 years of age (Harris et al., 2016), and its potential use for hypoglycaemia prophylaxis is currently being trialled (Harding, Hegarty, et al., 2015). The pre-hPOD randomised trial, designed to determine the optimal dose of 40% dextrose to prevent neonatal hypoglycaemia in infants at risk (Hegarty et al., 2016), found that any of the trialled doses of dextrose gel reduced the incidence of hypoglycaemia (RR 0.79, 95% confidence interval [CI] 0.64, 0.98, p = 0.03, number needed to treat 10). 200 mg/kg at one hour after birth was most effective with fewest limitations (RR 0.68, 95% CI 0.47, 0.99, p=0.04, number needed to treat 7) (Hegarty et al., 2016). In order to assess longer term effects of this approach on neurodevelopment, growth and health we assessed outcomes at two years of participants in the pre-hPOD trial.

5.3 Methods

Study design

Details of the pre-hPOD trial have been published (Hegarty et al., 2016). In brief, 416 infants at risk of hypoglycaemia (infant of a diabetic mother, small [birthweight <2.5 kg or <10th centile], large [birthweight >4.5 kg or >90th centile] or late preterm [35 or 36 weeks]) were randomised to one of four dosage arms of 40% dextrose gel (0.5 ml/kg [200 mg/kg] once, 1 ml/kg [400 mg/kg] once, 0.5 ml/kg for four doses [total 800 mg/kg] or 1 ml/kg once then 0.5 ml/kg for a further three doses [total 1,000 mg/kg]) or equivolume placebo gel. The primary outcome was neonatal hypoglycaemia (blood glucose concentration < 2.6 mmol/l).

Two Year Follow-up

All families who participated in the pre-hPOD dosage trial and who had consented at initial recruitment to further contact were invited to participate. Ethics approval was obtained from the Health and Disability Ethics Committees of New Zealand (13/NTA/8) and caregivers gave written informed consent.

At 24 months' corrected age, children underwent a comprehensive assessment of neurodevelopment, growth and general health by trained research doctors who were unaware of the child's randomisation group. Assessment included Bayley Scales of Infant Development 3rd edition (Bayley, 2006b), neurological examination, executive function (clinical assessment of inhibitory control and attentional flexibility (Ansell et al., 2017)) and Behavior Rating Inventory of Executive Function—Preschool Version (BRIEF-P) (Gioia et al., 2002).

Height, weight, head and abdominal circumference were measured to the nearest 0.1 cm. Triceps and subscapular skin-fold thicknesses were measured using a Harpenden caliper to the nearest 0.2 cm. Total body fat mass and fat free mass were estimated using multifrequency bioimpedance analysis (ImpediMed Imp SFB7).

Home and health information were collected by questionnaire. Asthma was defined as any of: diagnosis by doctor, medicine or inhaler use for wheeze or asthma in the preceding 12 months, or hospitalisation for wheeze or asthma (Ellwood et al., 2000). Eczema was defined as itchy rash coming and going for ≥6 months (Ellwood et al., 2000) or diagnosis and treatment by doctor for eczema. Visits to a doctor for suspected infections were recorded.

The two pre-specified co-primary outcomes were neurosensory impairment (any of: legal blindness; sensorineural deafness requiring hearing aids; cerebral palsy; Bayley Scales of Infant Development 3rd edition [BSID-III] cognitive, language or motor score more than one standard deviation below the mean) and executive function composite z-score <-1.5, derived from standardisation within the whole pre-hPOD 2-year cohort. Children unable to complete any domain of the BSID-III because of severe delay were assigned scores of 49. Secondary outcomes were the components of the primary outcomes, neurology, anthropometry, and health measures. The WHO Child Growth Standards were used to calculate z-scores using corrected age (World Health Organisation, 2010). The sample size was limited by the number of participants in the original trial, but we estimated that this study would have 80% power to detect a reduction in neurosensory impairment from 39% (based on a similar cohort assessed at 2 years' corrected (McKinlay et al., 2015)) to 24% (two-tailed alpha 0.05).

5.3.1 Statistical analysis

All analyses were pre-specified and performed using SAS version 9.4 (SAS Institute Inc. Cary NC). Relative risks (RR) or mean difference (MD) with 95% CI were estimated using generalised linear models, adjusted for recruitment centre, socioeconomic status at birth (NZ Deprivation Index 2013 (Atkinson, Salmond, & Crampton, 2014)), gestational age and sex. We planned to combine placebo

groups if there were no differences between them in the primary outcomes. Primary outcomes were compared between different dextrose gel dosage groups, between single and multiple dose groups, and between any dextrose gel and any placebo groups. Secondary analyses included examining any interactions between the effect of any dextrose gel versus placebo on primary outcomes and their components and the risk factor for hypoglycaemia (diabetic mother versus other) and gestational age (preterm versus term), and also determining the effect of hypoglycaemia on the primary outcomes and their components, including in the subgroup of those who became hypoglycaemic (only adjusted for socioeconomic status, gestational age and sex because the fully adjusted model failed to converge).

We used two-sided statistical tests and the alpha error of 5% for the co-primary outcomes was divided evenly, giving a p value of 0.025 for each. All analyses were performed on an intention-to-treat basis. A significance level of 5% was used for each secondary outcome. Dunnett's test was used for multiple comparisons. Linear trends were tested using orthogonal contrasts.

5.4 Results

In the pre-hPOD trial, 416 infants were randomised. One was incorrectly randomised after the trial had closed, 13 withdrew and 1 died prior to 2 years, leaving 401 children eligible for follow-up, of whom 360 were assessed at two years (90% of those eligible, 87% of those randomised) (Figure 5.1). The mean age of mothers of children followed up was 3 years older than those not followed up, and the gestational age at birth of those followed up was 0.4 weeks less than of those not followed up (Table 5.1). Other maternal and infant characteristics were similar in those followed up and not followed up, and also amongst all randomisation groups. Mean corrected age at follow up was 25 months and similar in all groups.

There were no differences in outcomes between placebo groups so these were combined into one placebo group for further comparisons. The overall incidence of neurosensory impairment was 19% (69/360). There were no children with cerebral palsy or blindness. The overall incidence of executive function composite z-score <-1.5 was 7% (26/357).

Increasing cumulative dextrose dose did not alter the risk of neurosensory impairment or low executive function scores (Table 5.2). Although there was a trend towards an improvement in executive function with increasing cumulative dextrose dose (p=0.03), this did not reach statistical significance with the split p value of 0.025 for each co-primary outcome. There were no differences in secondary outcomes with increasing dose of dextrose gel (Table 5.2 and 5.5). However, there was a trend for increasing

cumulative dextrose dose to be associated with improved composite language scores (p=0.05) and fewer abnormalities of co-ordination or tone (p=0.05).

When combined single and combined multiple doses of dextrose gel were compared with the combined placebo group, the risk of neurosensory impairment was similar amongst groups (Table 5.3). The multiple dextrose doses group had fewer low executive function scores compared to single or placebo groups, but this was not statistically significant (p=0.04). There were no other differences in secondary outcomes between single, multiple and placebo groups (Table 5.3 and 5.6).

When children who had received any dextrose dose were compared with those who received any placebo, the risk of neurosensory impairment was similar (Table 5.4). Although low executive function scores were less likely in the dextrose group (RR 0.48, 95% CI 0.23, 0.99), after adjustment this difference was no longer significant (p=0.07). Similarly, motor scores were higher in the dextrose group (mean difference 2.70, 95% CI 0.04, 5.37), but this difference was no longer significant after adjustment (p=0.06). There were no differences in other secondary outcomes between any dextrose and any placebo groups (Table 5.4 and 5.7).

Secondary analyses revealed no difference in risk of neurosensory impairment between infants of diabetic mothers versus infants with other risk factors, (adjusted p value for interaction=0.47), nor between preterm and term infants, (adjusted p value for interaction=0.87). There was no difference between children who did or did not develop neonatal hypoglycaemia in the risk of neurosensory impairment (RR 1.05, 95% CI 0.68, 1.64, p=0.81) or its components: Bayley-III cognitive score <85 (RR 0.90, 95% CI 0.47, 1.70, p=0.74); language score <85 (RR 1.04, 95% CI 0.62, 1.75, p=0.89); motor score <85 (RR 0.18, 95% CI 0.02, 1.48, p=0.11); deafness (not calculable, 0/164 dextrose, 1/196 placebo); low executive function (RR=0.77, 95% CI 0.35, 1.68, p=0.51). In the subgroup of children who developed neonatal hypoglycaemia there was also no effect of dextrose versus placebo on neurosensory impairment (RR 0.77, 95% CI 0.50, 1.19, p=0.23) or its components: Bayley-III cognitive score <85 (RR 0.73, 95% CI 0.39, 1.35, p=0.31); language score <85 (RR 0.71, 95% CI 0.42, 1.18), p=0.19); motor score <85 (RR=0.21 (0.04, 1.04), p=0.06); low executive function (RR 0.49, 95% CI 0.24, 1.02, p=0.06).

5.5 Discussion

In children born at risk of neonatal hypoglycaemia, prophylactic dextrose gel did not alter the risk of neurosensory impairment or low executive function scores at 2 years' corrected age, regardless of the dose used. The secondary outcomes were also similar in dextrose and placebo groups, with no adverse effects, providing reassurance about use of oral dextrose gel prophylaxis in neonates at risk of

hypoglycaemia. Our results are in keeping with a previous study demonstrating similar rates of neurosensory impairment between dextrose and placebo gel groups and no adverse effects when used for treatment of neonatal hypoglycaemia (Harris, Ansell, et al., 2015).

The primary aim of this follow-up study was to assess neurodevelopment, health and growth in children treated with prophylactic dextrose gel. As the pre hPOD trial was powered to detect differences in the rates of hypoglycaemia rather than later neurodevelopment, the study was underpowered to detect small but clinically important differences in the primary and secondary outcomes. However, since this was the first follow-up study of prophylactic oral dextrose gel, it was important to assess a wide range of outcomes, including growth and health, to detect possible adverse effects. Further studies are needed with sufficient power to detect small but potentially clinically important long term effects of prophylactic oral dextrose gel on neurodevelopmental outcomes.

Executive function is the ability to learn using working memory, problem solving, reasoning and cognitive flexibility. Thus, subtle detrimental effects on executive function seen at two years of age may later translate into poorer academic performance. Adverse effects on later executive function have been reported in infants born moderate to late preterm (Brumbaugh et al., 2013; Hodel et al., 2017), those born to diabetic mothers (DeBoer et al., 2005), and those who experienced neonatal hypoglycaemia (McKinlay et al., 2017). We found no statistically significant relationship between prophylactic dextrose gel and performance either on assessed executive function tasks specifically developed for this age group (Ansell et al., 2017), or on the parent-reported BRIEF-P. However, there was a trend towards a decreased risk of low executive function with increasing cumulative doses of prophylactic oral dextrose gel, with multiple doses, or with any dextrose dose compared to placebo, and in the subgroup of infants who became hypoglycaemic. At 2 years of age, executive function is still developing and it is possible that further testing once the children are older may clarify the clinical significance of these observations.

There were no relationships between any outcomes and the presence or absence of recorded hypoglycaemia. It is possible that prophylactic dextrose gel prevented periods of hypoglycaemia not detected on intermittent blood glucose monitoring. Continuous glucose monitoring has shown that up to 80% of episodes of neonatal hypoglycaemia may be unrecognised using intermittent blood glucose monitoring (Harris, Battin, Weston, & Harding, 2010). Further, in a prospective cohort study, exposure to neonatal hypoglycaemia was not associated with neurosensory impairment at 2 years (McKinlay et al., 2015), but at 4.5 years of age was associated with impaired executive and visual motor development in a dose dependent manner (McKinlay et al., 2017), suggesting that the effects of hypoglycaemia may not be evident at 2 years of age. It is also possible that the threshold we used to define hypoglycaemia is

not optimal for prediction of later outcomes. The threshold for defining hypoglycaemia remains a topic of debate (Thornton et al., 2015), but we used the widely used cut-off based on studies showing an association between glucose concentrations below 2.6 mmol/L and altered brain function (Burns et al., 2008; Lucas et al., 1988) and have not found a more discriminatory threshold to date (McKinlay et al., 2015, 2017).

A strength of this study is the high follow-up rate, as participants not followed up in studies are more likely to have worse outcomes than those followed up (Callanan et al., 2001). In addition, this was a prospective follow-up study of participants in a blinded randomised controlled trial with similar sociodemographic characteristics across randomisation groups, minimising the possible effect of unrecognised confounders on the outcomes. Our assessment was comprehensive, including a standard and widely accepted assessment of early development (BSID-III), in which low scores in cognitive and language domains are predictive of later intellectual function at age 4 years (Bode et al., 2014; Spencer-Smith et al., 2015), and also tests of more subtle neurodevelopment, and executive function; skills known to be affected by neonatal hypoglycaemia (DeBoer et al., 2005).

An important limitation of this study was that the original trial was designed to have sufficient power to compare the incidence of hypoglycaemia between groups, but not small differences in later developmental outcomes. Future follow-up of the 2,149 children recruited to the hPOD study (Harding, Hegarty, et al., 2015) of dextrose gel prophylaxis should help clarify if this intervention affects neurodevelopment or executive function. We performed multiple comparisons since we wished to maximise the chance of detecting any possible adverse effects, but this leads to increased risk of a type 1 error. Thus, these findings should be interpreted with caution. In addition, the majority of participants in the pre-hPOD trial were infants of diabetic mothers, so our results primarily reflect the outcomes of this risk group.

The use of dextrose gel for treatment of neonatal hypoglycaemia is expanding (Alsweiler, Woodall, Crowther, & Harding, 2019; Gregory et al., 2019; Wackernagel et al., 2020). Although it had no adverse effects on neurodevelopment, growth or health at 2 years of age, as yet there is insufficient evidence about long term effects of prophylactic dextrose gel, especially as large numbers of infants would be potentially eligible for such treatment. The follow-up of the larger hPOD trial with will have greater power to detect any effect of prophylactic dextrose gel both on short term efficacy and on later outcomes.

5.6 Conclusions

Prophylactic oral dextrose gel given to infants at risk of neonatal hypoglycaemia did not alter the risk of neurosensory impairment or low executive function scores and had no adverse effects to 2 years of age.

Figure 5.1 pre-hPOD profile of participants: recruitment to two years

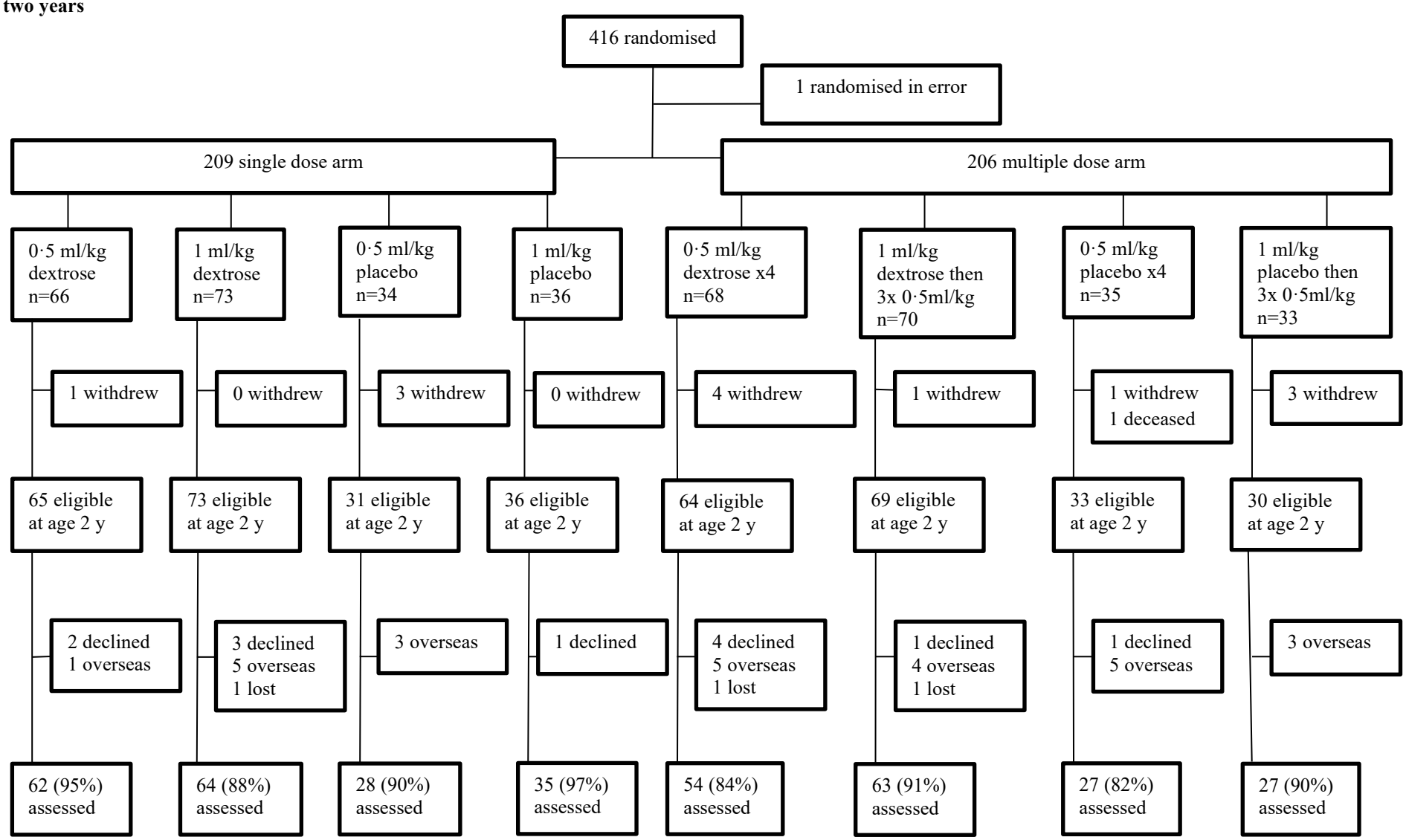


Table 5.1 Characteristics of mothers and infants who were and were not followed up at 2 years

	Not followed up	Followed up						
			Single dose			Multiple dose		
	Total	Total	Single placebo	Dextrose 0.5 ml/kg	Dextrose 1 ml/kg	Multiple placebo	Dextrose 0.5 ml/kg x 4	Dextrose 1 ml/kg x 1, 0.5 ml/kg x 3
Mothers (n=403)*	**55**	**358**	**63**	**62**	**62**	**54**	**54**	**63**
Age, years	30 (5)	33 (5)[a]	33 (6)	33 (5)	34 (5)	32 (6)	32 (5)	32 (5)
Booking BMI kg/m^2 [b]	29 (9)	29 (8)	29 (8)	29 (7)	29 (8)	29 (7)	29 (7)	28 (9)
Caesarean section	23 (42)	176 (49)	34 (54)	33 (53)	30 (47)	31 (57)	21 (39)	27 (43)
Parity[c]	1 (0-5)	1 (0-8)	1 (0-8)	1 (0-6)	0 (0-4)	1 (0-4)	1 (0-7)	1 (0-7)
Diabetic[d]	41 (75)	260 (73)	45 (71)	47 (76)	44 (72)	38 (70)	42 (78)	44 (70)
Highest level of education[e]								
High School	NA	65 (20)	13 (24)	11 (19)	11 (20)	13 (28)	9 (18)	8 (14)
Tertiary	NA	253 (80)	42 (76)	47 (81)	43 (79)	33 (72)	40 (82)	48 (86)
Infants (n=415)	**55**	**360**	**63**	**62**	**64**	**54**	**54**	**63**
Female	28 (51)	174 (48)	27 (43)	33 (53)	35 (55)	26 (48)	28 (52)	25 (40)
Gestation, weeks	38.7 (1.1)	38.3 (1.1)[a]	38.2 (0.9)	38.3 (1.2)	38.2 (1.2)	38.4 (1.2)	38.4 (1.2)	38.4 (1.2)
Birthweight, grams	3220 (620)	3250 (620)	3190 (650)	3280 (620)	3260 (650)	3330 (650)	3270 (550)	3190 (580)
Birthweight z-score	-0.07 (1.30)	0.17 (1.29)	0.05 (1.34)	0.29 (1.30)	0.24 (1.38)	0.32 (1.34)	0.17 (1.25)	-0.04 (1.12)
Twins	1 (2)	30 (8)	6 (10)	4 (6)	8 (13)	5 (9)	2 (4)	5 (8)
NZDPI	6 (1-10)	6 (1-10)	6 (1-10)	7 (1-10)	5 (1-10)	7 (1-10)	6.5 (1-10)	7 (1-10)
Prioritised ethnicity								
Māori	7 (12.7)	35 (9.7)	9 (14.3)	5 (8.1)	3 (4.7)	9 (16.7)	5 (9.3)	4 (6.4)
Pacific	11 (20.0)	57 (15.8)	9 (14.3)	12 (19.4)	11 (17.2)	9 (16.7)	7 (13.0)	9 (14.3)
Asian	15 (27.3)	91 (25.3)	15 (23.8)	13 (21.0)	16 (25.0)	18 (33.3)	17 (31.5)	12 (19.1)
NZ European	14 (25.5)	100 (27.8)	16 (25.4)	14 (22.6)	23 (35.9)	7 (13.0)	15 (27.8)	25 (39.7)
Other	8 (14.6)	77 (21.4)	14 (22.2)	18 (29.0)	11 (17.2)	11 (20.4)	10 (18.5)	13 (20.6)
Primary risk factor[f]								
Infant of diabetic	41 (75)	260 (72)	45 (71)	47 (76)	44 (69)	38 (70)	42 (78)	44 (70)
Preterm	3 (5)	24 (7)	3 (5)	4 (6)	6 (9)	3 (6)	2 (4)	6 (10)
Small	6 (11)	43 (12)	10 (16)	6 (10)	7 (11)	6 (11)	5 (9)	9 (14)
Large	5 (9)	33 (9)	5 (8)	5 (8)	7 (11)	7 (13)	5 (9)	4 (6)
Hypoglycaemia	22 (40)	164 (46)	35 (56)	23 (37)	31 (48)	28 (52)	23 (43)	24 (38)

Data are n (%), mean (SD), or median (range)
* There are 12 mothers of twins, of whom 10 appear in more than one column because each twin was assigned to a different treatment group
a $p<0.05$ for comparison between those who were and were not followed up
b Data missing for 12 not followed up, 10 single placebo, 7 dextrose 0.5ml/kg, 7 dextrose 1ml/kg, 6 multiple placebo, 6 dextrose 0.5ml/kg multiple, 9 dextrose 1ml/kg multiple
c Data missing for 12 not followed up, 10 single placebo, 7 dextrose 0.5ml/kg, 7 dextrose 1ml/kg, 6 multiple placebo, 6 dextrose 0.5ml/kg multiple, 9 dextrose 1ml/kg multiple
d Data missing for 1 dextrose 1ml/kg
e Data missing for 8 single placebo, 4 dextrose 0.5ml/kg, 10 dextrose 1ml/kg, 8 multiple placebo, 5 dextrose 0.5ml/kg multiple, 7 dextrose 1ml/kg multiple
f Risk factors prioritised in order: infant of diabetic mother, preterm, small, large
NA not available
NZDPI: New Zealand Deprivation Index: a measure of socioeconomic status (1 is least deprived)

Table 5.2 Primary and secondary neurodevelopmental outcomes at 2 years in children exposed to placebo or increasing cumulative doses of prophylactic dextrose gel after birth

Outcome	Placebo		Dextrose 200 mg				Dextrose 400 mg				Dextrose 800 mg				Dextrose 1 g				p linear trend+
	n	n (%) or mean (SD)	n	n (%) or mean (SD)	RR or MD (95%CI)	Adjusted RR or MD (95%CI), p	n	n (%) or mean (SD)	RR or MD (95%CI)	Adjusted RR or MD (95%CI), p	n	n (%) or mean (SD)	RR or MD (95%CI)	Adjusted RR or MD (95%CI), p	n	n (%) or mean (SD)	RR or MD (95%CI)	Adjusted RR or MD (95%CI), p	
Neurosensory impairment	116	26 (22)	62	10 (16)	0.72 (0.37-1.39)	0.74 (0.32-1.68), 0.81	64	14 (22)	0.98 (0.55-1.73)	1.04 (0.51-2.13), 1.00	54	6 (11)	0.50 (0.22-1.13)	0.51 (0.18-1.43), 0.33	63	11 (17)	0.78 (0.41-1.47)	0.76 (0.35-1.69), 0.85	0.25
Bayley-III cognitive score <85	116	15 (13)	62	3 (5)	0.37 (0.11-1.24)	0.39 (0.08-1.78), 0.39	64	9 (14)	1.09 (0.50-2.34)	1.17 (0.44-3.11), 0.99	54	4 (7)	0.57 (0.20-1.64)	0.60 (0.16-2.28), 0.80	63	6 (10)	0.74 (0.30-1.80)	0.73 (0.24-2.25), 0.92	0.86
Bayley-III language score <85	116	20 (17)	62	9 (15)	0.84 (0.41-1.74)	0.87 (0.36-2.13), 0.99	64	10 (16)	0.91 (0.45-1.82)	0.96 (0.41-2.25), 1.00	54	3 (6)	0.32 (0.10-1.04)	0.34 (0.08-1.46), 0.22	63	7 (11)	0.64 (0.29-1.44)	0.62 (0.23-1.68), 0.63	0.06
Bayley-III motor score <85	116	5 (4)	62	1 (2)	0.37 (0.04-3.13)	0.48 (0.04-5.21), 0.74	64	1 (2)	0.36 (0.04-3.04)	0.49 (0.04-5.46), 0.75	54	0			63	0			
Deaf	116	1 (1)	62	0			64	0			54	0			63	0			
Executive function score < -1.5 SD	115	13 (11)	61	5 (8)	0.73 (0.27-1.94)	0.77 (0.22-2.65), 0.97*	64	5 (8)	0.69 (0.26-1.85)	0.82 (0.24-2.85), 0.99*	54	2 (4)	0.33 (0.08-1.40)	0.37 (0.06-2.30), 0.52*	63	1 (2)	0.14 (0.02-1.05)	0.13 (0.01-1.75), 0.19*	0.03
Bayley-III cognitive score	116	99.6 (14.9)	62	100.1 (14.8)	0.47 (-3.96-4.90)	0.82 (-4.62-6.26), 0.99	64	100.1 (15.8)	0.47 (-3.92-4.85)	-0.20 (-5.59-5.18), 1.00	54	99.4 (11.7)	-0.26 (-4.90-4.38)	-0.63 (-6.32-5.06), 1.00	63	101.5 (14.1)	1.90 (-2.51-6.30)	2.23 (-3.17-7.62), 0.74	0.55
Bayley-III language score	116	99.7 (18.1)	62	100.8 (14.6)	1.10 (-3.99-6.20)	1.28 (-4.85-7.42), 0.97	64	104.7 (17.8)	5.00 (-0.04-10.04)	3.85 (-2.23-9.92), 0.36	54	103.8 (14.4)	4.12 (-1.21-9.46)	3.60 (-2.81-10.01), 0.48	63	103.6 (16.2)	3.90 (-1.17-8.97)	4.51 (-1.58-10.59), 0.22	0.05

Bayley-III motor score	116	102.7 (13.4)	62	104.2 (10.7)	1.55 (-2.15-5.26)	1.42 (-3.21-6.04), 0.89	64	105.6 (12.8)	2.89 (-0.78-6.56)	2.36 (-2.22-6.93), 0.56	54	106.6 (11.8)	3.94 (0.06-7.82)	3.60 (-1.24-8.43), 0.22	63	105.3 (10.2)	2.58 (-1.11-6.27)	2.81 (-1.77-7.40), 0.39	0.07
Bayley-III social emotional score	75	103.4 (13.4)	42	106.8 (16.1)	3.28 (-4.73-11.5)	3.30 (-3.87-12.42), 0.54	35	111.3 (18.5)	3.49 (-0.73-16.5)	7.74 (-0.81-16.30),0.09	32	103.6 (18.9)	0.19 (-8.70-9.08)	0.32 (-8.48-9.13), 0.99	43	106.3 (15.1)	3.23 (-4.83-11.28)	3.51 (-4.46-11.48),0.28	0.69
Bayley-III adaptive score	75	100.7 (16.2)	42	(98.3 (12.6)	-2.34 (-9.13-4.44)	-2.16 (-8.87-4.55), 0.88	35	105.3 (15.1)	4.69 (-2.51-11.89)	3.99 (-3.06-11.04), 0.47	32	101.4 (12.9)	0.72 (-6.71-8.15)	0.45 (-6.80-7.70), 0.88	43	102.0 (13.1)	1.39 (-5.34-8.13)	1.41 (-5.15-7.80), 0.97	0.38
Executive function score	115	9.9 (4.5)	61	10.4 (4.1)	0.56 (-0.71-1.82)	0.66 (-0.89-2.22), 0.71	64	10.5 (4.1)	0.66 (-0.58-1.91)	0.47 (-1.06-2.00), 0.89	54	11.1 (4.1)	1.30 (-0.02-2.62)	1.19 (-0.43-2.81), 0.23	63	10.5 (3.4)	0.67 (-0.58-1.93)	0.77 (-0.77-2.30), 0.58	0.15
BRIEF P GEC T-score >65	94	15 (16)	51	5 (10)	0.61 (0.24-1.59)	0.51 (0.16-1.65), 0.46	50	7 (14)	0.88 (0.38-2.01)	0.81 (0.30-2.24), 0.97	46	10 (22)	1.36 (0.66-2.79)	1.24 (0.52-2.98), 0.95	53	8 (15)	0.95 (0.43-2.08)	0.82 (0.31-2.17), 0.97	0.59
BRIEF P GEC T-score	94	51.5 (11.1)	51	51.3 (10.5)	-0.25 (-4.37-3.88)	-1.63 (-6.60-3.35), 0.86	50	50.7 (13.5)	-0.86 (-5.02-3.29)	-1.48 (-6.47-3.51), 0.90	46	52.8 (13.1)	1.22 (-3.05-5.49)	0.51 (-4.62-5.63), 1.00	53	52.7 (13.4)	0.14 (-2.94-5.21)	0.69 (-4.18-5.56), 0.99	0.44
Abnormal tone or coordination	115	9 (8)	62	7 (11)	1.44 (0.56-3.69)	1.61 (0.53-4.91), 0.72*	64	4 (6)	0.80 (0.26-2.49)	0.76 (0.18-3.17), 0.98*	54	2 (4)	0.47 (0.11-2.12)	0.48 (0.07-3.21), 0.79*	63	1 (2)	0.20 (0.03-1.56)	0.20 (0.01-2.65), 0.39*	0.05

No children had cerebral palsy or were blind.
Data are n (%); RR (95% CI), p or MD (95% CI), p
Adjusted values were adjusted for recruitment centre, socioeconomic status, gestation, sex and for multiple comparisons using Dunnett test.
*Log binomial model did not converge, modified Poisson used
NC = Not calculable, model did not converge

Table 5.3 Primary and secondary neurodevelopmental outcomes at 2 years in children exposed to placebo, a single dose of dextrose, or multiple doses of dextrose

Outcome	Placebo		Any single dose dextrose				Any multiple dose dextrose			
	n	n (%) or mean (SD)	n	n (%) or mean (SD)	RR or MD (95%CI)	Adjusted RR or MD (95%CI), p	n	n (%) or mean (SD)	RR or MD (95%CI)	Adjusted RR or MD (95%CI), p
Neurosensory impairment	116	26 (22.4)	126	24 (19.1)	0.85 (0.52-1.39)	0.89 (0.51-1.55), 0.86	117	17 (14.5)	0.65 (0.37-1.13)	0.65 (0.35-1.21), 0.21
Bayley-III cognitive score <85	116	15 (12.9)	126	12 (9.5)	0.74 (0.36-1.51)	0.78 (0.35-1.76), 0.73	117	10 (8.6)	0.66 (0.31-1.41)	0.67 (0.29-1.58), 0.49
Bayley-III language score <85	116	20 (17.2)	126	19 (15.1)	0.87 (0.49-1.55)	0.92 (0.49-1.73), 0.94	117	10 (8.6)	0.50 (0.24-1.01)	0.49 (0.22-1.10), 0.09
Bayley-III motor score <85	116	5 (4.3)	126	2 (1.6)	0.38 (0.07-1.86)	0.49 (0.10-2.42), 0.38	117	0	NC	NC
Deaf	116	1 (0.9)	126	0	NC	NC	117	0	NC	NC
Executive function score <-1.5 SD	115	13 (11.3)	125	10 (8.0)	0.71 (0.32-1.55)	0.79 (0.32-1.93), 0.80*	117	3 (2.6)	0.23 (0.07-0.78)	0.23 (0.06-0.94), 0.04*
Bayley-III cognitive score	116	99.6 (14.9)	126	100.1 (15.2)	0.47 (-3.16-4.09)	0.31 (-3.68-4.30), 0.98	117	100.5 (13.0)	0.90 (-2.79-4.59)	0.91 (-3.14-4.96), 0.84
Bayley-III language score	116	99.7 (18.1)	126	102.8 (16.4)	3.08 (-1.10-7.26)	2.59 (-1.91-7.08), 0.34	117	103.7 (15.4)	4.00 (-0.25-8.26)	4.09 (-0.47-8.66), 0.09
Bayley-III motor score	116	102.7 (13.4)	126	104.9 (11.8)	2.23 (-0.80-5.27)	1.89 (-1.50-5.28), 0.36	117	105.9 (10.9)	3.21 (0.12-6.30)	3.18 (-0.26-6.62), 0.08
Bayley-III social emotional score	75	103.4 (17.7)	77	108.8 (17.2)	5.43 (-0.01-10.9)	5.89 (-0.24-12.02), 0.06	75	105.3 (16.8)	1.93 (-3.54-7.41)	2.16 (-3.96-8.27), 0.65
Bayley-III adaptive score	75	100.7 (16.2)	77	101.5 (14.2)	0.85 (-3.72-5.43)	0.69 (-4.39-5.76), 0.94	75	101.8 (13.0)	1.11 (-3.50-5.72)	1.01 (-4.05-6.07), 0.87
Executive function score	115	9.9 (4.5)	125	10.5 (4.1)	0.61 (-0.42-1.65)	0.56 (-0.57-1.70), 0.44	117	10.8 (3.7)	0.96 (-0.09-2.01)	0.96 (-0.19-2.11), 0.12

BRIEF P GEC T-score >65	94	15 (16.0)	101	12 (11.9)	0.74 (0.37-1.51)	0.65 (0.30-1.41), 0.36	99	18 (18.2)	1.14 (0.61-2.13)	1.01 (0.51-2.00), 1.00
BRIEF P GEC T-score	94	51.5 (11.1)	101	51.0 (12.0)	-0.55 (-3.95-2.85)	-1.55 (-5.23-2.12), 0.54	99	52.7 (13.2)	1.17 (-2.24-4.59)	0.60 (-3.06-4.27), 0.91
Abnormal tone or coordination	115	9 (7.8)	126	11 (8.7)	1.12 (0.48-2.59)	1.14 (0.45-2.93), 0.93*	117	3 (2.6)	0.33 (0.09-1.18)	0.33 (0.08-1.39), 0.16*

No children had cerebral palsy or were blind.
Data are n (%); RR (95% CI), p or mean difference (95% CI), p
Adjusted values were adjusted for recruitment centre, socioeconomic status, gestation, sex and for multiple comparisons using Dunnett test.
*Log binomial model did not converge, modified Poisson used
NC= Not calculable, model did not converge

Table 5.4 Primary and secondary neurodevelopmental outcomes at 2 years in children exposed to placebo or any dextrose dose

Outcome	Placebo		Any dextrose dose		RR or MD (95%CI)	Adjusted RR or MD (95%CI), p
	n	n (%) or mean (SD)	n	n (%) or mean (SD)		
Neurosensory impairment	116	26 (22.4)	243	41 (16.9)	0.75 (0.49-1.17)	0.77 (0.50-1.19), 0.23
Bayley-III cognitive score <85	116	15 (12.9)	243	22 (9.1)	0.70 (0.38-1.30)	0.73 (0.39-1.35), 0.31
Bayley-III language score <85	116	20 (17.2)	243	29 (11.9)	0.69 (0.41-1.17)	0.71 (0.42-1.18), 0.19
Bayley-III motor score <85	116	5 (4.3)	243	2 (0.8)	0.19 (0.04-0.97)	0.22 (0.04-1.12), 0.07
Deaf	116	1 (0.9)	243	0	NC	NC
Executive function score <-1.5 SD	115	13 (11.3)	242	13 (5.4)	0.48 (0.23-0.99)	0.50 (0.24-1.06), 0.07*
Bayley-III cognitive score	116	99.6 (14.9)	243	100.3 (14.2)	0.68 (-2.50-3.86)	0.60 (-2.49-3.70), 0.70
Bayley-III language score	116	99.7 (18.1)	243	103.2 (15.9)	3.53 (-0.14-7.19)	3.32 (-0.17-6.81), 0.06
Bayley-III motor score	116	102.7 (13.4)	243	105.4 (11.4)	2.70 (0.04-5.37)	2.51 (-0.12-5.14), 0.06
Bayley-III social emotional score	75	103.4 (17.7)	152	107.1 (17.0)	3.71 (-1.04-8.45)	4.02 (-0.70-8.73), 0.10
Bayley-III adaptive score	75	100.7 (16.2)	152	101.6 (3.5)	0.98 (-3.00-4.96)	0.85 (-3.04-4.74), 0.67
Executive function score	115	9.9 (4.5)	242	10.6 (3.9)	0.78 (-0.13-1.69)	0.76 (-0.12-1.64), 0.09
BRIEF P GEC T-score >65	94	15 (16.0)	200	30 (15.0)	0.94 (0.53-1.66)	0.84 (0.48-1.44), 0.52
BRIEF P GEC T-score	94	51.5 (11.1)	200	51.8 (12.6)	0.30 (-2.67-3.27)	-0.47 (-3.31-2.37), 0.75
Abnormal tone or coordination	115	9 (7.8)	243	14 (5.8)	0.74 (0.33-1.65)	0.74 (0.33-1.65), 0.46*

No children had cerebral palsy or were blind.
Data are n (%); RR (95% CI), p or mean difference (95% CI), p
Adjusted values were adjusted for recruitment centre, socioeconomic status, gestation, sex.
*Log binomial model did not converge, modified Poisson used
NC= Not calculable, model did not converge

Table 5.5 Secondary health and growth outcomes at 2 years in children exposed to placebo or increasing cumulative doses of prophylactic dextrose gel after birth

Outcome	Placebo		Dextrose 200 mg				Dextrose 400 mg				Dextrose 800 mg				Dextrose 1 g				p linear trend[+]
	n	n (%) or mean (SD)	n	n (%) or mean (SD)	RR or MD (95%CI)	Adjusted RR or MD (95%CI), p	n	n (%) or mean (SD)	RR or MD (95%CI)	Adjusted RR or MD (95%CI), p	n	n (%) or mean (SD)	RR or MD (95%CI)	Adjusted RR or MD (95%CI), p	n	n (%) or mean (SD)	RR or MD (95%CI)	Adjusted RR or MD (95%CI), p	
Seizures	116	2 (2)	62	1 (2)	0.94 (0.09-10.11)	NC	64	1 (2)	0.91 (0.08-9.80)	NC	54	0			63	1 (2)	0.92 (0.09-9.96)	NC	
Asthma	116	24 (21)	62	12 (19)	0.94 (0.50-1.74)	0.96 (0.44-2.10), 1.00	64	12 (19)	0.91 (0.49-1.69)	0.96 (0.44-2.09), 1.00	54	9 (17)	0.81 (0.40-1.61)	0.83 (0.35-1.97), 0.96	63	15 (24)	1.15 (0.65-2.03)	1.13 (0.56-2.30), 0.98	0.89
Eczema	116	42 (36)	62	28 (45)	1.25 (0.87-1.80)	1.20 (0.76-1.90), 0.74	64	27 (42)	1.17 (0.80-1.70)	1.15 (0.72-1.84), 0.90	54	24 (44)	1.23 (0.84-1.80)	1.24 (0.77-2.00), 0.67	63	27 (43)	1.18 (0.81-1.72)	1.18 (0.74-1.89), 0.81	0.40
Allergy	116	46 (40)	62	27 (44)	0.10 (0.77-1.58)	1.08 (0.69-1.71), 0.98	64	30 (47)	1.18 (0.84-1.67)	1.20 (0.78-1.85), 0.72	54	25 (46)	1.17 (0.81-1.68)	1.19 (0.75-1.87), 0.78	63	33 (52)	1.32 (0.95-1.83)	1.32 (0.88-1.99), 0.29	0.10
Medical attention for suspected infections	116	19 (16)	62	11 (18)	1.08 (0.55-2.13)	1.12 (0.48-2.62), 0.99	64	9 (14)	0.86 (0.41-1.79)	0.87 (0.34-2.20), 0.99	54	12 (22)	1.36 (0.71-2.59)	1.38 (0.61-3.13), 0.75	63	13 (21)	1.26 (0.67-2.38)	1.26 (0.57-2.80), 0.90	0.37
Weight z-score	116	0.9 (1.3)	62	0.8 (1.2)	-0.08 (-0.45-0.29)	-0.10 (-0.56-0.37), 0.97	64	0.9 (1.1)	-0.03 (-0.40-0.34)	-0.02 (-0.48-0.44), 1.00	54	0.7 (1.3)	-0.18 (-0.57-0.21)	-0.19 (-0.68-0.30), 0.79	63	0.7 (1.1)	-0.17 (-0.54-0.20)	-0.18 (-0.65-0.28), 0.77	0.30

Height z-score	115	0.3 (1.1)	62	0.2 (1.2)	-0.03 (-0.37-0.32)	-0.05 (-0.48-0.38), 1.00	64	0.3 (1.2)	0.00 (-0.34-0.34)	-0.01 (-0.44-0.42), 1.00	53	0.0 (1.0)	-0.24 (-0.60-0.13)	-0.26 (-0.71-0.20), 0. 47	63	0.0 (1.0)	-0.25 (-0.59-0.09)	-0.26 (-0.68-0.17), 0.42	0.09
Weight for height z-score	115	1.0 (1.3)	62	0.9 (1.2)	-0.08 (-0.45-0.29)	-0.08 (-0.55-0.39), 0.98	64	0.9 (1.0)	-0.04 (-0.40-0.33)	-0.01 (-0.47-0.45), 1.00	53	0.9 (1.4)	-0.08 (-0.47-0.31)	-0.07 (-0.56-0.42), 0.99	63	0.9 (1.1)	-0.05 (-0.42-0.32)	-0.06 (-0.53- 0.40), 0.99	0.79
Head circumference z-score	115	0.8 (1.2)	61	0.8 (1.2)	-0.07 (-0.43-0.28)	-0.06 (-0.50-0.39), 1.00	63	0.8 (0.9)	-0.03 (-0.39-0.32)	0.01 (-0.43-0.45), 1.00	53	0.7 (1.2)	-0.16 (-0.54-0.21)	-0.15 (-0.61-0.32), 0.88	61	0.9 (1.2)	0.04 (-0.31-0.40)	0.02 (-0.43-0.46), 1.00	0.91
Triceps skinfold z-score	84	0.4 (1.2)	39	0.4 (1.3)	0.09 (-0.38-0.55), 0.71	0.05 (-0.53-0.62), 1.00	45	0.4 (1.3)	0.08 (-0.36-0.52), 0.72	0.06 (-0.49-0.61), 1.00	38	0.4 (1.3)	0.00 (-0.47-0.46), 0.99	-0.03 (-0.62-0.55), 1.00	41	0.2 (1.1)	-0.13 (-0.59-0.33), 0.58	-0.16 (-0.72-0.41), 0.92	0.46
Subscapular skinfold z-score	84	0.1 (1.3)	39	0.2 (1.3)	0.16 (-0.30-0.63)	0.14 (-0.45-0.72), 0.95	46	-0.1 (1.2)	-0.19 (-0.62-0.25)	-0.20 (-0.75-0.35), 0.82	37	-0.1 (1.2)	-0.13 (-0.60-0.34)	-0.15 (-0.75-0.44), 0.94	40	-0.2 (1.1)	-0.28 (-0.74-0.18)	-0.28 (-0.86 to 0.30), 0.61	0.12
Fat mass (kg)	88	2.8 (1.0)	44	2.7 (1.0)	-0.06 (-0.42-0.30)	-0.07 (-0.50-0.37), 0.99	55	2.6 (1.1)	-0.20 (-0.53-0.13)	-0.17 (-0.57-0.24), 0.74	42	2.7 (1.0)	-0.08 (-0.44-0.28)	-0.00 (-0.44-0.45), 1.00*	45	2.5 (0.9)	-0.24 (-0.59-0.12)	-0.16 (-0.59-0.27), 0.81*	0.55
Fat free mass (kg)	88	10.8 (1.8)	44	10.8 (1.9)	-0.01 (-0.65-0.63)	-0.03 (-0.59-0.53), 1.00	55	10.8 (1.9)	0.06 (-0.54-0.6)	0.14 (-0.38-0.66), 0.92	42	10.6 (2.0)	-0.18 (-0.83-0.47)	0.11 (-0.45-0.69), 0.97*	45	10.4 (1.4)	-0.34 (-0.98-0.30)	-0.03 (-0.59-0.53), 1.00*	0.87
Abdominal circumference (cm)	107	49.6 (3.9)	53	49.5 (4.1)	-0.15 (-1.40-1.10)	-0.23 (-1.81-1.35), 0.99	58	49.4 (3.5)	-0.17 (-1.39-1.04)	-0.14 (-1.68-1.39), 1.00	46	48.5 (4.1)	-1.07 (-2.39-0.24)	-1.09 (-2.74-0.56), 0.32	58	49.3 (3.5)	-0.37 (-1.58-0.85)	-0.43 (-1.95-1.10), 0.92	0.24

Data are n (%); RR (95% CI), p or MD (95% CI), p

Adjusted values were adjusted for recruitment centre, socioeconomic status, gestation, sex and for multiple comparisons using Dunnett test.

Fat mass and fat free mass were additionally adjusted for height

*Log binomial model did not converge, modified Poisson used

NC = Not calculable, model did not converge

Table 5.6 Secondary health and growth outcomes at 2 years in children exposed to placebo, a single dose of dextrose, or multiple doses of dextrose

Outcome	Placebo		Any single dose dextrose				Any multiple dose dextrose			
	n	n (%) or mean (SD)	n	n (%) or mean (SD)	RR or mean difference (95%CI)	Adjusted RR or mean difference (95%CI), p	n	n (%) or mean (SD)	RR or mean difference (95%CI)	Adjusted RR or mean difference (95%CI), p
Seizures	116	2 (1.7)	126	2 (1.6)	0.92 (0.13-6.43)	NC	117	1 (0.9)	0.50 (0.05-5.39)	NC
Asthma	116	24 (20.7)	126	24 (19.1)	0.92 (0.55-1.53)	0.96 (0.54-1.70), 0.98	117	24 (20.5)	0.99 (0.60-1.64)	1.00 (0.57-1.75), 1.00
Eczema	116	42 (36.2)	126	55 (43.7)	1.21 (0.88-1.65)	1.18 (0.83-1.67), 0.48	117	51 (43.6)	1.20 (0.88-1.65)	1.21 (0.85-1.72), 0.39
Allergy	116	46 (39.7)	126	57 (45.2)	1.14 (0.85-1.53)	1.14 (0.82-1.59), 0.57	117	58 (50.0)	1.25 (0.94-1.67)	1.26 (0.91-1.74), 0.20
Medical attention for suspected infections	116	19 (16.4)	126	20 (15.9)	0.97 (0.55-1.72)	0.99 (0.52-1.90), 1.00	117	25 (21.4)	1.30 (0.76-2.24)	0.32 (0.72-2.24), 0.49
Weight for age and sex z-score	116	0.9 (1.3)	126	0.8 (1.2)	-0.05 (-0.36-0.25)	-0.06 (-0.40-0.29), 0.91	117	0.7 (1.2)	-0.18 (-0.49-0.12)	-0.18 (-0.53-0.16), 0.39
Height for age and sex z-score	115	0.3 (1.1)	126	0.3 (1.2)	-0.01 (-0.29-0.27)	-0.03 (-0.35-0.29), 0.97	116	0.0 (1.0)	-0.24 (-0.53-0.04)	-0.26 (-0.58-0.06), 0.14
Weight for height and sex z-score	115	1.0 (1.3)	126	0.9 (1.1)	-0.06 (-0.36-0.25)	-0.04 (-0.39-0.30), 0.94	116	0.9 (1.2)	-0.06 (-0.37-0.25)	-0.07 (-0.41-0.28), 0.88
Head circumference for age and sex z-score	115	0.8 (1.2)	124	0.8 (1.1)	-0.05 (-0.35-0.24)	-0.02 (-0.35-0.30), 0.98	114	0.8 (1.2)	-0.05 (-0.35-0.25)	-0.06 (-0.39-0.28), 0.90
Triceps skinfold z-score	84	0.4 (1.2)	84	0.4 (1.3)	0.08 (-0.29-0.45)	0.06 (-0.36-0.47), 0.94	79	0.3 (1.2)	-0.07 (-0.44-0.31)	-0.09 (-0.52-0.32), 0.82
Subscapular skinfold z-score	84	0.1 (1.3)	85	0.0 (1.2)	-0.03 (-0.39-0.34)	-0.05 (-0.46-0.37), 0.96	77	-0.1 (1.1)	-0.21 (-0.58-0.17)	-0.22 (-0.65-0.21), 0.41
Fat mass (kg)	88	2.8 (1.0)	99	2.6 (1.1)	-0.14 (-0.42-0.15)	-0.12 (-0.43-0.19), 0.58	87	2.6 (0.9)	-0.16 (-0.45-0.13)	-0.08 (-0.40-0.24), 0.80
Fat free mass (kg)	88	10.8 (1.8)	99	10.8 (1.8)	0.03 (-0.48-0.54)	0.07 (-0.33-0.46), 0.91	87	10.5 (1.7)	-0.26 (-0.79-0.26)	0.04 (-0.37-0.45), 0.96
Abdominal circumference (cm)	107	49.6 (3.9)	111	49.5 (3.8)	-0.16 (-1.18-0.85)	-0.18 (-1.33-0.96), 0.91	104	48.9 (3.8)	-0.68 (-1.71-0.35)	-0.72 (-1.87-0.43), 0.28

Data are n (%); RR (95% CI), p or mean difference (95% CI), p

Adjusted values were adjusted for recruitment centre, socioeconomic status, gestation, sex and for multiple comparisons using Dunnett test.

Fat mass and fat free mass were additionally adjusted for height

NC= Not calculable, model did not converge

Table 5.7 Secondary health and growth outcomes at 2 years in children exposed to placebo or any dextrose dose

Outcome	Placebo		Any dextrose dose			
	n	n (%) or mean (SD)	n	n (%) or mean (SD)	RR or mean difference (95%CI)	Adjusted RR or mean difference (95%CI), p
Seizures	116	2 (1.7)	243	3 (1.2)	0.72 (0.12-4.23)	NC
Asthma	116	24 (20.7)	243	48 (19.8)	0.95 (0.62-1.48)	0.98 (0.63-1.51), 0.92
Eczema	116	42 (36.2)	243	106 (43.6)	1.20 (0.91-1.60)	1.19 (0.90-1.58), 0.22
Allergy	116	46 (39.7)	243	115 (47.3)	1.19 (0.92-1.55)	1.20 (0.92-1.55), 0.17
Medical attention for suspected infections	116	19 (16.4)	243	45 (18.5)	1.13 (0.69-1.84)	1.15 (0.71-1.88), 0.57
Weight for age and sex z-score	116	0.9 (1.3)	243	0.8 (1.2)	-0.11 (-0.38-0.15)	-0.12 (-0.39-0.15), 0.38
Height for age and sex z-score	115	0.3 (1.1)	242	0.1 (1.1)	-0.12 (-0.37-0.12)	-0.14 (-0.39-0.11), 0.27
Weight for height and sex z-score	115	1.0 (1.3)	242	0.9 (1.2)	-0.06 (-0.33-0.21)	-0.06 (-0.32-0.21), 0.68
Head circumference for age and sex z-score	115	0.8 (1.2)	238	0.8 (1.1)	-0.05 (-0.31-0.20)	-0.04 (-0.29-0.21), 0.76
Triceps skinfold z-score	84	0.4 (1.2)	163	0.4 (1.2)	0.01 (-0.31-0.33)	-0.02 (-0.34-0.30), 0.91
Subscapular skinfold z-score	84	0.1 (1.3)	162	0 (1.2)	-0.11 (-0.43-0.21)	-0.13 (-0.45-0.19), 0.43
Fat mass (kg)	88	2.8 (1.0)	186	2.6 (1.0)	-0.15 (-0.40-0.10)	-0.10 (-0.34-0.14), 0.40
Fat free mass (kg)	88	10.8 (1.8)	186	10.7 (1.8)	-0.11 (-0.56-0.34)	0.06 (-0.26-0.37), 0.73
Abdominal circumference (cm)	107	49.6 (3.9)	215	49.2 (3.8)	-0.41 (-1.30-0.47)	-0.45 (-1.33-0.43), 0.32

Data are n (%); RR (95% CI), p or mean difference (95% CI), p
Adjusted values were adjusted for recruitment centre, socioeconomic status, gestation, sex.
Fat mass and fat free mass were additionally adjusted for height
NC= Not calculable, model did not converge

6 The two-year outcomes of children born to diabetic mothers and randomised to dextrose gel prophylaxis or placebo to prevent neonatal hypoglycaemia: a sub-study of follow up of the hPOD randomised trial.

6.1 Introduction

Approximately 17% of pregnancies are complicated by diabetes (Goldenberg et al., 2016). The majority of diabetes in pregnancy is due to gestational diabetes, the prevalence of which varies by country, ethnicity and the diagnostic threshold (Farrar et al., 2016; HAPO Study Cooperative Research Group, 2008; Pu et al., 2015) but which affects approximately 15% of women during pregnancy (Egan et al., 2017; Guariguata et al., 2014; Melchior et al., 2017). It is uncertain if maternal diabetes causes long-term neurodevelopmental effects on the offspring. Several studies have shown no difference in early childhood neurodevelopment in children born to diabetic mothers compared to non-diabetic mothers (Daraki et al., 2017; R. A. DeRegnier et al., 2000; Rehan et al., 2002). Conversely, there is a body of evidence demonstrating adverse neurophysiological parameters and neurodevelopmental outcomes in offspring of mothers with gestational and pre-existing diabetes compared to the offspring of non-diabetic mothers (Dionne et al., 2008; A. Fraser et al., 2012; Hod et al., 1999; C. A. Nelson et al., 2003; Torres-Espínola et al., 2018). While randomised controlled trials of the management of gestational diabetes with metformin compared to insulin found no difference in rates of adverse neurodevelopment in the offspring (Ijäs et al., 2015; Wouldes et al., 2016), the children of mothers with gestational diabetes in these trials had lower developmental scores compared to standardised normal values (Ijäs et al., 2015; Tertti et al., 2015). Children of diabetic mothers have also been shown to have slower language development than age adjusted normal values (Tertti et al., 2015) throughout early childhood from 18 months' to seven years of age (Dionne et al., 2008).

Infants born to diabetic mothers are at increased risk of neonatal hypoglycaemia with up to half of these infants developing low BGC (Harris et al., 2012). The earlier the onset of diabetes in pregnancy the higher the risk of neonatal hypoglycaemia (Agrawal et al., 2000), with children of mothers with type 1 diabetes at higher risk than those of mothers with type 2 diabetes (Kline & Edwards, 2007; Owens et al., 2015). Both a higher maternal HbA1c (Arumugam & Abdul Majeed, 2011; Joshi et al., 2017; L. P. Lowe et al., 2012; Rowan et al., 2010) and insulin treatment of gestational diabetes are associated with a greater risk of neonatal hypoglycaemia (Balsells et al., 2000). Severe or recurrent neonatal hypoglycaemia in children of diabetic mothers is associated with a higher risk of delayed or abnormal motor development (Stenninger et al., 1998; Wouldes et al., 2016) and lower developmental quotients (Stenninger et al., 1998).

Symptomatic neonatal hypoglycaemia is associated with an increased risk of brain injury and adverse neurodevelopmental outcomes (Burns et al., 2008; Haworth & MCrae, 1965). Hypoglycaemia in at- risk infants (preterm, small (<10th centile or <2500 g), large (>90th centile or >4500 g), or born to mothers with diabetes), detected by screening and promptly treated, is not associated with neurodevelopmental impairment up to 4.5 years of age (McKinlay et al., 2015, 2017). However, infants who develop severe or recurrent hypoglycaemia are at higher risk of impaired executive function and visual motor function (McKinlay et al., 2017). In addition, both a rapid rise in glucose concentration after hypoglycaemia or slow recovery are associated with neurosensory impairment (Burakevych et al., 2019; McKinlay et al., 2015).

Dextrose gel is an effective treatment for neonatal hypoglycaemia (Harris et al., 2013) but this treatment has not been shown to improve neurodevelopmental outcomes (Harris et al., 2016). Dextrose gel prophylaxis reduces the risk of neonatal hypoglycaemia and need for admission to neonatal intensive care units for management of hypoglycaemia in infants who are late preterm, small, large or born to mothers with diabetes (Hegarty et al., 2016). Our aim was to determine the long-term neurodevelopmental effects of hypoglycaemia prevention with oral dextrose gel in the infants of women with diabetes in pregnancy.

6.2 Methods

6.2.1 Hypoglycaemia prevention with oral dextrose gel (hPOD) randomised controlled trial

Details are in chapter 2.3. In brief, 2149 infants at risk of hypoglycaemia (IDM, small [birthweight <2.5 kg or <10th centile], large [birthweight >4.5 kg or >90th centile] or late preterm [35 or 36 weeks' gestation]) were randomised to receive 0.5 ml/kg of 40% dextrose or 0.5 ml/kg of placebo gel at 1 hour of age (Harding, Hegarty, et al., 2015). BGC were measured using a glucose oxidase method at two hours of age and then according to local practice. The primary outcome of the hPOD trial was admission to neonatal intensive care.

6.2.2 hPOD trial two year follow-up study

Families who participated in the hPOD trial and who had consented at the time of trial recruitment to further follow-up and had not withdrawn were invited to participate in this follow-up study, which started in January 2017. Ethics approval was obtained from the Health and Disability Ethics Committees of New Zealand (15/STH/97) and caregivers gave written informed consent at the time of assessment. At 24 months' corrected age, children underwent a comprehensive assessment of neurodevelopment, growth

and general health by doctors trained in all assessments who were unaware of the child's randomisation group (details are in methods 2.4.). Assessment included Bayley Scales of Infant Development 3rd edition (Bayley-III) (Bayley, 2006b), neurological examination, executive function (clinical assessment of inhibitory control and attentional flexibility) and Behavior Rating Inventory of Executive Function—Preschool Version (BRIEF-P) (Gioia et al., 2002). Height, weight, head circumference and abdominal circumference were measured to the nearest 0.1 cm. Triceps and subscapular skin-fold thicknesses were measured using a Harpenden caliper (Baty International, Burgess Hill, UK) to the nearest 0.2 cm, and the mean of two measurements recorded. Total body fat mass and fat free mass were estimated using multifrequency bioimpedance analysis (Imp SFB7, ImpediMed, Carlbad, USA). Home and general health information were collected by questionnaire.

The primary outcome was neurosensory impairment at two years' corrected age, defined as any of: legal blindness; sensorineural deafness requiring hearing aids; cerebral palsy; Bayley-III cognitive, language or motor score more than one standard deviation below the mean; executive function composite z-score <-1.5, derived from standardisation within the whole pre-hPOD two-year cohort (Hegarty et al., 2016). Children unable to complete the cognitive, language or motor scales of the Bayley-III because of severe delay in any of these domains were assigned scores of 49. Secondary outcomes were the components of the primary outcome, neurology, anthropometry, and health measures.

This sub-study includes children who were born to mothers with diabetes, enrolled in the hPOD trial, and had been assessed at two years' corrected age by the end of February 2020. As the follow up study is ongoing, data management staff who are not involved in any other aspects of the study or the data analysis extracted data and allocated the two randomisation groups (dextrose gel or placebo) as gel A or gel B. All other research team members remain blinded to the group allocation.

Our hypothesis was that gel A versus gel B given to IDM would alter neuropsychological development at two years' corrected age. The aims of this sub-study were to determine:

- The effect of gel A versus gel B on neurodevelopment, growth and physical health
- The relationship between neonatal glycaemia (hypoglycaemia, hyperglycaemia, blood glucose stability) and neurodevelopment
- Whether these relationships differ in children with different types of maternal diabetes.
- Whether these relationships differ in children with additional risk factors (preterm, small, large)

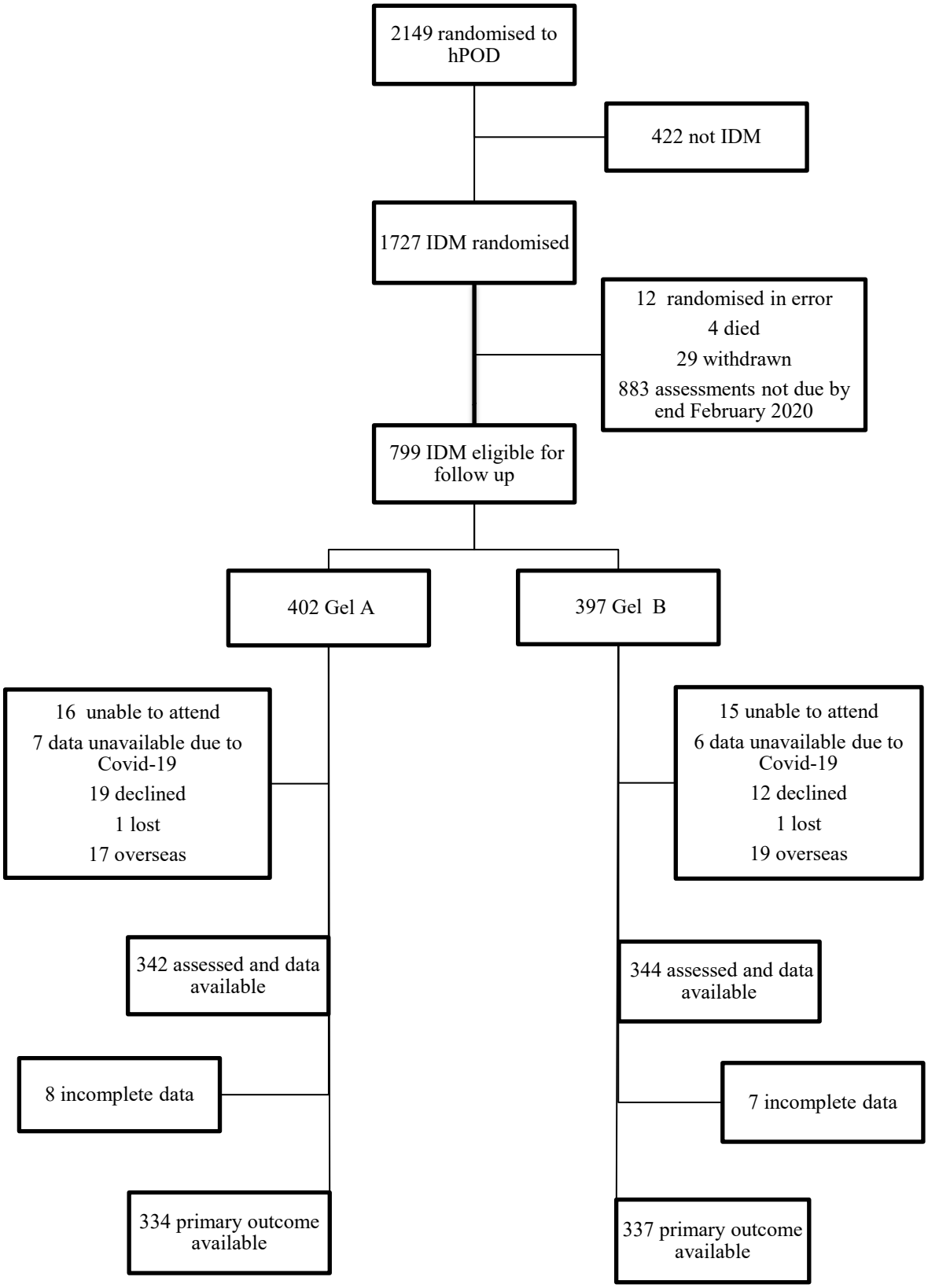
6.2.3 Statistical methods

Analyses were performed using JMP 15 (SAS Institute, Cary, NC). In the primary analysis (aim 1), children allocated to gel A were compared to those allocated to gel B for the pre-specified primary and secondary outcomes using logistic and linear regression, as appropriate, adjusted for recruitment centre, gestational age, sex and socioeconomic status at birth (New Zealand Deprivation Index 2013 (NZDEP) (Atkinson et al., 2014), or Socio-Economic Indexes for Areas 2016 (SEIFA) (Australian Bureau of Statistics)). These potential confounders were pre-specified with knowledge of their association with neurodevelopmental outcomes. Exposure effects were presented as odds ratio (OR) or mean difference (MD) with a 95% confidence interval. Secondary analyses of the primary outcome and its components included a comparison of children who were and were not exposed to hypoglycaemia, including severity and frequency, (aim 2); subgroup analysis to determine the influence of the type of maternal diabetes (aim 3) and other neonatal risk factors (aim 4) on the effect of gel treatment.

6.3 Results

A total of 2149 infants were randomised in the hPOD trial, of whom 1727 were IDM. Of these 1727 infants, 12 were randomised in error, 4 died before two years of age and 29 were withdrawn before two years of age leaving 1682 eligible for follow-up. At the cut-off date for this analysis on 29 February 2020, 799 children had become eligible for assessment, of whom 686 (86%) had been assessed and were included in this analysis (Figure 6.1).

Figure 6.1 hPOD CONSORT diagram randomisation to two year follow up



IDM: Infants of diabetic mothers

Mothers whose children were assessed were less likely to have gestational diabetes and more likely to have type 2 diabetes compared to mothers of those not assessed (Table 6.1). They were also more likely to have received insulin therapy. There was no difference in the rate of hypoglycaemia, severe hypoglycaemia or recurrent hypoglycaemia between assessed infants who received gel A versus gel B (Table 6.1).

Table 6.1 Characteristics of mothers and infants eligible for assessment at two years of age

	Total eligible		Gel A		Gel B		p value for difference between assessed and not assessed	p value for difference between those assessed in gel A and gel B
	Not assessed	Assessed	Not assessed	Assessed	Not assessed	Assessed		
Mothers (N=784)	113	671	60	335	53	336		
Age, years	32.8 (5.5)	32.6 (5.3)	33.2 (5.9)	32.7 (5.3)	32.4 (5.0)	32.5 (5.3)	0.70	0.65
Caesarean section	39 (34.5)	264 (39.3)	20 (33.3)	127 (37.9)	19 (35.9)	137 (40.8)	0.41	0.48
Gestational diabetes	105 (92.9)	573 (85.4)	59 (98.3)	278 (83.0)	46 (86.8)	295 (87.8)	0.02	0.08
Type 2 diabetes	5 (4.4)	64 (9.5)	1 (1.7)	37 (11.0)	4 (7.5)	27 (8.0)	0.05	0.19
Type 1 diabetes	3 (2.7)	34 (5.1)	0	20 (6.0)	3 (5.7)	14 (4.2)	0.21	0.30
Insulin therapy	52 (46.0)	415 (61.9)	23 (38.3)	215 (64.2)	29 (54.7)	200 (59.5)	<0.01	0.23
Highest education level							NC	0.71
Tertiary	NA	452 (75.1)	NA	225 (74.3)	NA	227 (75.9)		
Secondary	NA	150 (24.9)	NA	78 (25.7)	NA	72 (24.1)		
Children (N=799)	113	686	60	342	53	344		
Female	45 (39.8)	338 (49.3)	18 (30.0)	176 (51.5)	27 (50.9)	162 (47.1)	0.06	0.29
Gestation, weeks	38.7 (1.0)	38.5 (1.0)	38.7 (1.0)	38.5 (0.9)	38.7 (1.1)	38.5 (1.0)	0.05	0.46
Birthweight, grams	3351 (507)	3397 (520)	3328 (436)	3411 (503)	3378 (579)	3383 (538)	0.39	0.48
Birthweight z score	0.2 (1.0)	0.4 (1.0)	0.1 (0.9)	0.4 (1.0)	0.2 (1.2)	0.4 (1.0)	0.07	0.51
Multiple birth	2 (1.8)	32 (4.7)	0	15 (4.4)	2 (3.8)	17 (4.9)	0.12	0.86
*Socioeconomic index at birth, most deprived quintile	23 (20.5)	161 (23.6)	9 (15.0)	78 (22.9)	14 (26.9)	83 (24.3)	0.47	0.33
^Ethnicity							0.006	0.23
Māori	14 (12.4)	126 (18.4)	7 (11.7)	65 (19.0)	7 (13.2)	61 (17.7)		

Aboriginal / Torres Strait Islander	5 (4.4)	3 (0.4)	4 (6.7)	2 (0.6)	1 (1.9)	1 (0.3)		
Pacific	12 (10.6)	70 (10.2)	3 (5.0)	37 (10.8)	9 (17.0)	33 (9.6)		
Asian	31 (27.4)	134 (19.5)	17 (28.3)	55 (16.1)	14 (26.4)	79 (23.0)		
Australian or NZ European	35 (31.0)	222 (32.4)	20 (33.3)	110 (32.2)	15 (28.3)	112 (32.6)		
Other	16 (14.2)	131 (19.1)	9 (15.0)	73 (21.4)	7 (13.2)	58 (16.9)		
Additional risk factors	25 (22.1)	138 (20.1)	11 (18.3)	62 (18.1)	14 (26.4)	76 (22.1)	0.63	0.62
Preterm	4 (3.5)	38 (5.5)	1 (1.7)	14 (4.1)	3 (5.7)	24 (7.0)	0.35	0.38
Small	15 (13.3)	56 (8.2)	7 (11.7)	23 (6.7)	8 (15.1)	33 (9.6)	0.09	0.07
Large	8 (7.1)	60 (8.8)	3 (5.0)	31 (9.1)	5 (9.4)	29 (8.4)	0.56	0.56
Hypoglycaemia	38 (33.6)	268 (39.1)	23 (38.3)	140 (40.1)	15 (28.3)	128 (37.2)	0.27	0.32
Severe hypoglycaemia	9 (8.0)	65 (9.5)	4 (6.7)	31 (9.1)	5 (9.4)	34 (9.9)	0.60	0.71
Recurrent hypoglycaemia	2 (1.8)	33 (4.8)	0 (0)	15 (4.4.)	2 (3.4)	18 (5.2)	0.10	0.60
Corrected age at assessment, months	NA	24.5 (1.2)		24.5 (1.1)		24.5 (1.3)	NC	0.89
[+]Assessment within 24+/-1-month window	NA	523 (76.9)		255 (75.0)		268 (78.8)	NC	0.24

Data are mean (SD), number (%)
NA: not available
NC: not calculable
*Data missing for 2 infants in gel A assessed, 1 in gel B not assessed and 3 in gel B assessed groups
^Recorded at birth. Ethnicity prioritised: Māori, Aboriginal/Torres Strait Islander, Pacific, Asian, Australian or New Zealand European, Other
+Data available for 340 children each in gel A and gel B groups
Hypoglycaemia: BGC < 2.6mmol/L. Severe hypoglycaemia: BGC < 2.0 mmol/L. Recurrent hypoglycaemia ≥ 3 episodes. Episode defined as one or more consecutive measurements of BGC <2.6 mmol/L.

The overall incidence of neurosensory impairment was 22.7% and was similar in children who had received gel A and gel B (Table 6.2). There were no differences in any secondary outcomes between children who received gel A and gel B.

Table 6.2 Primary and secondary outcomes at two years' corrected age in children randomised to gel A or gel B

	Gel A (N=342)		Gel B (N=344)		
Outcome	Number assessed	n (%) or mean (SD)	Number assessed	n (%) or mean (SD)	*Adjusted OR or MD (95%CI), p
Neurosensory impairment[+]	334	75 (22.5)	337	77 (22.9)	0.9 (0.7 to 1.4), 0.69
Cerebral palsy	335	2 (0.6)	338	0	NC
Deaf	339	1 (0.3)	340	2 (0.6)	1.8 (0.1 to 24.6), 0.66
Blind	339	1 (0.3)	340	0	NC
Bayley-III cognitive composite score <85	340	24 (7.1)	340	25 (7.4)	1.0 (0.5 to 1.8), 0.95
Bayley-III language composite score <85	339	49 (14.5)	340	61 (17.9)	1.2 (0.8 to 1.8), 0.47
Bayley-III motor composite score <85	340	4 (1.2)	340	8 (2.4)	1.7 (0.4 to 6.0), 0.39
Executive function score < -1.5 SD	335	32 (9.6)	338	23 (6.8)	0.6 (0.3 to 1.0), 0.06
Mild neurosensory impairment	334	64 (19.2)	337	65 (19.3)	1.1 (0.7 to 1.6), 0.73
Moderate neurosensory impairment	339	9 (2.7)	340	10 (2.9)	1.0 (0.4 to 2.6), 1.00
Severe neurosensory impairment	339	2 (0.6)	340	2 (0.6)	1.4 (0.2 to 12.7), 0.78
Developmental delay	340	59 (17.4)	340	66 (19.4)	1.0 (0.7 to 1.6), 0.84
Bayley-III cognitive composite score	340	98.4 (11.5)	340	97.7 (10.5)	-0.1(-1.7 to 1.5), 0.90
Bayley-III language composite score	338	99.2 (15.6)	340	97.3 (14.7)	-1.3 (-3.6 to 0.9), 0.24
Bayley-III motor composite score	340	103.5 (10.1)	340	101.9 (9.6)	-1.3 (-2.8 to 0.2), 0.09
Bayley III social emotional composite score	127	107.4 (17.2)	112	104.6 (15.5)	-3.1 (-7.4 to 1.2), 0.15
Bayley III general adaptive composite score	129	100.2 (16.1)	111	98.5 (14.7)	-2.6 (-6.6 to 1.4), 0.21
Executive function score	335	11.0 (4.5)	338	11.2 (4.3)	0.3 (-0.4 to 1.0), 0.34
BRIEF P GEC T-score >65	282	33 (11.7)	277	33 (11.9)	1.1 (0.6 to 1.9), 0.79
BRIEF P GEC T-score	282	49.7 (12.7)	277	50.3 (12.7)	0.7 (-1.4 to 2.9), 0.49
Abnormality of tone or coordination	342	30 (8.8)	344	28 (8.1)	1.0 (0.6 to 1.7), 0.89

Seizures	338	18 (5.3)	340	9 (2.7)	0.5 (0.2 to 1.1), 0.10
Wheeze / asthma	338	80 (23.7)	340	75 (22.1)	0.9 (0.6 to 1.3), 0.60
Eczema	338	118 (34.9)	340	118 (34.7)	1.0 (0.7 to 1.4), 0.97
Allergy (food)	338	34 (10.1)	340	34 (10.0)	0.9 (0.6 to 1.6), 0.84
Infectious illness requiring medical attention	338	301 (89.1)	340	304 (89.4)	1.0 (0.6 to 1.6), 0.87
Weight (kg)	335	13.2 (1.9)	338	13.3 (1.8)	0.1 (-0.2 to 0.4), 0.58
Weight z-score	335	0.80 (1.11)	338	0.84 (1.05)	0.05 (-0.11 to 0.22), 0.55
Height (cm)	335	86.9 (3.5)	336	87.1 (3.6)	0.2 (-0.3 to 0.7), 0.45
Height z-score	335	-0.01 (1.05)	336	0.03 (1.10)	0.05 (-0.11 to 0.22), 0.53
Weight for height z-score	335	1.07 (1.22)	335	1.11 (1.08)	0.04 (-0.14 to 0.22), 0.65
BMI	335	17.4 (1.9)	335	17.4 (1.7)	0.0 (-0.2 to 0.3), 0.85
BMI z-score	335	1.14 (1.23)	335	1.18 (1.09)	0.04 (-0.14 to 0.22), 0.65
Head circumference (cm)	332	48.7 (1.5)	327	48.8 (1.6)	-0.1 (-0.4 to 0.2), 0.60
Head circumference z-score	332	0.74 (1.03)	328	0.68 (1.57)	-0.05 (-0.26 to 0.16), 0.66
Mid arm circumference (cm)	294	16.4 (1.5)	275	16.2 (1.4)	-0.1 (-0.3 to 0.1), 0.41
Mid upper arm circumference z-score	294	1.01 (1.10)	275	0.93 (1.07)	-0.07 (-0.25 to 0.11), 0.43
Subscapular skinfold (mm)	227	6.8 (2.0)	230	6.7 (2.3)	0.0 (-0.4 to 0.4), 0.83
Subscapular skinfold z-score		0.37 (1.31)		0.25 (1.22)	-0.08 (-0.31 to 0.15), 0.50
Triceps skinfold (mm)	232	8.3 (2.2)	235	8.2 (2.5)	0.0 (-0.4 to 0.5), 0.96
Triceps skinfold z-score		0.12 (1.23)		0.05 (1.28)	-0.01 (-0.24 to 0.22), 0.94
Abdominal circumference (cm)	305	49.5 (3.8)	299	48.9 (3.4)	-0.6 (-1.1 to 0.0), 0.06
Fat mass	223	2.6 (1.1)	213	2.7 (1.0)	0.1 (-0.1 to 0.3), 0.27
Fat free mass	223	10.6 (1.6)	213	10.5 (1.4)	-0.1 (-0.3 to 0.2), 0.72

Data are number (%), odds ratio (OR) or mean difference (MD), 95% confidence interval (95%CI), p
+ Not all children completed all parts of the assessment necessary to exclude neurosensory impairment
*Adjusted for recruitment centre, socioeconomic status, gestation, sex
Abdominal circumference, fat mass and fat free mass were additionally adjusted for height
NC: not calculable

Children born to mothers with pre-existing diabetes rather than gestational diabetes were more likely to develop hypoglycaemia or severe hypoglycaemia and those born to mothers who were treated with insulin were also more likely to develop hypoglycaemia or severe hypoglycaemia (Table 6.3).

Table 6.3 Neonatal hypoglycaemia in infants whose mothers had different types of diabetes and different treatments

	Type 1 diabetes N=37	Type 2 diabetes N=69	Gestational diabetes N=693	p value	Dietary or metformin treatment N=324	Insulin treatment N=475	p value
Hypoglycaemia	22 (59.5)	42 (60.9)	242 (34.9)	<0.0001	110 (34.0)	196 (41.3)	0.04
Severe hypoglycaemia	8 (21.6)	18 (26.1)	48 (6.9)	<0.0001	20 (6.2)	54 (11.4)	0.01
Recurrent hypoglycaemia	3 (8.1)	4 (5.8)	28 (4.0)	0.48	9 (2.8)	26 (5.5)	0.06

Hypoglycaemia: BGC < 2.6mmol/L
Severe hypoglycaemia: BGC < 2.0 mmol/L
Recurrent hypoglycaemia ≥ 3 episodes. Episode defined as one or more consecutive measurements of BGC <2.6 mmol/L

Children who developed neonatal hypoglycaemia in the first 48 hours after birth were more likely to have of neurosensory impairment than those who did not develop hypoglycaemia (Table 6.4). Although there was a trend towards higher rates of component outcomes in children who had developed hypoglycaemia compared to those who did not, none of comparisons were statistically significant. Neither severe hypoglycaemia nor recurrent hypoglycaemia were associated with the risk of neurosensory impairment or the component outcomes (Table 6.4).

There was no difference in risk of neurosensory impairment between children with different proportions of blood glucose results in the interquartile range of all blood glucose results, and no differences across quintiles in the outcomes contributing to neurosensory impairment (Figure 6.2). Only 2 infants had BGC > 8 mmol/L recorded in the first 48 hours after birth.

On secondary analysis, there was no evidence that the effect of gel treatment on the primary outcome or its components was influenced by type of maternal diabetes (adjusted p value for interaction=0.92) (Table 6.5), or if infants were born preterm or term (adjusted p value for interaction=0.33) (Table 6.6).

Table 6.4 Associations between hypoglycaemia and the risk of neurosensory impairment and its components in infants of diabetic mothers

	Hypoglycaemia N=265	No hypoglycaemia N=415	Adjusted OR (95% CI), p	Severe hypoglycaemia N=64	Adjusted OR (95% CI), p	Recurrent hypoglycaemia N=33	Adjusted OR (95% CI), p
Neurosensory impairment	72 (27.8)	80 (19.4)	1.6 (1.1 to 2.4), 0.03	15 (23.8)	1.2 (0.6 to 2.4), 0.61	5 (15.6)	0.6 (0.2 to 1.7), 0.34
Cerebral palsy	2 (0.8)	0 (0)	NC	1 (1.6)	10.5 (0.3 to 320.5), 0.18	1 (3.1)	NC
Deaf	2 (0.8)	1 (0.2)	2.4 (0.2 to 30.3), 0.51	0 (0)	NC	0 (0)	NC
Blind	1 (0.4)	0 (0)	NC	0 (0)	NC	0 (0)	NC
Bayley-III cognitive composite score <85	23 (8.7)	26 (6.3)	1.4 (0.7 to 2.6), 0.31	6 (9.4)	1.4 (0.5 to 3.7), 0.50	1 (3.0)	0.5 (0.1 to 4.0), 0.51
Bayley-III language composite score <85	54 (20.4)	56 (13.4)	1.5 (1.0 to 2.4), 0.07	12 (18.8)	1.5 (0.7 to 3.0), 0.31	2 (6.1)	0.3 (0.1 to 1.4), 0.12
Bayley-III motor composite score <85	5 (1.9)	7 (1.7)	1.2 (0.3 to 4.1), 0.82	2 (3.1)	1.8 (0.3 to 10.8), 0.53	1 (3.0)	4.9 (0.5 to 49.9), 0.18
Executive function score < -1.5 SD	24 (9.3)	31 (7.5)	1.4 (0.7 to 2.5), 0.33	5 (7.8)	0.9 (0.3 to 2.6), 0.83	1 (3.0)	0.5 (0.1 to 4.1), 0.56

Data are number (%), OR (odds ratio) or mean difference (MD), 95% confidence interval (95%CI), p
Adjusted for recruitment centre, socioeconomic status, gestation, sex
NC: not calculable
Data point missing for neurosensory impairment in 1 no hypoglycaemia and 2 hypoglycaemia
Data point missing for cerebral palsy in 2 no hypo, 5 hypo, 1 severe hypoglycaemia, 1 recurrent hypoglycaemia
Data point missing for Bayley language in 1 no hypoglycaemia
Data point missing for 1 deaf, 1 blind, 3 executive function in hypoglycaemia
Hypoglycaemia: BGC < 2.6mmol/L. Severe hypoglycaemia: BGC < 2.0 mmol/L. Recurrent hypoglycaemia ≥ 3 episodes. Episode defined as one or more consecutive measurements of BGC <2.6 mmol/L

Figure 6.2 hPOD proportion of blood glucose results within the interquartile range and the risk of neurosensory impairment

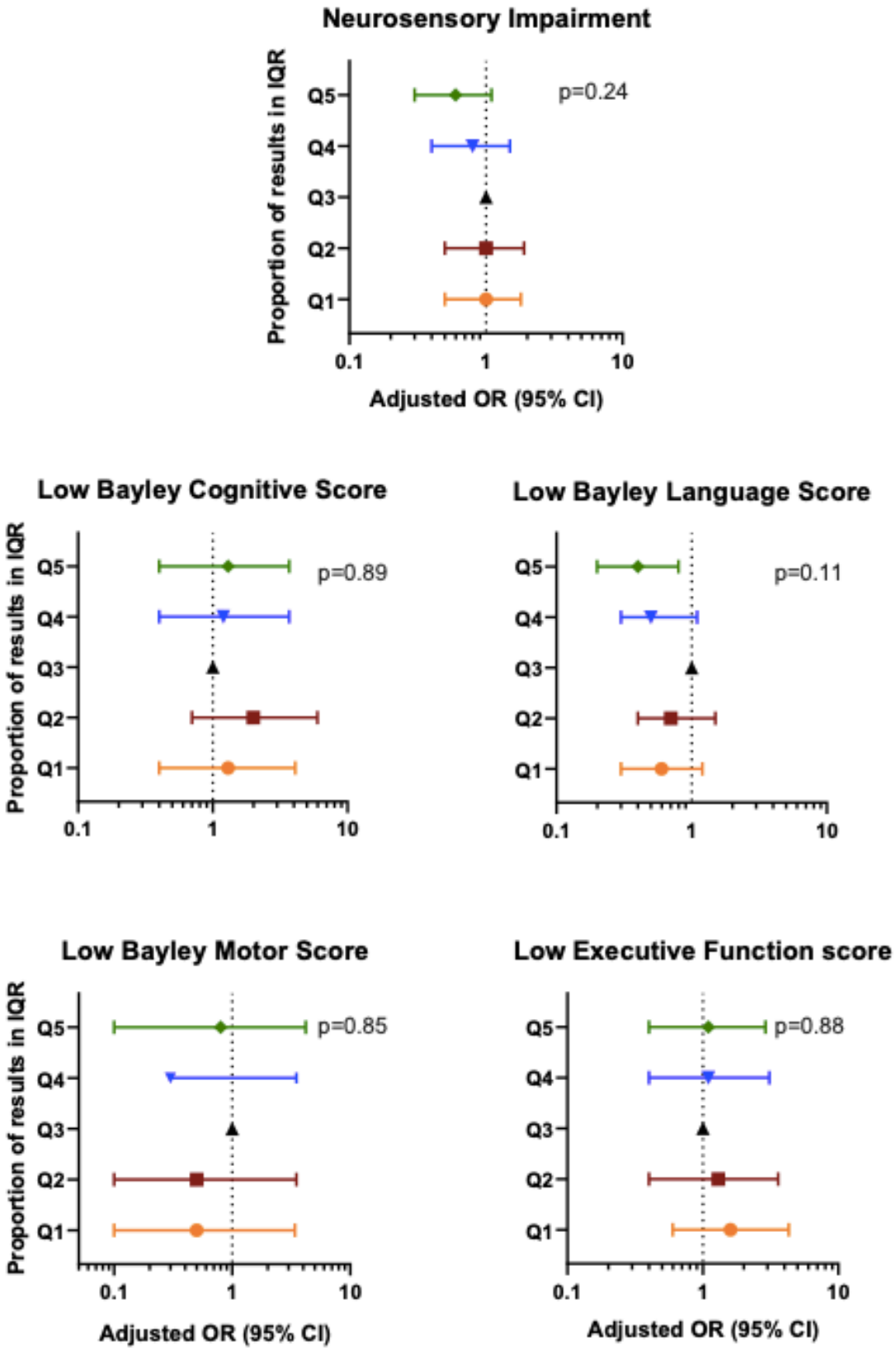


Figure 6.2 legend: The interquartile range of BGC in the first 48 hours after birth was 2.7 – 3.6 mmol/L. Babies were assigned into quintiles based on the proportion of BGC in the first 48 hours after birth within the interquartile range:Q1 0-<0.40, Q2 0.40-0.50, Q3 0.50-0.75, Q4 0.75-<1, Q5 1.0. The data are presented as associations between each quintile of the proportion of BGC in the first 48 hours after birth within the interquartile range and neurodevelopmental impairment.

Table 6.5 Effect of gel A vs gel B on the primary outcome and its components in infants whose mothers had different types of diabetes

	Type 1 diabetes			Type 2 diabetes			Gestational diabetes			Adjusted p value for interaction
Outcome	A N=20	B N=14	*Adjusted OR (95% CI), p	A N=37	B N=26	*Adjusted OR (95% CI), p	A N=281	B N=301	*Adjusted OR (95% CI), p	
Neurosensory impairment	4 (21.1)	3 (23.1)	NC	11 (31.4)	9 (36.0)	0.8 (0.2-3.4), 0.73	60 (21.4)	65 (21.7)	0.9 (0.6-1.4), 0.73	0.92
Cerebral palsy	0	0	NC	1 (2.8)	0	NC	1 (0.4)	0	NC	1.00
Deaf	0	0	NC	1 (2.7)	1 (4.9)	NC	0	1 (0.3)	NC	1.00
Blind	0	0	NC	1 (2.7)	0	NC	0	0	NC	0.71
Bayley-III cognitive composite score <85	1 (5.0)	1 (7.1)	NC	6 (16.2)	4 (15.4)	0.8 (0.1-5.4), 0.84	17 (6.0)	20 (6.7)	1.0 (0.5-2.1), 1.00	0.98
Bayley-III language composite score <85	2 (10.0)	2 (14.3)	NC	7 (18.9)	6 (23.1)	1.8 (0.4-8.5), 0.46	40 (14.2)	53 (17.7)	1.1 (0.7-1.8), 0.63	0.88
Bayley-III motor composite score <85	0	0	NC	1 (2.7)	0	NC	3 (1.1	8 (2.7)	2.2 (0.5-8.8), 0.27	0.34
Executive function score < -1.5 SD	2 (10.0)	1 (7.7)	0.0 (0.0-142.7), 0.37	2 (5.8)	3 (11.5)	3.1 (0.2-47.0), 0.41	28 9.9)	19 (6.4)	0.5 (0.2-0.9), 0.03	0.55

Data are number (%), OR (odds ratio), 95% confidence interval (95%CI), p
*Adjusted for recruitment centre, socioeconomic status, gestation, sex
NC: not calculable

Table 6.6 Effect of gel A vs B on the primary outcome and its components in preterm and term infants

	Preterm			Term			p value for interaction (adjusted)
	A N=14	B N=24	*Adjusted OR (95%CI), p	A N=326	B N=317	*Adjusted OR (95%CI), p	
Neurosensory impairment	6 (46.2)	7 (29.2)	0.4 (0.0 to 11.8), 0.59	69 (21.5)	70 (22.4)	1.0 (0.6 to 1.5), 0.90	0.33
Cerebral palsy	0	0	NC	2 (0.6)	0	NC	1.00
Deaf	0	1 (4.2)	NC	1 (0.3)	1 (0.3)	0.9 (0.0 to 16.5), 0.95	0.30
Blind	0	0	NC	1 (0.3)	0	NC	1.00
Bayley-III cognitive composite score <85	1 (7.1)	1 (4.2)	1.8 (0.0 to 76.8), 0.75	23 (7.1)	24 (7.6)	1.0 (0.5 to 1.9), 0.98	0.74
Bayley-III language composite score <85	5 (35.7)	5 (20.8)	NC	44 (13.5)	56 (17.7)	1.3 (0.8 to 2.1), 0.26	0.16
Bayley-III motor composite score <85	0	1 (4.2)	NC	4 (1.2)	7 (2.2)	1.7 (0.5 to 6.1), 0.42	0.44
Executive function score < -1.5 SD	2 (16.7)	2 (8.7)	NC	30 (9.3)	21 (6.7)	0.6 (0.3 to 1.1), 0.12	0.76

Preterm: 35 +0 to 36+6 weeks' gestation
Data are number (%), OR (odds ratio) or mean difference (MD), 95% confidence interval (95%CI), p
*Adjusted for recruitment centre, socioeconomic status, gestation, sex
NC: not calculable

There was no difference in risk of neurosensory impairment or the component outcomes between children who had additional risk factors for hypoglycaemia and those who did not (Table 6.7)

Table 6.7 Additional risk factors for hypoglycaemia and the risk of neurosensory impairment and its components.

	N	No additional risk factors for hypoglycaemia	N	Additional risk factors for hypoglycaemia	OR (95% CI), p	*Adjusted OR (95% CI), p
Neurosensory impairment	537	118 (22.0)	134	34 (25.4)	1.2 (0.8 to 1.9), 0.41	1.1 (0.7 to 1.8), 0.74
Cerebral palsy	537	2 (0.4)	136	0 (0)	NC	NC
Deaf	541	2 (0.4)	138	1 (0.7)	2.0 (0.2 to 21.9), 0.60	0.9 (0.0 to 17.2), 0.92
Blind	541	1 (0.2)	138	0 (0)	NC	NC
Bayley-III cognitive composite score <85	542	39 (7.2)	138	10 (7.3)	1.0 (0.5 to 2.1), 0.98	0.9 (0.4 to 2.0), 0.75
Bayley-III language composite score <85	541	85 (15.7)	138	25 (18.1)	1.2 (0.7 to 1.9), 0.50	1.1 (0.6 to 2.0), 0.69
Bayley-III motor composite score <85	542	10 (1.9)	138	2 (1.5)	0.8 (0.2 to 3.6), 0.75	0.4 (0.1 to 2.7), 0.36
Executive function score < -1.5 SD	539	42 (7.8)	134	13 (9.7)	1.3 (0.7 to 2.4), 0.48	1.0 (0.5 to 2.2), 0.96

Data are number (%), Odds ratio (OR), 95% confidence interval (95%CI), p
Additional risk factors for hypoglycaemia, n=163: preterm, n=42, small for gestational age, n=71, large for gestational age, n=68. Two additional risk factors, n=18
* Adjusted for recruitment centre, socioeconomic status, gestation, sex
NC not calculable

Sensitivity analyses

After removing 13 children (5 gel A, 8 gel B) with events or diagnoses that were likely to have affected the outcomes independent of the study intervention, there were no differences in the risk of neurosensory impairment between children who had received gel B compared to gel A, but the children who had received gel B were less likely to have a low executive score compared to those who received gel A (Table 6.8).

Table 6.8 Sensitivity analysis excluding children with diagnosis likely to affect outcomes

	Gel A		Gel B			
Outcome	N	n (%)	N	n (%)	OR (95%CI) A is referent	*Adjusted OR (95%CI), p
Neurosensory impairment	329	75 (22.8)	329	75 (22.8)	1.0 (0.7 to 1.4), 1.00	0.9 (0.6 to 1.4), 0.63
Cerebral palsy	330	2 (0.6)	330	0 (0)	NC	NC
Deaf	334	1 (0.3)	332	1 (0.3)	1.0 (0.1 to 16.2), 1.00	0.4 (0.0 to 9.3), 0.55
Blind	334	1 (0.3)	332	0 (0)	NC	NC
Bayley-III cognitive composite score <85	335	24 (7.2)	332	24 (7.2)	1.0 (0.6 to 1.8), 0.97	0.9 (0.5 to 1.8), 0.87
Bayley-III language composite score <85	334	49 (14.7)	332	59 (17.8)	1.3 (0.8 to 1.9), 0.28	1.1 (0.7 to 1.8), 0.55
Bayley-III motor composite score <85	335	4 (1.2)	332	6 (1.8)	1.5 (0.4 to 5.4), 0.51	1.3 (0.3 to 4.7), 0.74
Executive function score < -1.5 SD	330	32 (9.7)	330	21 (6.4)	0.6 (0.4 to 1.1), 0.11	0.5 (0.3 to 0.9), 0.03

Data are number (%), OR (odds ratio), 95% confidence interval (95%CI), p
*Adjusted for recruitment centre, socioeconomic status, gestation, sex
NC: not calculable

Sensitivity analysis excluding those 160 children assessed outside of the intended age window (24 months' corrected age +/- 1 month) did not significantly alter results (Table 6.9).

Table 6.9 Sensitivity analysis excluding children assessed outside of age window

	Gel A		Gel B			
Outcome	N	n (%)	N	n (%)	OR (95%CI) A is referent	*Adjusted OR (95%CI), p
Neurosensory impairment	253	53 (20.9)	267	56 (20.9)	1.0 (0.7 to 1.5), 0.99	1.0 (0.6 to 1.5), 0.86
Cerebral palsy	254	2 (0.8)	267	0 (0)	NC	NC
Deaf	255	1 (0.4)	268	1 (0.4)	1.0 (0.1 to 15.3), 0.97	0.7 (0.0 to 15.6), 0.83
Blind	255	1 (0.4)	268	0 (0)	NC	NC
Bayley-III cognitive composite score <85	255	15 (5.9)	268	20 (7.5)	1.3 (0.6 to 2.6), 0.47	1.3 (0.6 to 2.8), 0.46
Bayley-III language composite score <85	255	36 (14.1)	268	45 (16.8)	1.2 (0.8 to 2.0), 0.40	1.1 (0.7 to 1.9), 0.68
Bayley-III motor composite score <85	255	2 (0.8)	268	5 (1.9)	2.4 (0.5 to 12.5), 0.27	2.8 (0.5 to 15.0), 0.24
Executive function score < -1.5 SD	253	22 (8.7)	267	17 (6.4)	0.7 (0.4 to 1.4), 0.31	0.7 (0.3 to 1.4), 0.30

Data are number (%), OR (odds ratio), 95% confidence interval (95%CI), p
*Adjusted for recruitment centre, socioeconomic status, gestation, sex
NC: not calculable

6.4 Discussion

In children born to mothers with diabetes, prophylactic oral dextrose gel did not alter the risk of neurosensory impairment at two years' corrected age. These results, which are similar to the results of the pre-hPOD follow-up study (chapter 5), provide reassurance that dextrose gel prophylaxis is safe with similar rates of neurosensory impairment between prophylactic dextrose and placebo gel, and no adverse effects. Neonatal hypoglycaemia in IDM was associated with neurosensory impairment. However, neither the risk of hypoglycaemia nor later neurosensory impairment were reduced by prophylactic oral dextrose gel in the subgroup included in this analysis.

The 22% (152/671) rate of neurosensory impairment in children of mothers with diabetes born at 35 weeks or later, regardless of documented hypoglycaemia, was higher than population data. Children up to four years of age in Australia and New Zealand have been reported to have rates of disability of 3.4% and 5.8% respectively ("OECD Family Database," 2009), although these reported rates are based on caregiver reported impairment rather than standardised testing. This high rate of neurosensory impairment in children of diabetic mothers indicates that healthcare professionals should be aware of the need to be vigilant in children of mothers with diabetes in order to prompt early intervention and support when indicated. Our definition of neurosensory impairment included low executive function scores, unlike the CHYLD study where executive function contributed to the co-primary outcome "processing difficulty" (McKinlay et al., 2015). Given our broader definition of neurosensory impairment, a higher rate might be expected in our analyses. On the contrary, a higher rate of neurosensory impairment (39%) than in this sub-study was found in the CHYLD study at two years, but only 41% of these infants were born to mothers with diabetes and more had been born preterm (Harris et al., 2016) a well-recognised risk factor for adverse neurodevelopmental outcomes (Cheong, Anderson, et al., 2017).

Children born to mothers with either gestational diabetes or pre-existing diabetes have been identified in some studies as at greater risk of neurodevelopmental impairment compared to children of mothers who did not have diabetes (DeBoer et al., 2005; Dionne et al., 2008; A. Fraser et al., 2012; C. A. Nelson et al., 2003). Our hypothesis was that oral dextrose gel (either gel A or gel B) given to IDM would alter neuropsychological development at two years' corrected age. However, there were no differences between children who received gel A or gel

B in the rates of neurosensory impairment. The data from this sub-study suggest that there are potential adverse effects on the neurodevelopment of children exposed to maternal diabetes in utero regardless of postnatal intervention. Longitudinal follow up of children of mothers with pre-existing and gestational diabetes has previously demonstrated an association between higher maternal 2nd and 3rd trimester beta-hydroxybutyrate and adverse motor development between six and nine years of age after adjusting for sex and socioeconomic factors (Rizzo et al., 1995). A negative association between maternal HbA1c or urinary acetone concentrations and offspring sensory-motor function has also been seen in children of mothers with pre-existing diabetes (Ornoy et al., 1998). Importantly even HbA1c prior to the pregnancy as well as during pregnancy has been found to be negatively associated with offspring school grades in children of mothers with type 1 diabetes (Knorr et al., 2015). These data suggest that maternal diabetic control prior to and during pregnancy may be a key determinant of long-term neurodevelopment in the offspring. Further research is needed to determine if the management of maternal diabetes before and during pregnancy can reduce neurodevelopmental impairment in childhood.

There was no effect of oral dextrose gel on the risk of hypoglycaemia in this sub-study. Previously, prophylactic dextrose gel in babies at-risk of neonatal hypoglycaemia was found to reduce the risk of hypoglycaemia (Hegarty et al., 2016). There may have been differences in rates of hypoglycaemia that were not detected due to intermittent rather than continuous monitoring of BGC. 39% of infants developed hypoglycaemia, a rate similar to the 33% in a retrospective study of infants of mothers with diabetes (VanHaltren & Malhotra, 2013), but a lower rate than the 51% reported in at risk infants in the Sugar Babies study (Harris et al., 2012). Intermittent monitoring of BGC misses approximately 80% of episodes of hypoglycaemia compared to continuous interstitial monitoring of glucose concentration (Harris et al., 2010). However, the baseline characteristics were similar in groups so the rate of missed episodes of hypoglycaemia would also be expected to be similar between groups.

Hypoglycaemia in the first 48 hours after birth in IDM was associated with an increased risk of neurosensory impairment at two years' corrected age and a trend towards delayed language development. Children born to mothers with gestational diabetes have previously been identified as having delayed language development compared to controls (Dionne et al., 2008) or Bayley-3rd edition normal values (Tertti et al., 2015), but the association with hypoglycaemia was not explored in these studies. Delayed language development may be related to hearing

deficits as children born to mothers with diabetes are found to have an increased risk of hearing deficits compared to children of non-diabetic pregnancies (J. A. Lee et al., 2020). However, the rate of hearing impairment requiring hearing aids at age two years was less than 1% in this sub-study and therefore it is unlikely that hearing loss contributed to the rate of low language scores. Adverse neurodevelopment associated with hypoglycaemia has been documented in babies born to mothers without diabetes at two to six years of age (Wickström, Skiöld, Petersson, Stephansson, & Altman, 2018) and later at ten years of age, adverse effects on school achievement in literature and mathematics after transient neonatal hypoglycaemia, regardless of the presence or absence of diabetes or other risk factors (Kaiser et al., 2015). Although there was no association between hypoglycaemia and neurosensory impairment in the Children with Hypoglycaemia and Their Later Development (CHYLD) study (McKinlay et al., 2015) at two or four years of age (McKinlay et al., 2017), further detailed information about the glycaemic profile from continuous interstitial glucose measurements showed that either slow or rapid recovery following hypoglycaemia may be associated with worse neurodevelopmental outcomes (Burakevych et al., 2019). This difference between the outcomes reported in the CHYLD study and our study may reflect the increased power of our study with nearly double the number of children assessed.

We found no association of hypoglycaemia with reduced executive function in this group of children born to mothers with diabetes. Hypoglycaemia was associated with increased risk of low executive function at age four and half years, when 477 children were assessed in the CHYLD study. There were differences in the risk factors for hypoglycaemia between the CHYLD cohort and our study, with fewer than half of the 404 children assessed at age two years' corrected age being children of diabetic mothers in CHYLD, while this sub-study was solely of children of diabetic mothers. Adverse neurodevelopmental outcomes at age eight after neonatal hypoglycaemia were also seen in another group born to mothers with diabetes when they were compared to age matched controls from mothers without diabetes (Stenninger et al., 1998). Other studies which have investigated the relationship between neurodevelopment and the plasma glucose concentration after birth in children of diabetic mothers have not found an association, but these studies either only included the plasma glucose concentration in the first two to four hours after birth (Persson & Gentz, 1984) or used a lower blood/plasma glucose concentration threshold to define hypoglycaemia (1.7 mmol/L) (Rizzo et al., 1994). It is possible that children of diabetic mothers may be at higher risk of neurodevelopmental impairment as a result of hypoglycaemia than children with other risk factors for

hypoglycaemia. IDM have higher plasma insulin concentrations during hypoglycaemia than infants with other risk factors (preterm, small or large for gestational age), which may mean there is less alternative cerebral fuel, such as lactate, for the brain's metabolic requirements (Harris, Weston, et al., 2015; Hawdon et al., 1993). While ketones typically remain at low concentrations in neonates in the first 48 hours of life despite hypoglycaemia, lactate may be an important alternative fuel for neurones during hypoglycaemia (Harris, Weston, et al., 2015; Herzog et al., 2013; Maran et al., 2000).

The risk of hypoglycaemia was higher in those infants born to mothers with type 1 or type 2 diabetes compared to those born to mothers with gestational diabetes and in diabetes requiring insulin treatment, a risk factor which was also identified in a retrospective analysis of 576 IDM (Maayan-Metzger, Lubin, & Kuint, 2009). Previous studies have found the risk of neonatal hypoglycaemia is higher in infants of type 1 diabetic mothers compared to those with type 2 diabetes (Kline & Edwards, 2007; Owens et al., 2015) and that in infants of women with gestational diabetes hypoglycaemia was more likely if the mother required insulin during her pregnancy (Balsells et al., 2000). Insulin is used in all cases of type 1 diabetes and many cases of type 2 or gestational diabetes, so insulin treatment may simply reflect the proportion of women with pre-existing diabetes or could be associated with more variable glycaemic control, which was not measured in this study. The numbers of mothers with type 1 and 2 diabetes were small compared with gestational diabetes so this study was underpowered to detect differences in outcomes related to hypoglycaemia between diabetes types. There was also a high proportion of children of Māori, Pacific Island and Asian ethnicity in this study. The risk of gestational diabetes varies with ethnicity with Asian and Pacific mothers at higher risk (Pu et al., 2015; J. K. Silva, Kaholokula, Ratner, & Mau, 2006). Gestational and type 2 diabetes are also associated with overweight and obesity, which is more prevalent in Māori and Pacific ethnic groups (Ministry of Health, 2019).

There was a reduced risk of low executive function scores in children who were randomised to gel B when children with other events or diagnoses that might affect neurodevelopmental outcomes were excluded from the analysis. Executive function tasks in this follow-up study assessed attention, inhibition, working memory and cognitive flexibility. These are complementary to the parent rated scales of executive function in everyday context, which were assessed using the BRIEF-P questionnaire and were similar between diabetes types and in the presence or absence of neonatal hypoglycaemia. Executive function is associated with

academic achievement (Bull et al., 2008) and lower scores have previously been shown to be associated with hypoglycaemia (R. Shah et al., 2019). However, these skills are still evolving at age two years and the CHYLD study found no association of low executive function scores with hypoglycaemia at follow-up aged two years (McKinlay et al., 2015) but there was an association between severe and recurrent hypoglycaemia and lower executive function scores at age four and half years (McKinlay et al., 2017). If gel B was oral dextrose gel, then dextrose gel prophylaxis may be protective against parameters of glycaemic stability such as longer duration of hypoglycaemia. If gel B was placebo, the implication might be that dextrose gel was somehow mediating an adverse effect, perhaps through a more rapid rise in BGC. Instability in BGC with more excursions including both hypoglycaemia and hypoglycaemia has been demonstrated to be associated with poorer neurodevelopmental outcomes in preterm infants (Tottman, Alsweiler, Bloomfield, Pan, & Harding, 2017). In a study of at risk infants in whom interstitial glucose concentrations and BGC were measured over the first 48 hours of life, the response after hypoglycaemia was associated with neurodevelopmental outcome; those infants with either the fastest or slowest glucose responses after hypoglycaemia were at higher risk of adverse outcomes (Burakevych et al., 2019). Finally, the observed differences in executive function scores between children receiving gel A and B could be a type 1 error.

A strength of this study is the large number of participants and high follow up rate (86%) reducing the chance of missing adverse outcomes as participants not followed up are more likely to have worse outcomes than participants who are followed up (Callanan et al., 2001; McKinlay et al., 2017). This study includes a larger number of children than previously published studies of children born to diabetic mothers, prospectively followed up and comprehensively assessed for later neurodevelopmental and health outcomes. We used parent reported and objective tests of executive function as well as the standardised Bayley, 3rd edition developmental scales of infant development in order to detect more subtle measures of neurodevelopmental impairment.

The hPOD trial protocol (Harding, Hegarty, et al., 2015) was for all infants to be monitored for hypoglycaemia at two hours of age then according to local guidelines using suitable analysers such as iSTAT (Abbott Laboratories, Abbott Park, IL USA) or a combined metabolite/blood gas analyser (e.g. ABL 700, Radiometer Ltd, Copenhagen, Denmark). These analysers use the gold standard glucose oxidase method rather than less accurate point of care methods, which makes the diagnosis of hypoglycaemia reliable.

A limitation of this study is the blinded nature of analysis, necessary due to ongoing follow up of the remaining cohort. Follow up of the remaining participants will increase the power to detect differences in later neurodevelopmental outcomes. We performed multiple analyses, increasing the risk of introducing a type 1 error, but the focus was on the primary outcome, neurosensory impairment. The majority of mothers in this study had gestational diabetes and therefore the results reflect predominantly children born to mothers with gestational diabetes rather than pre-existing diabetes.

6.5 Conclusion

The ongoing hPOD follow-up study is evaluating the health and neurodevelopment of children born at risk of neonatal hypoglycaemia. This sub-study describes the results of the evaluation of children of diabetic mothers, who were assessed by the end of February 2020. The risk of neurosensory impairment at two years of age in children born to diabetic mothers was high and was associated with hypoglycaemia in the first 48 hours after birth. However, prophylactic oral dextrose gel given to IDM did not affect their risk of hypoglycaemia nor their risk of later neurosensory impairment. Longitudinal follow-up of children of diabetic mothers in the hPOD study is important to detect differences in outcomes that may become apparent as children's neurodevelopment evolves. Further research is needed to develop effective strategies, both antenatal and postnatal, to improve neurodevelopmental outcomes in children born to diabetic mothers.

7 Discussion

The incidence of diabetes in pregnancy is rapidly increasing (Goldenberg et al., 2016; Zhu & Zhang, 2016) due to an increase in the incidence of type 2 diabetes (J. M. Lawrence, Contreras, Chen, & Sacks, 2008) and GDM (Lavery, Friedman, Keyes, Wright, & Ananth, 2017) associated with the obesity epidemic. Estimates of global prevalence suggest diabetes during pregnancy occurs in 16% of live births (Ogurtsova et al., 2017) with obesity strongly associated with a higher risk of GDM (Chu et al., 2007). The perinatal risks for children born to mothers with diabetes during pregnancy include being born large for gestational age (Sacks et al., 2015) with associated risk of birth injury, respiratory distress syndrome, jaundice, and hypoglycaemia in the neonatal period (Crowther et al., 2005; González-Quintero et al., 2007; Landon et al., 2009). The neurodevelopment of children born to mothers with diabetes during pregnancy is more likely to be adversely affected than children born to healthy mothers (DeBoer et al., 2005; R.-A. DeRegnier, Long, Georgieff, & Nelson, 2007; C. A. Nelson et al., 2003), although this finding is not consistent (Ornoy et al., 1998; R. C. Temple et al., 2011).

The studies in this thesis were designed to determine if: i) antenatal interventions reduce the incidence of GDM; ii) glycaemic control in pregnancy is associated with neurodevelopmental outcomes; and iii) postnatal prophylaxis with oral dextrose gel in babies with risk factors, including babies born to diabetic mothers, improves neurodevelopmental outcomes.

7.1 Prevention of GDM

Our Cochrane overview of interventions to prevent GDM included 11 relevant Cochrane systematic reviews, with data from 71 trials which enrolled over 23,000 women. Despite the large numbers of women and trials there was insufficient high-quality evidence to identify any interventions of clear benefit in reducing GDM. Interventions during pregnancy that were found to be of possible benefit included a combination of diet and exercise, myo-inositol, vitamin D supplementation and metformin in overweight or obese women, but further trials are needed to clarify their effect. Surprisingly, none of the trials included in the reviews had data for interventions prior to or between pregnancies for the prevention of GDM. The earlier diet and exercise interventions are introduced during pregnancy, the greater the reduction in risk of GDM (Guo et al., 2018). Furthermore, observational studies demonstrate an association of regular reported exercise pre-conception with a reduced risk of GDM (Dempsey et al., 2004;

Oken et al., 2006; Redden, LaMonte, Freudenheim, & Rudra, 2011; Zhang, Solomon, Manson, & Hu, 2006). A combination of diet and exercise (Hemmingsen et al., 2017) or metformin (Madsen et al., 2016) are of benefit in reducing or delaying the risk of developing type 2 diabetes in people with impaired glucose tolerance. Therefore, it would be expected that the same interventions might be of benefit in reducing the risk of GDM if instigated prior to conception. Pre-conception trials are likely to be challenging as the outcome of GDM in a future pregnancy may not occur for months to years and even then, not in all participants, and it is difficult to find funding and recruit to such long-term trials. However, the potential benefits make such trials worth the effort, and they are certainly possible. For example, pre-conception supplementation with folic acid has been demonstrated to reduce the incidence of neural tube defects (De-Regil, Peña-Rosas, Fernández-Gaxiola, & Rayco-Solon, 2015). In order to make recruitment to a pre-conception randomised controlled intervention trial attractive to potential participants, a multi-arm trial could be considered with diet, exercise or combination interventions compared to standard care so that participants have a 3:1 chance of an intervention. In addition, the trial could invite women with a previous pregnancy complicated by GDM to participate in a randomised trial of an intervention to reduce the incidence of GDM before her next pregnancy. Pre-intervention details of diet and exercise at baseline should be documented and repeated at regular intervals during the trial to record compliance. Follow-up will need to be of adequate duration to document future pregnancy outcomes, and ideally, neurodevelopment of the offspring. Additional outcomes not related to pregnancy could also be included as other benefits to health may be anticipated such as weight loss in those women who were overweight or obese at baseline.

The Cochrane collaboration aims to update reviews when new and relevant information becomes available that might change the findings or credibility in order to maintain the accuracy of the sum of available evidence (Cumpston & Handler, 2020). There were eight reviews in our overview that had been published more than three years earlier, thus potentially missing recent trials that might have altered the strength of evidence in individual reviews. Recently published randomised controlled trials investigating the effect of myo-inositol in preventing GDM that were not included in the overview have found that a low dose of myo-inositol (1.1 g per day) in women with a family history of diabetes had no effect on the risk of GDM (Farren et al., 2017) while 2 g per day of myo-inositol in overweight women reduced the risk of GDM, (Santamaria et al., 2016) raising the possibility that women with specific risk factors may benefit from myo-inositol. Two recent non-Cochrane systematic reviews of diet,

exercise or a combination intervention concluded that there was reduction in GDM risk in higher risk groups (Guo et al., 2018) and in different world regions (Bennett et al., 2018). In order to maintain the accuracy of the Cochrane systematic reviews, authors should update according to Cochrane guidance if significant trials are published that alter findings. Subsequently, our Cochrane overview search should be updated within two years in order to detect new data from ongoing and future trials that have been included in systematic reviews, and that might therefore necessitate an update of the overview.

There is now an agreed set of core outcomes for trials investigating interventions to prevent or treat GDM (Egan et al., 2020). The Cochrane overview of treatments for GDM included 18 short and long term maternal, child and health service outcomes (Martis et al., 2018). These multiple outcomes are relevant as they are all complications associated with GDM. The initial published protocol for our overview also included many of these outcomes (R. L. Lawrence et al., 2016). However, as our overview focussed on preventing GDM we changed the protocol to a predefined single outcome of GDM and chose not to include additional outcomes related to the effects of GDM. This was a similar approach to that used in other Cochrane overviews on prevention, including the Cochrane overview on prevention of cerebral palsy (E. Shepherd, Salam, et al., 2017). While it would be useful to determine if preventing GDM reduced the incidence of complications of GDM such as preterm birth, this was not within scope of the overview. If preterm birth had been included as an outcome 70 systematic reviews which included preterm birth as an outcome would have met the inclusion criteria, many with no relevance to GDM (Medley et al., 2018). However, there may be an argument for including additional outcomes in order to detect possible adverse effects of interventions, as was done in the overview on prevention of preterm birth which included preterm birth but also perinatal death as outcomes (Medley et al., 2018). Consideration of future updates of this overview should include possible adverse outcomes such as perinatal death.

There were several potential sources of bias in some randomised controlled trials included in the overview. Some trials limited testing for GDM to women who had risk factors such as prior GDM, macrosomia in a previous baby, higher maternal age, being overweight, or a family history of diabetes. The Cochrane systematic review on the use of probiotics with or without dietary advice included one trial in which only higher risk women were tested for GDM (Raakel Luoto et al., 2010). By testing only high-risk women, selection bias is introduced because the reduction in risk, if any, may be greater in participants with risk factors for GDM. Moreover,

this approach may miss up to half of the women with GDM (Östlund & Hanson, 2003). Future trials of interventions to prevent GDM should be adequately powered and test all participating women for GDM. Furthermore, in trials of vitamin D supplementation, the baseline serum vitamin D concentration should be recorded, as it is possible that treating vitamin D deficiency may be of benefit, but supplementing those with normal serum vitamin D concentrations may have less effect (Sablok et al., 2015). Obesity, skin tone and sun exposure can influence vitamin D metabolism (Arunabh, Pollack, Yeh, & Aloia, 2003), so women with a range of BMI, of different ethnicities and living in different regions of the world should be included in a multi-centre trial to define who might benefit from vitamin D supplementation.

7.2 The association of maternal glycaemic control with offspring neurodevelopment

The children of mothers with diabetes who were followed up in the CHYLD study had a high rate of neurosensory impairment at age four and a half years (41%). However, neurosensory impairment was not associated with maternal glycaemic control during pregnancy, as assessed by HbA1c in the second and third trimesters, the 1-hour polycose result, or the proportion of BGC in the range 4-7 mmol/L in the six hours prior to birth. This lack of association between maternal glycaemic control and neurosensory impairment may be because maternal glycaemic control in women with GDM truly has no effect on the neurodevelopment of offspring. Alternatively, it may be that these measurements are not adequate indicators of glycaemic control relevant to neurodevelopmental outcomes. Previously, associations have been observed between aspects of offspring neurodevelopment and maternal HbA1c (Ratzon et al., 2000) and second and third trimester beta-hydroxybutyrate concentrations (Rizzo et al., 1995). However, contrary results have also been seen with no association between HbA1c in the first, second or third trimesters and offspring cognitive function age 13 to 19 years (Bytoft et al., 2016), or between third trimester beta-hydroxybutyrate concentrations and IQ at age two to five years in children born to mothers with pre-existing diabetes, GDM and no diabetes (Rizzo et al., 1994). Another possible reason the 1-hour polycose result was not associated with neurosensory impairment is that the 1-hour polycose and the oral glucose tolerance tests standardise the carbohydrate load given and the response to this load, but may not reflect the real life response to varied dietary components (Hou et al., 2015; Musa-Veloso, Poon, Harkness, O'Shea, & Chu, 2018). Post-prandial blood or plasma glucose concentrations may be more representative glycaemic parameters to explore in relation to offspring neurodevelopment.

The proportion of blood glucose results within 4-7 mmol/L in the 6 hours before birth was not associated with the risk of neurosensory impairment nor neonatal hypoglycaemia in our study, but the frequency and timing of maternal testing was irregular. It is possible that more regular and frequent testing as recommended by the British (National Institute for Health and Care Excellence, 2015) and Australasian guidelines (McElduff et al., 2005) may demonstrate a relationship between maternal blood glucose results in the 6 hours before giving birth and neonatal hypoglycaemia as the results would give a more accurate glycaemic profile with more potential to accurately determine the proportion of time the BGC were in range. The recent TARGET trial randomised woman with GDM to tighter glycaemic targets or standard targets to assess the effect of size at birth and perinatal morbidity (Crowther, Alsweiler, Hughes, & Brown, 2018), and follow-up of the offspring at 4.5 years is currently under way. The results of this trial will give vital data on whether tighter glycaemic control in GDM pregnancies improves offspring neurosensory impairment. In addition, assessment at age nine years is underway for participants in the CHYLD study. This later evaluation of school academic performance in these children may give a clearer indication of any effect of maternal diabetes on neurodevelopment at this age in comparison to other risk groups in the study.

7.3 The effect of prophylactic oral dextrose gel on early childhood neurodevelopment

The pre-hPOD and hPOD follow-up studies were designed to determine if there was an effect of prophylactic oral dextrose gel in babies born at risk of developing hypoglycaemia on later neurodevelopment. Children born at risk of neonatal hypoglycaemia have an increased risk of adverse neurodevelopmental outcomes compared those without documented hypoglycaemia (R. Shah et al., 2019). The majority of episodes of hypoglycaemia in IDM occur within 12 hours of birth (Voormolen et al., 2018) and even one episode of hypoglycaemia is associated with worse school performance (Kaiser et al., 2015) so waiting to treat hypoglycaemia may be too late to prevent harm. Prophylactic oral dextrose gel previously had been found to reduce the risk of neonatal hypoglycaemia in the pre-hPOD study (Hegarty et al., 2016). Therefore, we hypothesised that prophylaxis with oral dextrose gel may reduce the incidence of neurosensory impairment.

However, prophylactic oral dextrose gel did not improve neurodevelopment at age two years in the pre-hPOD dosage trial in babies with a range of risk factors for hypoglycaemia. The pre-hPOD trial was powered to detect a reduction in the incidence of hypoglycaemia, and was underpowered to detect small differences in neurodevelopmental outcomes. Therefore, there may have been a type 2 error. While we found trends towards improved executive function in association with increasing total dose or multiple doses of dextrose, and improved language composite scores and fewer abnormalities of tone and co-ordination in association with increasing total dose of dextrose, these were not statistically significant, and further research is needed to determine if these relationships are clinically significant. The six-year follow-up of the pre-hPOD cohort is currently underway and will examine the effect of prophylactic oral dextrose gel on later neurodevelopment, with later follow-up being more likely to detect adverse outcomes in these neurodevelopmental domains (Brosig et al., 2018; McKinlay et al., 2017; R. Shah et al., 2019).

There was also no effect of prophylactic oral dextrose gel on hypoglycaemia or neurodevelopmental outcomes at 2 years of age in children born to mothers with diabetes (hPOD sub-study). It is unclear why the same reduction in risk of hypoglycaemia seen in the pre-hPOD trial (Hegarty et al., 2016) was not seen in our sub-study of children of mothers with diabetes. The original pre-hPOD trial reported hypoglycaemia based on intermittent monitoring of blood or plasma glucose concentrations which may miss up 81% of episodes of hypoglycaemia as these episodes may be shorter that the testing frequency (Harris et al., 2010). Analysis of the continuous interstitial glucose monitoring data collected during the pre-hPOD trial (Hegarty et al., 2016) may provide additional data on whether prophylactic dextrose gel prevents transient episodes of low interstitial glucose concentrations. Moreover, our sub-study only examined children of diabetic mothers, while the pre-hPOD trial included all babies at risk of neonatal hypoglycaemia. It is possible that the dose of dextrose gel chosen for the hPOD trial may not been sufficient or that the intervention was not early enough to prevent hypoglycaemia in IDM who have higher plasma insulin and lower ketone concentrations, an alternative cerebral fuel, than other risk groups (Harris, Weston, et al., 2015). Follow-up of the 2149 children in the main hPOD trial will determine if prophylactic oral dextrose gel improves executive function or neurodevelopmental impairment in children with different risk factors for neonatal hypoglycaemia and in particular in children of diabetic mothers.

We used the commonly accepted threshold for hypoglycaemia of a BGC < 2.6 mmol/L, based on evidence that abnormal evoked potentials in neonates and infants do not occur if the BGC is maintained above this threshold (Koh, Aynsley-Green, et al., 1988) and that the risk of low motor and mental developmental scores in children born preterm increases with increasing number of days with episodes below this threshold (Lucas et al., 1988). However, recent evidence from the Glucose in Well Babies (GLOW) study suggests that many healthy term infants also develop BGC < 2.6 mmol/L (Harris et al., 2020). It may be that a combination of hypoglycaemia and also other "high risk" conditions, such as preterm birth or being SGA or born to a mother with diabetes, is associated with the adverse neurodevelopmental outcomes rather than hypoglycaemia alone. In at-risk infants, there are low concentrations of ketones associated with hypoglycaemia in the first 48 hours and also, in some babies, inadequate lactate as an alternative cerebral fuel source (Harris, Weston, et al., 2015). Healthy term babies might have different profiles of lactate and ketones in the context of hypoglycaemia compared with at risk-infants, thus potentially altering their risk of adverse neurodevelopmental outcomes. The follow-up of participants in the GLOW study may indicate if asymptomatic hypoglycaemia in healthy term infants is also associated with adverse neurodevelopment, but larger numbers would be required to detect small differences in outcomes.

In IDM, neonatal hypoglycaemia was associated with an increased risk of neurosensory impairment. Our study is the largest to date to report prospectively collected data on hypoglycaemia and long-term neurodevelopmental outcomes for children born to mothers with diabetes. Previous studies with prospective (Haworth et al., 1976) or retrospective (Stenninger et al., 1998) data for IDM included very small numbers (37 and 56 infants respectively). Both studies had lower thresholds for defining hypoglycaemia and results were conflicting. The prospective study reported no association between hypoglycaemia (≤ 1.1 mmol/L in SGA or ≤ 1.7 mmol/L in appropriate weight infants) and abnormal developmental quotient or neurological examination at four and a half years of age (Haworth et al., 1976), but the retrospective study reported that neonatal hypoglycaemia (< 1.5 mmol/L) was associated with adverse neurodevelopment at 8 years of age (Stenninger et al., 1998). More recently, neither the CHYLD study (McKinlay et al., 2015) nor the pre-hPOD follow-up study (Chapter 6) found an association between neonatal hypoglycaemia and neurodevelopmental impairment at two years' corrected age, although there was an association between neonatal hypoglycaemia and executive function later, at four and a half years of age (McKinlay et al., 2017). However, both studies included children with other risk factors for hypoglycaemia. Studies with preterm birth

as the risk factor for hypoglycaemia have also found contrasting results. One study of 543 preterm infants found there was an association between neonatal hypoglycaemia and adverse neurodevelopmental outcomes at 18 months of age (Lucas et al., 1988), whereas studies of 543 and 743 preterm infants found no increase in risk of adverse neurodevelopment associated with hypoglycaemia at three to 18 years of age (Goode et al., 2016; Tin, Brunskill, Kelly, & Fritz, 2012). Our finding in this large sub-study that hypoglycaemia is associated with higher risk of adverse neurodevelopment in children born to mothers with diabetes is important. It suggests that poor neurodevelopmental outcomes following a diabetic pregnancy may be modifiable if the risk of hypoglycaemia can be reduced by interventions either during pregnancy or postnatally. However, the mothers of IDM at higher risk of neonatal hypoglycaemia were more likely to require insulin treatment compared to dietary or metformin treatment. Thus, it is also possible that neonatal hypoglycaemia is a marker for diabetes severity in the mother, and not an independent risk factor for neurodevelopmental impairment. However, this finding was in contrast to another prospective cohort of 506 infants which found no difference in risk of neonatal hypoglycaemia between infants born to mothers requiring insulin compared to those with dietary control (Voormolen et al., 2018). The analysis of the data from the hPOD 2-year follow-up study, once completed, is expected to include approximately 1500 participants born to mothers with diabetes and will provide additional data on the association between hypoglycaemia in infants born to mothers with diabetes and adverse neurodevelopmental outcomes.

The rates of neurosensory impairment varied in our cohorts (41% CHYLD, 19% pre-hPOD, 23% hPOD). There are several possible reasons for this. Firstly, neurosensory impairment was defined differently between the studies: executive function was included in the primary outcome for the hPOD follow-up while in the pre-hPOD follow-up study it was a separate co-primary outcome and in the CHYLD study it was a component of the processing difficulty co-primary outcome. Including executive function in the definition of neurosensory impairment in the hPOD sub-study may have led to a higher rate of neurosensory impairment. Executive function, along with motion coherence threshold, contributed to the outcome of processing difficulty in the CHYLD study, but motion coherence thresholds were not included in the primary outcome in the pre-hPOD or hPOD follow-up studies. This was due to most of the pre-hPOD and hPOD assessments being done at the participant's home, rather than the controlled study environment that was used for CHYLD, making it difficult to collect standardised motion coherence data. Secondly, although socioeconomic status (using the New Zealand Deprivation

Index (NZDPI) as marker) was similar for participants in each of the studies, the CHYLD study had more participants from rural settings and different ethnic proportions, including a higher incidence of Māori children, typically associated with lower socioeconomic status, which may not be adequately reflected by the NZDPI. Socioeconomic factors are a strong influence of children's intellectual development (Heikura et al., 2007). Thirdly, our CHYLD and hPOD sub-group studies only included IDM while the pre-hPOD cohort also included infants who were small or large for gestational age or late preterm. However, the pre-hPOD and hPOD cohorts had similar rates of neurosensory impairment suggesting that risk factor did not influence outcomes. Finally, the CHYLD follow-up was at four and half years, while the pre-hPOD and hPOD assessments were done at two years' corrected age. Although some aspects of adverse neurodevelopment become more apparent by the later age (Brosig et al., 2018; R. Shah et al., 2019), the rates of neurosensory impairment were similar (36%) at two years of age in the CHYLD study (Harris et al., 2016) to the rates at four and half years of age. A limitation in all three follow-up studies was the lack of control groups, so the rate of neurosensory impairment using these definitions in the general population in New Zealand and Australia is unknown. Unfortunately, funding was not available to recruit a control cohort for these studies, but a useful adjunct would be the longitudinal assessment of a control group in order to determine the rates of neurosensory impairment, its components and school performance in a comparison population not exposed to maternal diabetes or other risk factors for neonatal hypoglycaemia.

7.4 Practice Implications

There is insufficient evidence to support changes in clinical practice for the pre-conception or antenatal care of women at risk of GDM or with diabetes.

Although prophylactic oral dextrose gel can reduce the risk of hypoglycaemia in some infants, further data on the effect on later neurodevelopment are required before this should be considered for introduction into clinical practice.

7.5 Future research directions

Further research is needed to develop effective strategies, both antenatal and postnatal, to improve neurodevelopmental outcomes in children born to diabetic mothers. Myo-inositol supplementation, a combination of diet and exercise, metformin in overweight or obese women, and vitamin D supplementation are all interventions during pregnancy that might

reduce the risk of GDM, but further trials are needed to clarify their effect. Trials are also needed of interventions before or between pregnancies. Multi-arm, multi-centre trials comparing several different interventions against routine care should be considered in order to improve interest in recruitment and obtain sufficient high quality data to identify effective interventions for preventing GDM. Such trials could be directed at women with a history of GDM or known risk factors for GDM in the first instance.

The glycaemic markers we investigated may not be the best measures of glycaemic control during pregnancy and other glycaemic markers such as fasting and post prandial BGC, and HbA1c at regular intervals during pregnancy should be explored in relation to offspring neurodevelopmental outcomes with adjustment for socioeconomic factors, maternal adiposity, infant gestation and sex. There were no adverse effects of using prophylactic oral dextrose gel, but no benefits evident at age 2 years. The results of the ongoing hPOD 2-year follow-up and the later pre-hPOD and hPOD 6-year follow-up studies will add further information on the long-term effects of prophylactic oral dextrose gel. The current Cochrane systematic review of oral dextrose gel to prevent hypoglycaemia in at risk infants (Hegarty, Harding, Crowther, Brown, & Alsweiler, 2017) needs updating with the neonatal and long term neurosensory development results of the pre-hPOD and neonatal results of the hPOD studies.

7.6 Summary

Our studies suggest that firstly, children born following a pregnancy complicated by GDM are at high risk of neurosensory impairment. This does not appear to be associated with maternal glycaemic control in pregnancy or labour based on the indicators available. Secondly, neonatal hypoglycaemia in infants born to mothers with GDM is associated with neurosensory impairment. While these findings suggest that interventions to prevent either GDM or hypoglycaemia may improve neurodevelopmental outcomes our overview demonstrated that there currently are no known effective interventions to reduce the risk of GDM in pregnant women. Thirdly, prophylactic oral dextrose gel, while previously having been shown to reduce the incidence of hypoglycaemia in at-risk babies, did not prevent hypoglycaemia in our cohort of IDM and did not reduce the incidence of neurosensory impairment. These findings demonstrate that antenatal intrapartum and postnatal interventions individually may not be enough to improve neurosensory outcomes in children born following a pregnancy complicated

by GDM. The focus should shift to pre-conception interventions to prevent women developing GDM in order to improve the neurodevelopmental outcomes of their children.

8 Appendix

8.1 Cochrane overview additional tables

Table 8.1 Ongoing reviews

Protocol citation	Pre-specified outcome in protocol
Bergamaschi DP, Mariath AB, Abbade JF, Grillo LP, Diniz CSG, Hinnig PF. Selenium supplementation during pregnancy for improving maternal and newborn outcomes. Cochrane Database of Systematic Reviews 2012, Issue 3.	Secondary pre-specified outcomes include GDM.

Table 8.2 Reviews awaiting further classification

Review citation	Overview of pre-specified outcomes in review with no outcome data	Main conclusion(s) of review
Showell MG, Mackenzie-Procter R, Jordan V, Hodgson R, Farquar C. Inositol for subfertile women with polycystic ovary syndrome. Cochrane Database of Systematic Reviews 2018, Issue 12.	No data in included trials on GDM. Secondary outcomes include GDM.	"Based upon very low-quality evidence, we are uncertain whether MI improves live birth rate or clinical pregnancy rate for subfertile women with PCOS undergoing IVF pre-treatment by taking MI versus standard treatment. We are also uncertain whether MI decreases miscarriage rates or multiple pregnancy rates for these same women taking MI compared to standard treatment. No pooled evidence is available for the use of MI compared to placebo, another antioxidant, insulin-sensitising agents, ovulation induction agents, or another type of inositol for women with PCOS undergoing pre-treatment for IVF. Also, no pooled evidence is available on the use of MI among women undergoing ovulation induction. We need trialists to further investigate this question using better-quality placebo-controlled blinded randomised trials with adequate power to assess the clinically relevant outcomes of live birth, adverse events, and clinical pregnancy and ovulation rates, to determine the efficacy and safety of inositol. We need this research to encompass both women with PCOS who are undergoing pre-treatment for IVF and women with PCOS who are undergoing ovulation induction. We also need large, good quality randomised controlled trials to compare inositol versus another antioxidant, another type of inositol (D-chiro-inositol), insulin-sensitising agents, and ovulation induction agents."
Tieu J, Coat S, Hague W, Middleton P, Shepherd E. Oral anti-diabetic agents for women with established diabetes/impaired glucose tolerance or previous gestational diabetes planning pregnancy, or pregnant women with pre-existing diabetes. Cochrane Database of Systematic Reviews 2017, Issue 10.	No data in included trials on GDM. Primary outcomes include GDM.	"There is currently insufficient evidence to evaluate the use of oral anti-diabetic agents in women with established diabetes, impaired glucose tolerance or previous gestational diabetes planning a pregnancy or pregnant women with pre-existing diabetes. Low- to very low-quality evidence suggests possible reductions in pregnancy-induced hypertension, caesarean section birth and neonatal hypoglycaemia with metformin (an oral anti-diabetic agent) compared with insulin in pregnant women with type 2 diabetes, and no clear differences in pre-eclampsia, induction of labour or babies who are large-for-gestational age. Therefore, decisions about the use of oral anti-diabetic agents for these women will probably depend on factors such as women's preferences, available resources, and local or national clinical practice guidelines. Despite limited evidence of the effects of oral anti-diabetic agents for women included in this review, the potential benefits relating to women's acceptability and adherence with oral anti-diabetic agents suggest that further evidence is required. Large, high-quality randomised controlled trials are required to evaluate the effects of oral anti-diabetic agents in women with established diabetes, impaired glucose tolerance, or previous gestational diabetes who are planning a pregnancy and pregnant women with pre-existing diabetes. In particular, trials could compare oral anti-diabetic agents with insulin or dietary and lifestyle control, and compare different oral anti-diabetic agents. Trials could attempt to collect and report on the standard outcomes suggested in this review, such as short-term maternal and infant outcomes including glycaemic control parameters and women's views, long-term maternal and infant outcomes, and outcomes relating to the use and costs of health services. We have identified three ongoing studies, and four are awaiting classification. We will consider these in the next update of this review."

Tieu J, Shepherd E, Middleton P, Crowther CA. Interconception care for women with a history of gestational diabetes for improving maternal and infant outcomes. Cochrane Database of Systematic Reviews 2017, Issue 8.	No trials identified. Primary outcomes include GDM.	The role of inter-conception care for women with a history of GDM on maternal and infant health outcomes remains unclear. Research should be conducted to investigate the effects of inter-conception care for women with a history of GDM on health outcomes for mothers and their infants. Although such trials are faced with difficulties in identifying women in this time period between pregnancies, women with a history of GDM do represent a population at risk for potentially reversible poor health outcomes. Trials should consider the role of different forms of intervention including dietary, lifestyle and pharmacological therapies, in addition to the duration of such interventions. Such trials should not only evaluate the effects on maternal and infant health outcomes, but also the acceptability and cost-effectiveness, to enable translation to clinical practice. Furthermore, future research should focus on long-term follow-up, evaluating the effects of such interventions on the long-term health outcomes associated with GDM for both mothers and their infants."
Opray N, Grivell RM, Deussen AR. Directed preconception health programs and interventions for improving pregnancy outcomes for women who are overweight or obese. Cochrane Database of Systematic Reviews 2015, Issue 7.	No trials identified. Secondary outcomes include GDM.	"As there is no current evidence from randomised controlled trials to support which, if any, preconception interventions are likely to have a beneficial impact on pregnancy outcomes for overweight and obese women, no conclusions to inform practice can be made at this time. The absence of randomised controlled trials relating to preconception interventions for overweight and obese women to improve pregnancy outcomes reveals an area where further research is required. With increasing numbers of women of reproductive age becoming overweight or obese (Callaway 2006; Vahration 2009), more understanding is required about how to best approach and intervene in the preconception period."
Jahanfar S, Jaafar SH. Effects of restricted caffeine intake by mother on fetal, neonatal and pregnancy outcomes. Cochrane Database of Systematic Reviews 2015, Issue 6.	No data in included trials on GDM. Secondary maternal outcomes include GDM.	"Little evidence is available from the one included randomised controlled trial (RCT) that contributed data for our prespecified outcomes to evaluate the effect of caffeine on fetal, neonatal and maternal outcomes. However, the included trial did not evaluate all of the prespecified outcomes from our review protocol. There is a need for high-quality, properly designed RCTs in this field. Proper randomisation, adequate allocation concealment, blinding of outcome assessors, participants and data analysts and clear attrition policies are crucial to ensure appropriate comparisons between caffeinated and decaffeinated groups. Various outcome measurements including fetal and maternal outcomes should be considered in future studies. We recommend a comprehensive RCT to investigate all of the primary and secondary outcomes suggested in our review protocol."

Middleton P, Crowther CA. Reminder systems for women with previous gestational diabetes mellitus to increase uptake of testing for type 2 diabetes or impaired glucose tolerance. Cochrane Database of Systematic Reviews 2014, Issue 3.	No data in included trial on GDM. Secondary outcomes include GDM in subsequent pregnancy.	"While only one trial fulfilled our inclusion criteria and the overall quality of evidence was low, it showed that postal reminders increased the uptake of testing for type 2 diabetes in women with previous gestational diabetes (GDM). Other forms of reminder systems (e.g. email and telephone reminders) could potentially be effective, although our review was not able to compare these approaches due to lack of studies. The number of women diagnosed with GDM is projected to rise due to expected increases in BMI and maternal age, as well as possible changes to diagnostic thresholds, so healthcare systems will require effective postpartum reminder and diabetes screening programmes. The effects of other forms of reminder systems need to be assessed to see whether test uptake is also increased when email and telephone reminders are deployed. We also need a better understanding of why some women fail to take opportunities to be screened postpartum. As the ultimate aim of increasing postpartum testing is to prevent the subsequent development of type 2 diabetes, it is important to determine whether increased test uptake rates also increase women's use of preventive strategies such as lifestyle modifications."
Jeffreys AE, Siassakos D, Draycott T, Akande VA, Fox R. Deflation of gastric band balloon in pregnancy for improving outcomes. Cochrane Database of Systematic Reviews 2013, Issue 4.	No trials identified. GDM primary outcome.	"At present, there is no evidence to favour either elective deflation or maintaining gastric band balloon inflation in pregnancy. This lack of evidence is reflected in the wide variation in management of the gastric band in pregnancy which is seen in observational studies (Carelli 2011; Dixon 2001; Dixon 2005; Lapolla 2010; Sheiner 2009). Management decisions regarding band status in pregnancy should continue to be made according to the clinical context. Maternal weight at the beginning of pregnancy, nausea and vomiting, tolerability of the band, gestational weight gain, fetal growth, maternal wishes, and pregnancy complications should probably all be taken into account, but this review has not produced evidence to guide practice. Issues surrounding management of the gastric band should be discussed with women who should be involved in management decisions. Close surveillance of both mother and fetus should continue throughout pregnancy to identify any complications at an early stage (Guelinckx 2009). Effective care requires communication between all members of the multidisciplinary team including obstetricians, bariatric surgeons, bariatric physicians, dieticians and midwives. As the prevalence of obesity is predicted to rise, so too the incidence of pregnancies following laparoscopic adjustable gastric banding is likely to increase. As the optimal management of women with a gastric band in pregnancy is unknown, there is a need for further research in this area to guide clinicians and pregnant women. This review supports the need for a randomised controlled trial in the area. A systematic review of observational studies could improve our understanding of gastric band management and help to design a randomised controlled trial. A randomised controlled trial would need to have three comparison arms to reflect current practice; elective deflation of the band balloon at the beginning of pregnancy, intention to leave the balloon inflated for the duration of pregnancy, and deflation of the balloon at the beginning of pregnancy with re inflation during the second trimester. Outcome measures should mirror those we intended to assess in this review, as they are both clinically important and meaningful to clinicians and patients (outcomes were selected as important for this review by a Maternity Service User Panel). Such a randomised controlled trial would need to be sufficiently powered to detect differences in primary maternal and perinatal outcomes for different forms of band management. Any bias should be minimised by adequate randomisation using random sequence generation, concealment of allocation to participants, study personnel and outcome assessors.

Furber CM, McGowan L, Bower P, Kontopantelis E, Quenby S, Lavender T. Antenatal interventions for reducing weight in obese women for improving pregnancy outcome. Cochrane Database of Systematic Reviews 2013, Issue 1.	No trials identified. Secondary maternal outcomes include GDM.	"It is interesting to note from observational cohort studies that obese pregnant women may lose weight and have better outcomes than those who gain weight within recommended guidance, especially those who are morbidly obese. However weight loss in morbidly obese pregnant women does not eliminate risks associated with pregnancy (Hinkle 2010; Beyerlein 2011; Blomberg 2011). These observational studies indicate that the impact of weight loss when obese and pregnant are complex, and also variable across obese categories. Although there may be lesser likelihood of pre-eclampsia, caesarean birth and a large for gestational age fetus at term, the potential for increased risk of small-for-gestational age infants indicates that weight loss when pregnant and obese is not without risk. More robust evidence of the outcomes of weight loss when pregnant and obese across obesity categories is required so that we can confidently understand outcomes, especially those that impact on the neonate. As there is no evidence from randomised controlled trials of interventions during pregnancy that weight loss in obese pregnant women is beneficial, recommendations advocating weight reduction in pregnancy when obese cannot be supported. We suggest that until evidence is available, no practice recommendations can be made. The absence of randomised controlled trials related to reducing weight in obese pregnant women may be a reflection of the lack of evidence from observational cohort studies of the safety of weight loss in this group. There is no robust evidence that indicates the benefits, or harm, of losing weight when obese and pregnant. Until evidence is available, it may not be appropriate to conduct a randomised controlled trial designed to promote weight loss in obese women in pregnancy. Furthermore, it is unlikely that an ethics committee would provide favourable opinion to any such study based on current evidence. More understanding is required of the weight trajectory of obese women during pregnancy. Prospective observational cohort studies of obese women during pregnancy will provide more data that explains weight changes for this group, and short and long term outcomes. Further studies are required to explore the efficacy of the latest guidance from the Institute of Medicine (Blomberg 2011; Rasmussen 2009b), especially as this guidance has not stratified recommendations for weight gain across all obese categories (Artal 2010). Qualitative research will provide more insights into the weight management strategies utilised by obese women during pregnancy, especially those who deliberately lose weight."
Han S, Crowther CA, Middleton P. Interventions for pregnant women with hyperglycaemia not meeting gestational diabetes and type 2 diabetes diagnostic criteria. Cochrane Database of Systematic Reviews 2012, Issue 1.	No data in included trials on GDM. Secondary outcomes include GDM in subsequent pregnancy.	"This review found interventions for women with pregnancy hyperglycaemia not meeting GDM and T2DM diagnostic criteria helped reduce the number of macrosomic and LGA babies. It is important to note that the results of this review were based on four small randomised trials with moderate to high risk of bias without follow-up outcomes for women or their babies. Until additional evidence from large well designed randomised trials becomes available, current evidence is insufficient to make conclusive suggestions on management for women with pregnancy hyperglycaemia not meeting GDM and T2DM diagnostic criteria. Further larger trials with sufficient power to assess the effects of lifestyle intervention and metabolic monitoring on maternal and infant health outcomes are needed. Outcomes such as longer term health outcomes for women and their babies after being managed for pregnancy hyperglycaemia during pregnancy and health service cost should be included."

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