**Study Protocol**

Gestational diabetes mellitus and school-age cognitive outcomes (GIST): a matched cohort study.

**ADMINISTRATIVE INFORMATION**

Full title: Gestational diabetes mellitus and school-age cognitive outcomes: a matched cohort study

Short title: **G**DM and **s**chool age ou**t**comes (The GiST study))

Registration: The pre-hPOD clinical trial is registered with Australian New Zealand Clinical Trials Registry (ACTRN [12613000322730](https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12613000322730))

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This study protocol follows the SPIRIT checklist.

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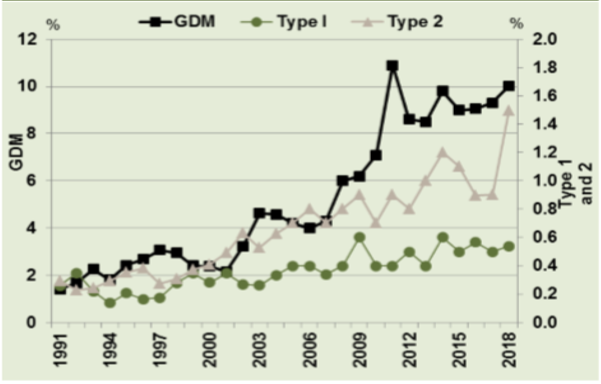
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# Introduction

## Background and Rationale

Diabetes in pregnancy due to gestational diabetes (GDM) is rapidly becoming more common worldwide.1 In New Zealand, more than 12% of women have diabetes in pregnancy, up from 2% thirty years ago, of which 83% is due to GDM (Figure 1),2 with women of Māori, Pasifika, Asian and Indian ethnicities the most likely to be affected.3 There are increased short-term risks for both mothers and babies in pregnancies with GDM, with an increased risk of pregnancy complications (pre-eclampsia, shoulder dystocia), large for gestational age, and neonatal hypoglycaemia.4 Currently, there are no interventions proven to prevent women developing GDM.5 Treatment of GDM with diet, lifestyle change, oral hypoglycaemic agents and insulin reduces the risk of serious perinatal complications.6,7 However, it is less clear if children born following a diabetic pregnancy are at increased risk of cognitive impairment or long-term metabolic complications, and if treatment of GDM can mitigate these risks.8,9



**Figure 1.** Prevalence of Diabetes in Pregnancy, Auckland City Hospital, 1991-2018.

There have been multiple, retrospective, observational studies, some of which have shown that the offspring of women who had diabetes in pregnancy are at increased risk of cognitive impairment, 10-13 while others have found no effect.14,15 Many of the original studies were undertaken in an era when diabetes in pregnancy was uncommon, studied small cohorts, did not differentiate between the different types of diabetes in pregnancy and were not able to adjust for potentially significant confounders, such as maternal obesity and socioeconomic status (SES).16,17 A recent prospective cohort study from Singapore found that early childhood changes in electrophysiology, which are associated with attention and memory in later life, were lower in infants whose mothers had had GDM,18 which suggests that they may be at increased risk of cognitive impairment in childhood.

There is also inconsistency in the results from database studies. The Avon Longitudinal cohort study was able to adjust for many confounders, but had limited power (33 women with GDM (0.4%)), and found that diabetes in pregnancy was associated with reduced educational attainment.19 However, a Greek database study, also with limited power (55 women with GDM) found no effect of GDM on pre-school neurodevelopmental outcome.20 A large study from Sweden found an increased risk of poorer school achievement following diabetes in pregnancy.21 However, the incidence of diabetes in pregnancy was low (0.5%), there were no data about the type of diabetes in pregnancy, and there was limited adjustment for potential confounders. A more recent database study, also from Sweden, which adjusted for more confounders, found men whose mothers had diabetes in pregnancy (type not specified) had poorer academic achievement at 16 years of age but were not different from siblings who had not been exposed to diabetes in pregnancy, suggesting that the association between maternal diabetes in pregnancy and offspring cognitive outcomes may be explained by shared familial characteristics and not an intrauterine mechanism.22 To date, there have been no studies which have included Māori or Pasifika women, or which have been done in New Zealand.

There is also uncertainty regarding the effect of GDM on long-term metabolic complications in the offspring.23 Infants of women with GDM have more fat mass than infants born to women who did not have GDM,24,25 and this risk is reduced with treatment of GDM.26 Children born to mothers with GDM also have a higher BMI, but there is uncertainty if this effect is independent of the maternal BMI.27-29 Treatment of GDM in a randomised controlled trial did not reduce the risk of elevated BMI in childhood,30 suggesting that elevated maternal BMI rather than GDM may be causative for increased childhood BMI. Children born to mothers with type 2 diabetes have a higher risk of developing diabetes than their siblings born before their mother developed diabetes.31 Adults who were born to mothers with diet treated GDM were also at increased risk for developing type 2 diabetes or pre-diabetes,32 suggesting that a hyperglycaemic fetal environment can have long term effects on pancreatic development.

Women with GDM are at higher risk of having other risk factors for impaired cognitive function, educational achievement and metabolic complications in their offspring, including maternal obesity and SES. Maternal obesity is a risk factor both for the development of GDM33 and for cognitive impairment.20,34,35 35% of pregnant Māori and Pasifika women are morbidly obese (BMI ≥35), with 15% of morbidly obese women developing GDM.2 However, many previous studies to determine the risk of cognitive impairment in the children of mothers with GDM have not adjusted for these risk factors,17 so it is unclear if GDM is an independent risk factor for cognitive impairment, or a confounder.

In addition to the potential effects of high blood glucose concentrations before birth on the developing brain, there is also a risk from neonatal hypoglycaemia (low glucose concentrations) after birth, a common complication of diabetes in pregnancy.36 Hypoglycaemia in babies is associated with impaired evoked potentials,37 and in babies born preterm who developed recurrent hypoglycaemia had an increased risk of neurodevelopmental impairment.38 Children who experienced even a single low blood glucose concentration after birth had lower academic achievements at 10 years than babies without low blood glucose concentrations.39 When babies at-risk were screened and treated to maintain their blood glucose concentration ≥ 2.6 mM their neurodevelopmental outcomes were similar to at-risk babies who did not develop hypoglycaemia at two 40 and four years after birth.41 However, there was an increased risk of low executive function and visual-motor function at four years after birth; skills that are likely to affect school achievement.41

We conducted a randomised controlled trial in Auckland maternity hospitals of prophylactic oral dextrose gel in babies at risk of neonatal hypoglycaemia (pre-hPOD) in 2013-2014 and recruited 300 babies born to diabetic mothers of whom 258 had GDM.42 We have now completed 2-year follow-up of the pre-hPOD cohort, achieving 90% follow-up (361/401). The rate of neurosensory impairment was similar in dextrose and placebo groups (41/243 [16.9%] vs 26/117 [22.2%], RR 0.77 [0.50-1.19], p=0.23).43 These children are now being assessed again at 6-7 years of age to determine the long-term effects of prophylactic oral dextrose gel. This provides an opportunity to determine the long-term effects of GDM on neurocognitive and cardiometabolic function by comparing trial participants whose mothers had GDM with children whose mothers did not have GDM.

## Objectives and Hypotheses

Primary Aim: to determine if maternal GDM is associated with impaired school-age neurocognitive development in the offspring, independent of the effect of maternal obesity and socioeconomic status (SES).

Secondary aims: To determine if maternal GDM is associated with

1. School-age obesity OR
2. impaired school-age cardiometabolic function

in the offspring, independent of the effect of maternal obesity and socioeconomic status (SES).

Specifically, to determine at 6-7 years’ corrected age the effect of GDM on:

1. Neurocognitive function
   1. Language
   2. Memory
   3. Executive function
   4. Sensory processing
   5. Motor function
   6. Academic achievement
2. Health and wellbeing
   1. Emotion and behaviour
   2. Physical health
   3. Body size
3. Cardiometabolic function
   1. Body composition
   2. Muscle strength
   3. Central and peripheral blood pressure and resting heart rate

Primary hypotheses:

Children of mothers who had GDM will have impaired neurocognitive development at school-age compared to children of mothers who did not have GDM.

# Methods

## Study Design

A retrospective, observational, matched cohort study at 6-7 years of age.

Children who participated in the pre-hPOD study are being assessed at 6-7 years of age as part of the Neonatal Nutritional Interventions Early School-age Outcomes Studies (NIEOS) study. A sub-group of children in the pre-hPOD study, whose mothers had GDM (GDM-exposed), will be matched with children born at Auckland City Hospital during the pre-hPOD recruitment whose mothers did not have GDM (GDM-non-exposed).

### Pre-hPOD

The pre-hPOD dosage trial was a two-centre randomised, double-blind, placebo-controlled dosage trial undertaken at Auckland City Hospital and Waitakere Hospital between August 2013 and November 2014. A total of 415 infants were recruited to the Pre-hPOD Study, of whom 259 (62%) were born to mothers with GDM.44

Inclusion criteria:

* Infants at risk of hypoglycaemia: infants of diabetic mothers, preterm, small (< 2.5 kg or <10th centile) or large (>4.5 kg or >90th centile)
* AND unlikely to require NICU admission for other reasons (>35 weeks’ gestation, birthweight >2.2 kg, no apparent indication for NICU admission at time of randomisation)
* AND <1 hour old
* 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.

The primary outcome was neonatal hypoglycaemia, defined as any blood glucose concentration <2.6 mmol/L in the first 48 h after birth. Secondary outcomes were admission to a NICU (defined as admission for >4 h); admission to a NICU for hypoglycaemia; hyperglycaemia (blood glucose concentration >10 mmol/L); breastfeeding at discharge from hospital (full or exclusive); received any formula prior to discharge from hospital; formula feeding at 6 weeks of age; cost of care until discharge home, and maternal satisfaction at 6 weeks after birth.

Compared to babies randomised to placebo, the risk of hypoglycaemia was lowest in babies randomised to a single dose of 200 mg/kg dextrose gel (relative risk [RR] 0.68; 95% confidence interval [CI] 0.47, 0.99, P=0.04) but was not significantly different between dose groups (P=0.21).44 Compared to multiple doses, single doses of gel were better tolerated, quicker to administer, and less messy, but these limitations were not different between dextrose and placebo gel groups. Babies who received any dose of dextrose gel were less likely to develop hypoglycaemia than those who received placebo (RR 0.79; 95% CI 0.64, 0.98, P=0.03; number needed to treat of 10, 95% CI 5, 115). Rates of NICU admission were similar (RR 0.64; 95% CI 0.33, 1.25, P=0.19), but admission for hypoglycaemia was less common in babies randomised to dextrose gel (RR 0.46; 95% CI 0.21–1.01, P=0.05). Rates of breastfeeding were similar in both groups. Adverse effects were uncommon and not different between groups.

### Two-year Follow-up Study

Two-year follow-up was conducted for the pre-hPOD trial as part of the main protocol. All surviving children were eligible for assessment at 24 months’ corrected age ± 1 month. Children received a comprehensive assessment of neurodevelopment, vision, general health and socio-demographic characteristics of the family. Written informed consent was obtained from caregivers at the two-year follow-up. There was no difference between the groups in neurodevelopmental impairment or executive function at 24 months’ corrected age. 45

## Participants and Study Setting

### Eligibility

Inclusion criteria

1. Gestational age ≥ 35 weeks

2. Birth weight ≥ 2.2 kg

3. Age at assessment +/- 6 months of matched child

Exclusion criteria

1. Major congenital abnormality

2. Admitted to NICU in first 1 hour after birth.

3. Maternal polycose test or glucose tolerance test result during the pregnancy unavailable.

GDM-Exposed: Children who participated in the pre-hPOD study and were born to mothers with GDM.

GDM-Non-exposed: Children born at Auckland City Hospital during pre-hPOD recruitment period (+/- 1 year) whose mothers had a normal one-hour 50 g oral glucose challenge (polycose) test (routine GDM screening at 24-28 weeks’ gestation in New Zealand) or a normal two-hour 75 g oral glucose tolerance test. Eligible children will be matched using the following variables in a hierarchical manner: 1. Sex,

2. Maternal BMI\* (recommended weight (≤24.9 kg/m2), overweight (25.0–29.9 kg/m2), obesity (≥ 30 kg/m2)46

3. Ethnicity (Māori, Pasifika, Asian/Indian, Other),

4. New Zealand deprivation index at birth (a measure of socio-economic status, derived from pregnancy booking address)47 (low deprivation (1-7), high deprivation (8-10)),

5. Gestational age at birth (35/36 weeks, 37/38 weeks, 39 + weeks). If matching not possible within GA strata then a match within +/- 1 weeks will be attempted.

\* In the pre-hPOD GDM cohort BMI – underweight, 9; recommended, 69; overweight, 61; obese 87

Children in the pre-hPOD trial whose mothers did not have GDM and who are matched with a GDM-Exposed case are eligible for inclusion.

### Matching

Eligible children will be matched based on the above variables using individual matching, aiming to have the frequency of each variable similar between the pre-hPOD and control groups. Control children will be assessed as close as possible to the median age of assessment of the children in the pre-hPOD cohort

### 2.1.2 Contact Tracing

Contact tracing for the GDM-exposed cohort will be performed using the Pre-hPOD cohort database which contains the contact details provided by families at the time of recruitment and at 2 years. Those who have previously withdrawn will be marked as not eligible. GDM-Non-exposed will be identified from the prospectively maintained Auckland City Hospital maternity database, which contains data for all the matching criteria. Approximately 6,000 non-exposed children will be eligible to be matched (6,000 births per year, 15 months pre-hPOD recruitment, 25% non-eligible due to maternal diabetes, preterm or multiple pregnancy). Up to ten non-exposed children will be identified for each exposed, to allow for exclusions, difficulty in tracing and for parents who decline to participate.

A check will be made of NHI numbers to ensure we avoid contacting families whose child has died. Around the time the child reaches six years’ corrected age (according to EDD), families will be sent a letter, along with the Participant Information Sheet (PIS), inviting them to participate in the follow-up study and asking them to contact the study team. After one to two weeks, if we have not heard from the family, a member of research team will attempt to make contact by phone to check if the information has been received and to discuss the study. If we are unable to make contact, we will trace families via alternative contacts in the hospital database, via the primary health provider, or if necessary by a home visit.

### Home Visit Safety Plan

If Home visits are required during contact track and tracing, or for the assessments, assessors will follow the GiST Standing Operating Procedure: Staff and Participants Safety for Home-based Visiting SOP which accompanies this protocol.

## Assessments

Children will be assessed at 6-7 years’ corrected age, +/- 3 months compared to matched case, by suitably trained assessors (Table). Assessments will be conducted at school wherever possible because this avoids the need for families to organise transport, or time off work, and so facilitates participation regardless of family resources and environment. However, if requested, the assessment can also be done at another venue such as our research clinic, local medical centre, or in the child’s home. Once informed consent has been obtained, the child’s school will be contacted, and a suitable time/place organised to undertake the assessment. Caregivers will be invited to attend the school assessment if they wish. The assessment will be conducted in a standardised order with breaks as required. The physical assessments have been designed so that the child does not need to undress (except for removal of shoes and sliding up of sleeves).

### Neurocognitive Function

Neurocognitive development will be assessed using NIH Toolbox focussing on language (receptive vocabulary and oral reading recognition),48 memory (episodic),49 executive function (inhibition, control, attention; planning, organisation and cognitive flexibility),50 and motor function (dexterity and psychomotor control).51 Visual perception will be assessed using motion coherence.52 The Toolbox tests and Motion Coherence Test will be administered via a tablet computer.

Academic skills in numeracy will be assessed using the Checkout Game.53 Numeracy underpins mathematical problem solving and creativity, and plays a key role in innovation and technological discovery.54 We will also ask the child’s teacher for a global assessment of the child’s progress in reading and maths, and whether they require or have received reading recovery, including whether the child has been formally screened (e.g., Observation Survey of Early Literacy Achievement, which is performed at 6 years of age in most schools).

### Health and Wellbeing

Children will be weighed in light clothes without shoes by electronic scale to the nearest 0.1 kg and height will be measured using a laser stadiometer to the nearest mm. Body mass index will be calculated (kg/m2).

Caregivers will complete questionnaires about the child’s emotional and behavioural development using the Strengths and Difficulties Questionnaire (SDQ),55 and functional health and wellbeing using the Child Health Questionnaire (CHQ).56 Parent questionnaires will be available online or in hard copy.

The SDQ is a brief questionnaire for 4- to 17-year old children that assesses emotional and behavioural difficulties. The 25 items (questions) are divided into 5 scales, four of which (emotional symptoms, conduct problems, hyperactivity/inattention, peer problems) comprise the Total Difficulties Score (range 0-40). The fifth scale, prosocial behaviour, represents the strengths of a child. Borderline and abnormal thresholds have been defined for the scales and the Total Difficulties Score.57 We will use the New Zealand one-sided version for 4- to 10-year old children (without impact score).

The CHQ assesses general health and health-related quality of life, including 14 physical and psychosocial concepts. We will use the parent short form with 28 items. Two summary outcome measures will be derived, physical functioning and psychosocial scaled scores.58

### Cardiometabolic Function

Left mid-arm circumference will be measured to the nearest mm with a lasso measuring tape. Triceps skinfolds will be measured in duplicate to the nearest 0.2 mm using skinfold calipers. If the difference between measures is >0.6 mm, a third measurement will be taken. The median value will be used in analysis. Arm fat and muscle area will be calculated from arm circumference and triceps skinfold thickness.59,60 Whole-body lean mass and fat mass will be measured using bioelectrical impedance spectroscopy (BIS).61

Handgrip strength will be measured using a dynamometer to the nearest 0.1 kg. Children will have three attempts per hand while standing. The maximum value will be used in analysis. Peak grip strength for weight will be calculated with allometric scaling (kg/kg0.67).62 Combined grip strength is the sum of right and left peak grip strength.63 Grip strength is correlated with muscle mass and cardiometabolic fitness, including insulin sensitivity.64-66

Vascular development will be assessed by peripheral and central blood pressure. Brachial systolic and diastolic blood pressure will be measured to the nearest mmHg by oscillometric device on the left arm after sitting for ≥5 minutes. Cuff width will cover at least two-thirds of the arm length. Age- and sex-specific z-scores will be derived.51 Central blood pressure will be assessed by suprasystolic wave form analysis, providing central aortic systolic blood pressure (mmHg) and Aortic Augmentation Index (pulse wave reflection).67,68 Central blood pressure measurements will be repeated after grip strength testing, as this may unmask hypertension in children.69 Resting heart rate will be recorded as an indicator of sympathetic activity and cardiovascular fitness.70-72

Table. Summary of early-school age assessment

|  |  |  |  |
| --- | --- | --- | --- |
| **Function/Attribute** | **Specific Skill/Focus** | **Instrument/Test** | **Duration (80 min)** |
| **Domain 1: Neurocognitive Function** | | | |
| Language | Receptive vocabulary | Picture Vocabulary Test | 4 min |
| Memory | Episodic memory | Picture Sequence Memory Test | 7 min |
| Executive function | Inhibition, control, attention | Flanker Test | 4 min |
| Planning, organisation, cognitive flexibility | Dimensional Change Card Sort Test | 4 min |
| Visual perception | Motion Coherence Threshold | 7 min |
| Motor function | Dexterity | Pegboard Dexterity Test | 4 min |
| Psychomotor control | Standing Balance Test | 6 min |
| Academic achievement | Numeracy | Checkout game | 10 min |
| Reading | Oral Reading Recognition Test | 4 min |
| Teacher global assessment | Reading  Maths | (5 min teacher questionnaire) |
| **Domain 2: Health and Wellbeing** | | | |
| Emotion and behaviour | Impact on relationships (family, friends) and learning | NZ Strengths and Difficulties Questionnaire (SDQ)  Child Health Questionnaire (CHQ) (psychosocial sections) | (10 min parent report) |
| Physical health | Impact on activity and learning | Child Health Questionnaire (somatic sections) |
| Body size | Stature | Height by laser stadiometer | 2 min |
| Weight | Weight by digital scale |
| **Domain 3: Cardiometabolic Function** | | | |
| Body composition | Excess adiposity | Mid-arm circumference and triceps skinfolds  Bioelectrical impedance spectroscopy (whole body fat mass)  Derived: body mass index, arm fat area | 10 min |
| Musculoskeletal development | Muscle strength/mass | Handgrip strength  Bioelectrical impedance spectroscopy (whole body lean mass)  Derived: arm muscle area | 2 min |
| Vascular development | Pre-hypertension  Pre-atherosclerosis | Aortic (central) blood pressure and arterial pulse wave reflection (Augmentation Index) by suprasystolic pressure wave form analysis, before and after hand grip testing  Brachial (peripheral) blood pressure  Resting heart rate | 5 min |

## Outcomes

### Primary outcome

Composite Cognitive Standard Score, defined as the NIH Toolbox Early Childhood Composite Cognitive Score, an average age-adjusted standard score for the Flanker Test, Dimensional Change Card Sort (DCCS) Test, Picture Vocabulary Test and Picture Sequence Memory Test.

### Secondary outcomes

Neurocognitive Function:

* Picture Vocabulary Test age-adjusted standard score (mean 100, SD 15)ʃ\*
* Oral Reading Recognition Test age-adjusted standard score (mean 100, SD 15)ʃ
* Picture Sequence Memory Test age-adjusted standard score (mean 100, SD 15)§\*
* Flanker Test age-adjusted standard score (mean 100, SD 15)§#\*
* DCCS Test age-adjusted standard score (mean 100, SD 15) §#\*
* Pegboard Dexterity Test age-adjusted standard score: dominant hand (mean 100, SD 15)
* Standing Balance Test age-adjusted standard score (mean 100, SD 15)
* Any neurocognitive impairment: ≥1 standard score <85 (>1 SD below normative test mean) for language (Picture Vocabulary Test or Oral Reading Recognition Test), memory (Picture Sequence Memory Test), executive function (Flanker Test or DCCS Test) or motor function (Pegboard Dexterity Test dominant hand or Standing Balance Test)
* Any moderate-severe neurocognitive impairment: ≥1 standard score <70 (>2SD below normative test mean) for language (Picture Vocabulary Test or Oral Reading Recognition Test), memory (Picture Sequence Memory Test), executive function (Flanker Test or DCCS Test) or motor function (Pegboard Dexterity Test dominant hand or Standing Balance Test)
* Executive dysfunction: Flanker or DCCS standard score <85
* Motor impairment: Pegboard Dexterity Test or Standing Balance Test standard score <85
* Motion Coherence Threshold (%)
* Checkout Game: total numeracy score and low numeracy (total score <25) 73
* Teacher Global Assessment in mathematics, reading and writing (below or well below expected level on curriculum)
* Current learning support (current individual education plan or current additional learning support) as reported by teachers

*ʃ Crystallised cognition: verbal knowledge and skills; more influenced by education and cultural exposure.*

*§ Fluid cognition: capacity to solve problems, think and act quickly and encode new episodic memories; especially influence by biological processes and less dependent on past exposure.*

*# Executive function*

*\*Primary outcome components*

Anthropometry and cardiometabolic function:

* Weight, height and BMI, and age- and sex-specific z-scores (WHO)74
* Overweight (BMI z-score >1 and ≤2) or obese (BMI z-score >2)74
* Triceps skinfold (mm) and age- and sex-specific z-score75
* Arm muscle area (cm2) and age- and sex-specific z-score60,76
* Whole-body fat and lean mass (kg) and associated indices (kg/m2)
* Dominant and non-dominant peak handgrip strength (maximum of three measures, kg) and handgrip strength index with allometric scaling (total kg/kg0.67)62
* Combined handgrip strength (sum of dominant and non-dominant peak handgrip strength, kg) and combined handgrip strength index with allometric scaling (total kg/kg0.67)
* Peripheral (brachial) systolic and diastolic blood pressure and age-, height- and sex-specific percentile (mean of 2 recordings, pre- and post-handgrip test)51
* Elevated blood pressure (mean peripheral systolic blood pressure 121 to 130 mmHg or 90th to 94th centile or diastolic 81 to 90 mmHg or 90th to 94th centile) or hypertension (mean peripheral systolic blood pressure >130 mmHg or ≥95th centile or diastolic >90 mmHg or ≥95th centile)77
* Aortic systolic central pressure pre- and post-handgrip test and age- and sex-specific z-score68
* Aortic Augmentation Index
* Resting heart rate and elevated heart rate for age and sex (>90th percentile)70

*Age-specific z-scores will be calculated using corrected age.*

Parent questionnaires

* SDQ: Total Difficulties Score and proportion of children with borderline or abnormal result (score ≥14); Prosocial social score and proportion of children with borderline or abnormal result (score ≤5)
* CHQ: physical functioning and psychosocial summary scale scores (mean 50, SD 10) and proportion more than 1 SD below normative mean for age (<40)

## Study Timeline

The first children in the Pre-hPOD Study cohort turned 6 years’ corrected age in September 2019, and assessments of the GDM- exposed cohort began in the second half of 2020. We will aim to start recruitment and assessment of GDM- non-exposed, matched for age at assessment, August 2021, pending ethical approval. Data collection is anticipated to be completed in 2023.

## Blinding

Assessors will be blinded to the maternal glycaemic status, antenatal and neonatal history of participants.

## Data Collection, Management and Analysis

### Data Collection Methods

Toolbox and motion coherence tests will be administered using tablet-based applications. Raw data files will be transferred to Liggins secure servers for digital archiving. Summary scores and measures will be imported electronically to electronic case record forms (eCRF) using the REDCap data management system. Where possible, parent and teacher questionnaires will be completed via REDCap electronic surveys; if hard copy questionnaires are required, data will be entered at the data management centre into the REDCap electronic survey forms. Physical measures will be entered directly into REDCap eCRFs by assessment personnel.

### Data Management

Wed-based data management will be provided by the Clinical Data Research Hub (CDRH), based at the Liggins Institute, University of Auckland ([www.ligginstrials.org](http://www.ligginstrials.org)). Study data will be stored in eCRFs using the REDCap data management system.78 Electronic data capture will be employed, where possible. For fields requiring manual data entry, range and logic checks will be applied to prevent data entry errors. A CDRH Data Monitor will review all eCRFs for completeness and logic errors. If the data monitor identifies a potential error, an electronic query will be raised in REDCap and referred to the relevant assessor. Once data queries are resolved, eCRFs will be locked by the Data Monitor.

### Statistical Methods

Statistical analysis will be performed in SAS (SAS Institute). Baseline characteristics of the pre-hPOD follow-up cohort will be compared against those lost to follow-up to inform discussion on the external validity of results. Within the follow-up cohort, exposure groups (GDM and non-GDM) will be compared for baseline characteristics.

For the primary analysis, exposure groups will be compared for the pre-specified primary and secondary early school-age outcomes using generalised linear models appropriate for the dependent variable of interest. Models will be adjusted for all matching criteria, size at birth (SGA, AGA or LGA) and prophylactic oral dextrose gel. Treatment effects will be expressed as marginal least squares adjusted mean differences or odds ratio, with 95% confidence intervals. A two-tailed p<0.05 will be considered statistically significant. Data will also be collected on school decile, maternal smoking, diabetes control in pregnancy (treatment with diet/oral medications or insulin), breastfeeding, and maternal age to allow for exploratory analysis of possible mediators.

In secondary analysis, models for the primary outcome will be additionally adjusted for baseline prognostic variables with significant imbalance and modified per protocol analyses will be performed.

### Sample size and power

The sample size is bounded by the number recruited to pre-hPOD and the follow-up rate. In the original pre-hPOD cohort, 259 babies were born to mothers with GDM, four were twins, and 13 were born preterm. Assuming 90% follow-up, there will be 218 eligible GDM exposed children assessed during our HRC programme, matched with 218 non-GDM exposed controls, for a total of 436 participants. Executive function has a mean of 103, SD 12.6. We will be able to detect a difference in the primary outcome of executive function of 3.9 (0.3 standard deviation) at 90% power.

# Ethics and Dissemination

## Research Ethics Approval

Ethical approval for the pre-hPOD follow-up has been given from the Health and Disability Ethics Committee (HDEC, 19/STH/2020Am01). A separate approval will be requested from HDEC for this protocol. A progress report will be provided to HDEC annually.

## Locality Approval

Locality approval will be sought from the University of Auckland and ADHB.

## Protocol Amendments

All amendments to the final version of this protocol will require review and approval of the Steering Committee (section 4.1) and will be submitted to HDEC. All amendments, including approval date, will be recorded with this protocol (Appendix 5.4).

## Consent / Assent

Parents of children who completed 2-year assessments were informed that there would be ongoing follow-up at school age, pending funding. Caregivers who have expressed a previous wish to withdraw from the study or declined further contact will not be contacted again. Caregivers will be provided with the Participant Information Sheet and will be given enough time to consider the study. We will offer to meet with them and their whānau to provide further information and answer questions. Processes used to ensure confidentiality will be explained. Following this, written informed consent (hard copy or electronic) will be obtained on behalf of each participant by a caregiver. Assent will be sought from the children on the day of the assessment and recorded on an age-appropriate assent form.

## Confidentiality

REDCap databases will be stored on secure servers at the University of Auckland and access will be controlled by unique user ID and password. REDCap is HIPAA compliant and includes eCRF level control and tracking logs. eCRFs will be identifiable only by study ID. Identifiable information, e.g., NHI and contacts, will be stored in a separate REDCap database. Download of data will be restricted to the data management team and primary investigator. Downloaded data will be deidentified. Raw electronic data files will be stored on secure servers at the University of Auckland, accessible only to the researchers. Any hard copy records will be stored in a locked cabinet at the Liggins Institute.

Study reports will contain only summary data and individual participant data will not be reported. At the completion of the study, all electronic data will be permanently digitally archived at the Liggins Institute. Any remaining hard copy records will be stored in a locked cabinet in a secure office and will be accessible only to the study investigators. Records will be retained for 10 years after the age of majority.

All research staff will be certified in best practice for clinical trials (ICH-GCP E6 and PHRP).

## Participant Report

A short summary of the findings will be sent to the caregivers at the completion of the assessment, and with their consent, to the child’s school and primary health provider. If concerns exist about a child’s health, referral to an appropriate health agency, usually the child’s primary health provider, will be made with the consent of the caregivers. Caregivers and their health professionals will have the opportunity to request a more detailed report of specific assessment results if required.

For those who request it on the consent form, a summary of study findings will be sent to caregivers at the time of publication of the main results.

## Withdrawal

Parents and caregivers will retain the right to withdraw their child from the study at any stage without the need to provide a reason.

## Declaration of Interests

Investigators will declare any financial, intellectual or other potential conflicts of interest to the Steering Committee. The Steering Committee will decide on how any conflicts of interest are to be managed.

## Access to Data

The Steering Committee will have access to the full dataset and oversee analysis, interpretation and reporting of results. Approval will be sought from the Steering Committee prior to publication of study data. Care will be taken to avoid duplication in reporting of results.

For each main publication, the corresponding data set will be electronically archived with the CDRH. Anonymised data may be shared with external researchers upon request, according to the Data Sharing Protocol of the CDRH (https://wiki.auckland.ac.nz/display/ontrack/Data+Sharing).

## Dissemination Policy

The primary mode of research dissemination will be via peer-reviewed publications, as these are most likely to impact on the research and practising community. Most major publications are accompanied by media releases to accelerate international as well as local dissemination. Regular lectures and teaching sessions will be given to professional groups and to the public. For example, Liggins public lectures always include public-facing web pages aimed at participants and releases on social media.

## Authorship

The Council of Science Editors standards for authorship will be applied (www.councilscienceeditors.org). The Steering Committee will be responsible for planning manuscripts and resolving authorship disputes. Investigators and research staff who do not meet the criteria for authorship will be acknowledged as non-author contributors.

## Māori Responsiveness

Our follow-up team is led by a Māori researcher, Jenny Rogers (Ngai Tahu) who specifically focuses on culturally appropriate approaches to families and trains and supports assessors accordingly. Peter Keegan (Waikato-Maniapoto, Ngati Porou), who is an expert in Māori-medium education, supports the NIEOS team in Māori immersion education environments.

The NIEOS team have consulted with the Liggins Institute Māori Advisory Committee, who will provide ongoing oversight of the programme. We have also consulted with Sarah-Jane Paine from Te Kupenga Hauora Māori. Ongoing engagement with Kura Kaupapa Māori immersion school communities (Kura Tuatahi Centennial Park School, Te Kuiti, Te Kura Kaupapa Māori o Te Hiringa, Tokoroa, and Te Kura O Te Kaokaoroa O Patetere, Putaruru) will be part of a parallel workstream within this research programme and processes and participants will overlap with and inform this follow-up study.

# Study Management

## Steering Committee

The Steering Committee will take overall responsibility for all aspects of the study, meeting on a bimonthly basis. Matters arising between meetings may be dealt with by email. The Principal Investigator and Study Coordinator will be responsible for maintaining a record of correspondence and minutes of meetings.

The Steering Committee comprises:

Jane Alsweiler, Paediatrics: Child and Youth Health, University of Auckland, New Zealand

Jane Harding, Liggins Institute, University of Auckland (Programme Principal Investigator)

Gavin Brown, Education and Social Work, University of Auckland, New Zealand

Caroline Crowther, Liggins Institute, University of Auckland, New Zealand

Chris McKinlay, Liggins Institute, University of Auckland (Study Principal Investigator)

The Steering Committee will report to the Follow-up Programme Grant Steering Group, chaired by Jane Harding, and the hPOD Study Steering Group (Chair Jane Harding)

Management Committee

A Study Coordinator will be appointed to oversee day-to-day running of the study. They will be supported by a Management Committee which will meet regularly.

The Management Committee comprises Jane Alsweiler, Chris McKinlay, and the Study Coordinator.

## Standard Operating procedures

Standing operating procedures (SOPs) will be developed by the Management Committee for key study activities and processes (Appendix 5.6)

## Finance

Funding has been obtained from Auckland Medical Research Foundation (Project Grant 1120019)

# Appendices

## Participant Documents

The following participant documents are to accompany this protocol:

|  |  |  |
| --- | --- | --- |
| Title | Version | Date |
| Participant Information and Consent | 3 | Aug 2021 |
| Teacher PIS and consent | 2 | Aug 2021 |
| Child Assent Form | 2.2 | Nov 2021 |
| Parent invite letter | 2.1 | Nov 2021 |
| Letter to Principals | 1 | Aug 2021 |
| School intro letter | 2 | Aug 2021 |

## Case Report Forms

The following electronic case report forms (eCRF) are to accompany this protocol:

|  |  |  |
| --- | --- | --- |
| Title | REDCap Database | Instance |
| Physical | NIEOS Data | Liggins |
| Neurocognitive | NIEOS Data | Liggins |
| Teacher Questionnaire | NIEOS Data | Liggins |
| Child Health Questionnaire (CHQ-28) | NIEOS Data | Liggins |
| Strengths and Difficulties Questionnaire (SDQ) | NIEOS Data | Liggins |

## Ethical and Locality Approval

The following letters of approval are to accompany this protocol:

|  |  |  |
| --- | --- | --- |
| Title | Reference | Date |
| HDEC national ethical approval | 21/NTA/112 | 30 Sept 2021 |
| ADHB locality approval | 9184 | 8 October 2021 |

## Protocol Amendments

|  |  |  |  |
| --- | --- | --- | --- |
| Protocol version, Date | Amendment(s) | Date accepted by Steering Group | Date ethics notified (or NA) |
| 18 November 2021 | Obesity classifications for matching criteria simplified | 3 Nov 2021 | Annual report |
| 2.3 15 March 2022 | Only follow-up children residing in Auckland | 30 April 2021 | Annual report |
| 2.3 15 March 2022 | Revised matching criteria (collapsed Maternal BMI criteria, ethnicity criteria, SES) | 7 March 2022 | Annual report |
| 2.3 15 March 2022 | Removed size at birth as a matching criterion, will be adjusted for in the analysis | 7 March 2022 | Annual report |
| 2.3 15 March 2022 | Frequency Matching | 7 March 2022 | Annual report |
| 2.3 15 March 2022 | Maternal polycose test result unavailable added as an exclusion criterion | 7 March 2022 | Annual report |
| 2.4 17 August 2022 | Follow-up of children in Greater Auckland | 24 May 2022 | Annual report |
| 2.5 28 August 2022 | Individual Matching | 22 August 2022 | Annual report |
| 2.6 20 November 2023 | GA matching flexibility +/- 1 week | Email 20 Nov 2023 | Annual report |
| 2.7 2 February 2025 | Including statistican details and updating primary outcome as per the SAP | Email 11 Oct 2023 | Annual report |

## NIH Toolbox Battery

* Picture Vocabulary Test: Assesses receptive vocabulary administered in a computer adaptive test format. Participants select the picture that most closely matches the meaning of the word.
* Oral Reading Recognition Test: Measures reading decoding skill and crystallised abilities. Participants read and pronounce letters and words as accurately as possible.
* Picture Sequence Memory Test: Assesses cognitive processes involved in the acquisition, storage, and retrieval of new information.
* Flanker Inhibitory Control and Attention Test: Assesses the allocation of participants’ limited capacities to deal with an abundance of environmental stimulation.
* Dimensional Change Card Sort: Assesses the capacity to plan, organise, and monitor the execution of behaviours that are strategically directed in a goal-oriented manner.
* 9-hole Pegboard Dexterity Test: Assesses ability to coordinate the fingers and manipulate objects in a timely manner.
* Standing Balance Test: Assesses standing static balance. Participant assumes and maintains up to 5 poses for 50 seconds each. Poses include solid surface, foam surface, eyes open in tandem stance on a solid surface. Postural sway is recorded for each pose using an iPod Touch that the participants wear at waist level.

## Standard Operating Procedures

The standard operating procedures (SOP) are to accompany this protocol:

|  |  |  |
| --- | --- | --- |
| Title | Active version | Date |
| Authorship | 1.1 | 2020.8.18 |
| Data Management Plan | 2.1 | Aug 2021 |
| Home visit SOP | 1.0 | Aug 2021 |

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