**The GiST Study**

**The gestational diabetes mellitus and school-age cognitive outcomes: a matched cohort study**

**STATISTICAL ANALYSIS PLAN**

Version 1.3.6

Date: 27 October 2023

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# Introduction

This statistical analysis plan (SAP) outlines the analysis and reporting of the Gestational diabetes mellitus and school-age cognitive outcomes (GiST) Study, which is a matched cohort study involving a subgroup of children from the Hypoglycaemia Prevention with Oral Dextrose (pre-hPOD) Study who were exposed to gestational diabetes and control children not so exposed, matched in a hierarchical manner for sex, maternal BMI, ethnicity, New Zealand deprivation index and gestational age at birth. Children in the pre-hPOD cohort are being assessed as part of the wider Neonatal Nutritional Interventions Early School-age Outcomes Studies (NIEOS). Control children in the GiST Study are being assessed using an identical protocol.

This SAP has been prepared with reference to the following key documents:

* Neonatal Nutritional Interventions Early school-age Outcomes Studies (NIEOS) protocol, version 1.7.
* GiST Study Protocol v2.5
* The SAP for the Pre-hPOD Early School-age Outcomes Study, version\_1.3
* NIH\_Toolbox\_App\_Administrators\_Manual\_v1.17
* NIH\_Toolbox\_Scoring\_and\_Interpretation\_Manual\_9-27-12
* Hegarty JE, Harding JE, Gamble GD, Crowther CA, Edlin R, Alsweiler JM. Prophylactic oral dextrose gel for newborn babies at risk of neonatal hypoglycaemia: a randomised controlled dose-finding trial (the Pre-hPOD Study). PLoS Med. 2016;13(10):e1002155.
* Griffith R, Hegarty JE, Alsweiler JM, Gamble GD, May R, McKinlay CJD, et al. Two-year outcomes after dextrose gel prophylaxis for neonatal hypoglycaemia. Arch Dis Child Fetal Neonatal Ed. 2020; DOI: 10.1136/archdischild-2020-320305.

## Roles and Responsibilities

The GiST Steering Committee has overall responsibility for all aspects of the study. The Steering Committee comprises:

* Jane Alsweiler, Paediatrics: Child and Youth Health, University of Auckland (Study Principal Investigator)
* 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, Paediatrics: Child and Youth Health, University of Auckland

The Steering Committee will have access to the full dataset and oversee analysis, interpretation and reporting of results.

As part of her PhD project, Francesca Amitrano has substantially contributed to the implementation of the study defining the strata for matching, undertaking assessments, helping in coordinating activities during a transitional period between study coordinators, developing this SAP, undertaking the analysis for inclusion of partial results in her thesis.

## Background and Rationale

Diabetes in pregnancy due to gestational diabetes (GDM) is rapidly becoming more common worldwide.1 In New Zealand, more than 83% of women with diabetes in pregnancy have GDM,2 with women of Indian ethnicity the most likely to be affected.3 As reported elsewhere,4 there are several short-term risks, for both mothers and babies, associated with GDM and treatment with diet, lifestyle change, oral hypoglycaemic agents and insulin reduces the risk of serious perinatal complications.5, 6 Nevertheless, it is unclear if children born following a diabetic pregnancy are at increased risk of cognitive impairment or long-term metabolic complications, and if the treatment of GDM can mitigate these risks.7, 8

Some retrospective, observational studies have shown that the offspring of women who had diabetes in pregnancy are at increased risk of cognitive impairment, 9-12 while others have found no effect.13, 14 However, significant limitations in these studies were the small cohorts investigated, the lack of discrimination between the different types of diabetes in pregnancy, and the failure to adjust for potentially important confounders, such as maternal obesity and socioeconomic status (SES).15, 16 Maternal obesity is a risk factor both for the development of GDM17 and for cognitive impairment.18-20 35% of pregnant Māori and Pasifika women are morbidly obese (BMI ≥35), with 15% of morbidly obese women developing GDM.2 Up to now, there have been no studies which have included Māori or Pasifika women, or which have been undertaken in New Zealand.

There is also uncertainty regarding the effect of GDM on long-term metabolic complications in the offspring.21 Children born to mothers with GDM seem to have a higher BMI, but it is unclear if this effect is independent of maternal BMI.22-24 Treatment of GDM in a randomised controlled trial did not reduce the risk of elevated BMI in childhood,25 suggesting that elevated maternal BMI rather than GDM may be causative for increased childhood BMI.

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.26 Hypoglycaemia in babies is associated with impaired evoked potentials,27 and babies born preterm who developed recurrent hypoglycaemia had an increased risk of neurodevelopmental impairment.28 Children who experienced even a single low blood glucose concentration after birth had lower academic achievements at 10 years than those who did not experience low blood glucose concentrations.29 When babies at risk were screened and treated to maintain their blood glucose concentration ≥ 2.6 mmol/L their neurodevelopmental outcomes were similar to at-risk babies who did not develop hypoglycaemia at two 30 and four years after birth.31 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.31

In 2013-2014 at Auckland maternity hospitals a randomised controlled trial of prophylactic oral dextrose gel was conducted in babies at risk of neonatal hypoglycaemia (pre-hPOD) and recruited 300 babies born to diabetic mothers of whom 200 had GDM.32 At 2-year follow-up of the pre-hPOD cohort, 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).33 At 6-7 years of age these children have been assessed again to determine the long-term effects of prophylactic oral dextrose gel. Having this cohort of children followed up at school age has provided 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 children exposed *in utero* to GDM have poorer school-age neurocognitive function than matched children not exposed to GDM,.

Secondary aims: to determine if children exposed *in utero* to GDM have increased rates of obesity, and/or impaired cardiometabolic function at school-age compared with matched children not exposed to GDM.

Specifically, the GiST Study will determine at 6-7 years’ corrected age, if children exposed to GDM have poorer outcomes than matched peers not exposed to GDM with respect to:

1) Neurocognitive function

* 1. Language
  2. Memory
  3. Executive function
  4. Sensory processing
  5. Motor function
  6. Academic achievement

1. Health and wellbeing
   1. Emotion and behaviour
   2. Physical health
   3. Body size
2. Cardiometabolic function
   1. Body composition
   2. Muscle strength
   3. Central and peripheral blood pressure and resting heart rate

Primary hypothesis:

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

The GiST study is a retrospective, observational and matched cohort study at 6-7 years of age of GDM-exposed and non-GDM-exposed children.

GDM-exposed children participated in the pre-hPOD study and were born to mothers with GDM. 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.34 This group of children has been assessed at 6-8 years of age and included in the GiST study.

Non-GDM-exposed children were born at Auckland City Hospital during the pre-hPOD recruitment period (±1 year), to mothers with a normal glycaemic profile, detected by either one-hour 50 g oral glucose challenge (polycose) test (routine GDM screening at 24-28 weeks’ gestation in New Zealand) or two-hour 75 g oral glucose tolerance test (OGTT).3 Children were not included in the study if the maternal polycose test or OGTT results were unavailable or abnormal.3 At 6-8 years of age, children from this cohort who met the inclusion criteria in the GiST study were matched individually to the GDM-exposed children.

The GiST study inclusion criteria:

1. Gestational age ≥35 weeks

2. Birth weight ≥2.2 kg

The GiST study exclusion criteria:

1. Major congenital abnormality

2. Admitted to a neonatal intensive care unit (NICU) in the first 1 hour after birth

The eligible GDM-exposed children were 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)35

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

4. New Zealand deprivation index at birth (a measure of socio-economic status, derived from pregnancy booking address,36 low deprivation (1-7), high deprivation (8-10))

5. Gestational age at birth (35/36 weeks, 37/38 weeks, ≥39weeks)

The permutations of these variables resulted in 144 strata for matching, 61 of which included the pre-hPOD GDM-exposed children. The matching was done at the individual level with the aim of having equal numbers of children in each stratum in the exposed and non-exposed groups.

## Assessments

Children in the GiST study were assessed at 6-7 years’ corrected age. Assessments were conducted by suitably trained assessors at school wherever possible, or at another venue, such as the Liggins Institute Clinical Research Unit or at the child’s home if requested. The assessments evaluated neurocognitive function, educational progress, emotional-behavioural function, general health and well-being and anthropometry and cardiometabolic function, as detailed below.

### Neurocognitive Function

### NIH Toolbox

Cognitive and motor elements of neurocognitive function were measured with tests from the tablet-based National Institutes of Health (NIH) Toolbox, focusing on language,37 episodic memory,38 executive function,39 and dexterity and balance.40 The Picture Vocabulary Test was used to assess receptive vocabulary, i.e., general vocabulary knowledge, and the Oral Reading Recognition Test was used to assess reading decoding ability. These were administered by computer adaptive testing, i.e., items were selected by the iPad application from a large bank, based on subject performance.41 Episodic memory, which is the ability to store and recall information, was assessed with the Picture Sequence Memory Test. Within executive function, attention and inhibitory control were assessed with the Flanker Test, which measures capacity for new learning and information processing in novel situations, and cognitive flexibility was assessed with the Dimensional Change Card Sort (DCCS)Test. These tests of executive function include accuracy and reaction scores, which are combined for the overall test score. If children had difficulty with the Flanker and DCCS Tests (unable to complete practice tests or performance below chance levels on standard items), the NIH Toolbox “developmental extension” was used. If children mastered the extension items they could move to the standard items, thereby allowing a test score to be obtained. If children were unable to complete a cognitive test due to known or presumed impairment, i.e., no score was obtained, a score of 55 was assigned (3 SD below the normative mean).

The Nine-hole Pegboard Test was used to assess manual dexterity (dominant and non-dominant hands), which measures the time required for the child to accurately place and remove nine small pegs into a pegboard. Static standing balance was assessed with the Standing Balance Test, which involves the child assuming and maintaining up to five poses for 50 seconds each, including eyes open on a solid surface, eyes closed on a solid surface, eyes open on a foam surface, eyes closed on a foam surface and eyes open in a tandem stance on a solid surface (only for children 7 years of age or above). Anterior and posterior postural sway is recorded for each pose using an iPhone that is worn at waist level. This generates a score reflecting overall balance ability and two ratio scores comparing performance in pose 2 vs. 1 and 4 vs. 1.

Each NIH Toolbox item yields an age-adjusted scale score which has a mean of 100 and a SD of 15, with higher scores indicating higher levels of ability. E.g., an age-adjusted Picture Vocabulary Test scale score around 100 suggests average vocabulary ability for the age level. Scores around 115 indicate above-average vocabulary ability, and scores around 130 indicate superior ability. On the other hand, scores around 85 suggest below-average vocabulary ability, and scores at 70 or below suggest the participants have significant impairment in language ability. Fully corrected T-scores (mean 50 and SD 10) are also available, which correct for demographic characteristics (education, sex and race/ethnicity), but these were not used as they were judged to be less relevant to the New Zealand context.

The NIH Toolbox includes a normative Early Childhood Composite Score which provides a global measure of cognitive function and is derived from the average of the standard score Picture Vocabulary (crystallised ability) and Picture Sequence Memory, Flanker and DCCS Tests (crystallised abilities). The Oral Reading Recognition Test, which is also a measure of crystallised ability, is not included in the Composite Score. The Composite Score is not available for children who require the Flanker and DCCS extensions, even if they achieve sufficiently with standard items resulting in a test score.

### Motion Coherence Threshold

Visual perception was assessed using the Motion Coherence Test, which involves presentation of random dot kinematograms on a computer tablet (horizontal motion with varying coherence), using an adaptive staircase procedure.42, 43 This generates a motion coherence threshold as a percentage, with lower percentages indicate better visual perception. Motion coherence is a measure of global motion perception and reflect the integrity and function of the dorsal visual stream of the brain, which is essential for the development of visually guided motor function.44, 45

### Checkout Game

The Checkout Game assesses children’s numeracy skills, including forming sets, numeral recognition, pattern recognition, number sequence counting, and mental operations.46 The total score is 32 which is calculated by adding the scores for all five tasks. At school entry (5 years of age), scores at 10 or below indicate low numeracy skills, scores between 11 and 24 indicate adequate progression in numeracy and scores at or above 25 indicate proficiency. Because children in the GiST Study are expected to have completed at least one year of formal schooling, a score <25 was used as the threshold for low numeracy.

### Assigned scores

If a child attempted an NIH toolbox test but could not complete it because of underlying neurodevelopmental disorder or presumed cognitive impairment, a score of 55 was assigned, i.e., 3 SD below the normative mean. For the Pegboard Dexterity Test, the standard score for the dominant hand will be used in analysis; if this is missing, and not assigned, the standard score for the non-dominant hand will be used. For the Checkout Game and Motion Coherence Threshold, the assigned scores are 10 and 100%, respectively. If the Early Childhood Composite Score was missing due to use of developmental extension, the mean standard score (test or assigned) for component items was substituted.

### Anthropometry and cardiometabolic function

### Anthropometry

Weight (electronic scale to the nearest 0.1 kg), height, and left mid-arm circumference (tape measure to the nearest 0.1 cm) were measured by standard techniques. These measurements will be converted into age and sex-specific *z*-scores using the WHO Growth Charts. BMI and BMI *z*-scores will also be calculated.47, 48

### Skin-fold thickness

A Harpenden calliper was used to measure triceps skin fold thickness to the nearest 0.2 mm. Two measurements were taken and if these differed by >0.6 mm, a third measurement was taken. For analysis, median values will be used, which will be converted into age and sex-specific *z*-scores using the WHO Child Growth Standards.47

### Bioimpedance analysis

Children’s body composition was measured by bioimpedance spectroscopy analysis (ImpediMed Imp SFB7 device), which provides an estimate of whole-body fat and lean mass.49 Two measurements were made, and if the difference in fat mass percentage between these measures differed by >1%, a third measurement was taken. For analysis, median values will be used. Data will also be presented as fat and lean mass index (kg/m2).

### Arm muscle area

Arm muscle area will be calculated from arm circumference and triceps skinfold thickness,50 along with age and sex-specific z-scores.48

### Handgrip strength

Handgrip strength was measured by a dynamometer to the nearest 0.1 kg. Children had three attempts per hand while standing. The maximum value for each hand will be used and summed in analysis (combined grip strength). Relative peak combined grip strength for weight will be calculated with allometric scaling (kg/kg0.67).51, 52

### Blood pressure

Vascular development was assessed by peripheral and central blood pressure. Brachial systolic and diastolic blood pressure was measured to the nearest mmHg by oscillometric device on the left arm after sitting for ≥5 minutes. Cuff width needed to cover at least two-thirds of the arm length. Central blood pressure was assessed by suprasystolic wave form analysis, providing central aortic systolic blood pressure (mmHg) and Aortic Augmentation Index (pulse wave reflection).(53, 54)Central blood pressure measurements were repeated after grip strength testing, as this may unmask hypertension in children.53 Blood pressures will be converted to age- and sex-specific *z*-scores.17 Resting heart rate was recorded as an indicator of sympathetic activity and cardiovascular fitness.54-56

### Parent questionnaires

### Strength and Difficulties Questionnaire

The SDQ measures emotional and behavioural development and has 25 items divided into five scales, four of which (emotional symptoms, conduct problems, hyperactivity, and peer problems) comprise the Total Difficulties Score (range 0 to 40), with higher scores indicate more emotional and behavioural difficulties.57 The fifth scale, prosocial behaviour, represents the strengths of a child. Borderline and abnormal thresholds have been defined for the SDQ Total Difficulties Score (≥14) and Prosocial Behaviour Score (≤5).

### Child Health Questionnaire

The CHQ was used to measure children’s physical health, as well as the impact of any health problem on children’s emotion, self-esteem, school and family activities, social relationships, and impact on parents. The parent short form with 28 items was used.58 Two summary outcome measures will be derived: physical functioning and psychosocial scaled scores.

### Teacher questionnaire

The child’s teacher was asked to provide a global assessment of their progress in reading, maths, and writing, in relation to peers and the national curriculum, and whether they currently receive additional learning support, including whether the child has an individualised education programme.

## **Study Outcomes**

## 3.1 Primary outcome

NIH Childhood Composite Cognitive Standard Score (Composite Cognitive Score),*†* calculated from the mean of the age adjusted normalized scores of each of the four component measures, Picture Vocabulary, Flanker, DCCS and Picture Sequence Memory. NIH Childhood Composite Cognitive Standard Score has mean 100 and SD 15.59

*† if this is unavailable, the mean of the scores for Picture Vocabulary Test, Flanker Test, DCCS, Picture Sequence Memory Test is used*

## 3.2 Secondary outcomes

1. Picture Vocabulary Test age-adjusted standard score (mean 100, SD 15)ʃ\*
2. Oral Reading Recognition Test age-adjusted standard score (mean 100, SD 15)ʃ
3. Picture Sequence Memory Test age-adjusted standard score (mean 100, SD 15)§ \*
4. Flanker Test age-adjusted standard score (mean 100, SD 15)§#\*
5. DCCS Test age-adjusted standard score (mean 100, SD 15) §#\*
6. Pegboard Dexterity Test age-adjusted standard score: dominant hand (mean 100, SD 15)60
7. Standing Balance Test age-adjusted standard score (mean 100, SD 15)61
8. 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)
9. 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)
10. Executive dysfunction: Flanker or DCCS standard score <85
11. Motor impairment: Pegboard Dexterity Test or Standing Balance Test standard score <85
12. Checkout Game ⅉ: low numeracy (total score <25) 62
13. Motion Coherence Threshold (%)63
14. Strength and Difficulties Questionnaire (SDQ): behavioural difficulties (total difficulties score > 14), social difficulty (Prosocial Score ≤5)64
15. Weight, height and BMI, and age- and sex-specific z-scores (WHO)47
16. Overweight (BMI z-score >1 and ≤2) or obese (BMI z-score >2)47
17. 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)65

*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*

ⅉ *Due to a ceiling effect for the total numeracy score in the GDM exposed children, the measurement of the continuous variable lost value and has been removed.*

## 3.3 Tertiary outcomes

* Teacher Global Assessment in mathematics, reading and writing (below or well below expected level on curriculum)
* Teacher peers’ comparison assessment in mathematics, reading and writing (below or well below; above or well above; below or above the peers).
* Current learning support (current individual education plan or current additional learning support) as reported by teachers
* Strength and Difficulties Questionnaire (SDQ): Total Difficulties Score, Prosocial Behaviour Score64
* Child Health Questionnaire (CHQ): physical functioning and psychosocial summary scale scores (mean 50, SD 10)
* Triceps skinfold (mm) and age- and sex-specific z-score66
* Arm muscle area (cm2) and age- and sex-specific z-score48, 67
* 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)51
* 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)68
* Aortic systolic central pressure pre- and post-handgrip test and age- and sex-specific z-score69
* Aortic Augmentation Index
* Resting heart rate and elevated heart rate for age and sex (>90th percentile)54

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

## **Statistical analysis**

Analysis will be performed using SAS software, version 9.4 (SAS Institute).

## 4.1 Sample size and power

The sample size is bounded by the number of GDM exposed children recruited to pre-hPOD and the follow-up rate. In the original pre-hPOD cohort, 259 babies were born to mothers with GDM. The follow up rate at 6-7 years of age was 75% and with 1:1 matching with controls (194 exposed, 194 non-exposed), we estimated that for continuous outcomes the GiST Study would have 80% power to detect mean differences equivalent to ≥0.3 SD (two tailed alpha 0.05). For binary outcomes, the study would have 80% power to detect a risk difference of ≥14% with a background rate of 50%,70, 71 or a risk difference of ≥10% with a background rate of 10% (two tailed alpha 0.05).

## 4.2 Data cleaning

Data are entered into the REDCap data management system at the time of assessment. Branching logic and range checks are used to reduce data entry errors. All electronic case report forms (eCRF) are checked by an independent data monitor and queries are raised as appropriate, as per the NIEOS Data Monitoring SOP. All data queries were resolved by discussion with the assessor and/or NIEOS Principal Investigator, following which the eCRF was locked.

Before analysis, continuous data will be plotted, and outliers will be further checked for potential errors. Any corrections will be made in REDCap before export of data for analysis.

## 4.3 Derived variables

All analyses will be performed using SAS version 9.4 (SAS Institute Inc, Cary NC, USA) unless

otherwise specified.

### 4.4 Data availability

A STROBE diagram (Figure 1) will summarise the flow of the matched GDM exposed and Non-GDM-exposed children followed-up at 6 to 7 years’ corrected age. It will report the number of children who were:

* + Eligible for follow-up at 6 to 7 years’ corrected age
  + Not recruited with reasons: lost, declined, overseas
  + Assessed at 6 to 7 years’ corrected age
  + Assessed for the primary outcome

## 4.5 Descriptive statistics

Data will be presented as mean (SD) or median (IQR) for continuous outcomes, as appropriate, and number (%) for categorical variables. Denominators will be provided for all outcomes.

## 4.6 Cohort characteristics

Characteristics of the GDM exposed children will be compared to Non-GDM-exposed children by Student’s t test or Fisher’s Exact test.

## 4.7 Primary analysis

For the primary analysis, exposure groups will be compared for the pre-specified primary, secondary and tertiary early school-age outcomes, using generalised linear models appropriate for the dependent variable of interest. Models will be adjusted for all matching criteria (sex (categorical), maternal BMI (continuous), prioritised ethnicity (categorical as for matching), NZ deprivation index (continuous), gestational age (continuous)) and exposure effects will be expressed as marginal least squares adjusted mean differences or risk differences, with 95% confidence intervals. For categorical data, a relative effect estimate will also be provided, given as odds ratio with 95% confidence intervals. A hypothesis test will be performed for the primary outcome (alpha 0.05). Missing data will not be imputed. The initial analysis will be performed blind to group allocation.

## 4.8 Secondary analysis

## 4.8.1 Confounding

The primary outcome analysis may be additionally adjusted for potential confounding by prognostic baseline cohort characteristics with imbalance judged by the Steering Group to be clinically important. A secondary exploratory model will be additionally adjusted for birthweight z score.

### 4.8.2 Sensitivity analysis

Sensitivity analysis for the primary outcome will exclude children who have been postnatally diagnosed with congenital, genetic or acquired conditions which are known to influence cognitive function.

### 4.8.3 Post hoc analysis

Additional exploratory analyses may be undertaken that will be clearly identified as post hoc.

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# Appendix: Shell tables and figures

Figure 1: Participant flow diagram in the GiST study

A diagram with text on it

Description automatically generated

Table 1: Cohort characteristics of early school-age children, and their mothers in the GiST study

| Characteristic | Non-GDM-exposed  N= | GDM-exposed  N= |
| --- | --- | --- |
| *Maternal* |  |  |
| Age—years |  |  |
| BMI at booking—kg/m2 |  |  |
| ≤24.9 kg/m2 |  |  |
| 25.0–29.9 kg/m2 |  |  |
| ≥30 kg/m2 |  |  |
| Nulliparous |  |  |
| Caesarean delivery |  |  |
| NZ Deprivation Index |  |  |
| Low (1-7) |  |  |
| High (8-10) |  |  |
| Gestational Diabetes |  |  |
| Pre-eclampsia |  |  |
| Maternal hypertension |  |  |
| Antenatal corticosteroids |  |  |
| *Infants* |  |  |
| Female |  |  |
| Gestation—weeks |  |  |
| 35-36 weeks GA |  |  |
| 37-38 weeks GA |  |  |
| ≥39 weeks GA |  |  |
| Birthweight—g |  |  |
| Birthweight z-score |  |  |
| Birthweight customised centile |  |  |
| Apgar score at 5 minutes |  |  |
| Prioritised ethnicity |  |  |
| Māori |  |  |
| Pacific |  |  |
| Indian |  |  |
| Other Asian |  |  |
| NZ European |  |  |
| Other |  |  |
| Small for gestational age (birthweight<10th percentile) |  |  |
| Population |  |  |
| Customised |  |  |
| Large for gestational age (birthweight>90th percentile)  Population |  |  |
| Customised |  |  |

Data are mean (standard deviation) or number (percent). \* P <0.05, \*\* P <0.01 for comparison with Non-GDM-exposed children. The population-based centiles obtained with reference to the Fenton growth chart.72

Table 2. Primary and secondary outcomes at early school age for GDM-exposed and non-GDM-exposed children in the GiST study

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Non-GDM exposed | N | GDM-exposed | N | aRD, aMD (95%CI)  *aOR [95% CI]* | P |
| **Primary outcome**  Cognition Early Childhood Composite Score |  |  |  |  |  |  |
| **Secondary outcomes** |  |  |  |  |  |  |
| Picture Vocabulary Test scale score |  |  |  |  |  |  |
| Flanker Test scale score |  |  |  |  |  |  |
| DCCS Test scale score |  |  |  |  |  |  |
| Picture Sequence Memory Test scale score |  |  |  |  |  |  |
| Oral Reading Recognition Test scale score |  |  |  |  |  |  |
| Nine-hole Peg Board Test scale score |  |  |  |  |  |  |
| Standing Balance Test scale score |  |  |  |  |  |  |
| Motion Coherence Threshold (%) |  |  |  |  |  |  |
| Neurocognitive impairment |  |  |  |  |  |  |
| Moderate-severe neurocognitive impairment |  |  |  |  |  |  |
| Executive dysfunction |  |  |  |  |  |  |
| Motor impairment |  |  |  |  |  |  |
| Low numeracy |  |  |  |  |  |  |
| Strength and Difficulties Questionnaire (SDQ)  Total Difficulties score > 14 |  |  |  |  |  |  |
| Prosocial Score ≤5 |  |  |  |  |  |  |
| Weight—kg |  |  |  |  |  |  |
| Height—cm |  |  |  |  |  |  |
| BMI—kg/m2 |  |  |  |  |  |  |
| Z-scores for age and sex *ʃ* |  |  |  |  |  |  |
| Weight |  |  |  |  |  |  |
| Height |  |  |  |  |  |  |
| BMI |  |  |  |  |  |  |
| Overweight |  |  |  |  |  |  |
| Obese |  |  |  |  |  |  |
| High blood pressure  Elevated blood pressure |  |  |  |  |  |  |
| Hypertension |  |  |  |  |  |  |

Data are number (percent) or mean (standard deviation). Analyses are adjusted for potential confounding by all matching criteria (sex, maternal BMI, prioritised ethnicity, NZ deprivation index, gestational age). *ʃ* Calculated by using the WHO growth reference for school-aged children.47

Table 3: Tertiary outcomes at early school age for GDM-exposed and non-GDM-exposed children in the GiST study

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Non-GDM exposed | N | GDM-exposed | N | aRD, aMD (95%CI)  *aOR [95% CI]* | P |
| Strength and Difficulties Questionnaire |  |  |  |  |  |  |
| Total Difficulties score |  |  |  |  |  |  |
| Prosocial Behaviour score |  |  |  |  |  |  |
| Child Health Questionnaire |  |  |  |  |  |  |
| Physical Functioning Score |  |  |  |  |  |  |
| Low physical functioning |  |  |  |  |  |  |
| Psychosocial Functioning Score |  |  |  |  |  |  |
| Low psychosocial function |  |  |  |  |  |  |
| Teacher global curriculum assessment: below or well below |  |  |  |  |  |  |
| Maths |  |  |  |  |  |  |
| Reading |  |  |  |  |  |  |
| Writing |  |  |  |  |  |  |
| Teacher peers’ comparison assessment:  worse or much worse |  |  |  |  |  |  |
| Maths |  |  |  |  |  |  |
| Reading |  |  |  |  |  |  |
| Writing |  |  |  |  |  |  |
| Current learning support |  |  |  |  |  |  |
| Triceps skinfold-mm |  |  |  |  |  |  |
| Z-score |  |  |  |  |  |  |
| AMA—cm2 |  |  |  |  |  |  |
| Z-score |  |  |  |  |  |  |
| Whole-body fat mass—kg |  |  |  |  |  |  |
| Fat mass index—kg/m2 |  |  |  |  |  |  |
| Whole-body lean mass—kg |  |  |  |  |  |  |
| Lean mass index—kg/m2 |  |  |  |  |  |  |
| Handgrip strength (dominant)-kg |  |  |  |  |  |  |
| Handgrip strength (non-dominant)-kg |  |  |  |  |  |  |
| Relative handgrip strength (dominant) kg/kg0.67 |  |  |  |  |  |  |
| Relative handgrip strength  (non-dominant)- kg/kg0.67 |  |  |  |  |  |  |
| Handgrip strength (combined)—kg |  |  |  |  |  |  |
| z-score |  |  |  |  |  |  |
| Relative handgrip strength (combined)—kg/kg0.67 |  |  |  |  |  |  |
| Peripheral BP |  |  |  |  |  |  |
| Systolic—mmHg |  |  |  |  |  |  |
| Systolic centile |  |  |  |  |  |  |
| Diastolic—mmHg |  |  |  |  |  |  |
| Diastolic centile |  |  |  |  |  |  |
| Central systolic BP pre-handgrip—mmHg |  |  |  |  |  |  |
| Central systolic BP pre-handgrip-z-score |  |  |  |  |  |  |
| Central systolic BP post-handgrip—mmHg |  |  |  |  |  |  |
| Central systolic BP post-handgrip— z-score |  |  |  |  |  |  |
| Aortic Augmentation index |  |  |  |  |  |  |
| Heart rate—beats per minute |  |  |  |  |  |  |
| Elevated hearth rate |  |  |  |  |  |  |

Data are number (percent) or mean (standard deviation). Analyses are adjusted for potential confounding by all matching criteria (sex, maternal BMI, prioritised ethnicity, NZ deprivation index, gestational age). Z-scores calculated by using the WHO growth reference for school-aged children.47