

BMJ Open Do changes in weight status affect cognitive function in children and adolescents with obesity? A secondary analysis of a clinical trial

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ABSTRACT

Objectives It is unclear whether an association exists between obesity in children/adolescents and cognitive function, and whether the latter can be altered by body mass index (BMI) standard deviation score (SDS) reductions. We aimed to determine whether an association exists between BMI SDS and cognitive function in children/adolescents with obesity engaged in an obesity intervention. Second, we sought to determine if BMI SDS reduction at 12 months was associated with improved cognitive function.

Design Secondary analysis of a clinical trial.

Participants Participants (n=69) were recruited from an obesity intervention. Eligible participants (recruited June 2013 to June 2015) were aged 6–16 years, with a BMI ≥98th centile or BMI >91st centile with weight-related comorbidities.

Outcome measures Primary outcome measure was change in BMI SDS from baseline at 12 months. Dependent variables of cognitive functioning and school achievement were assessed at baseline and 12 months, using dependent variables of cognitive functioning (elements of Ravens Standard Progressive Matrices, Wide Range Achievement Test-fourth edition and Wechsler Intelligence Scale for Children-fourth edition).

Results At baseline, BMI SDS was not associated with all aspects of cognitive function tested (n=69). Reductions in BMI SDS over time did not alter cognitive function overall. However, there was a greater reduction in comprehension standard scores in participants who increased their BMI SDS (adjusted estimated difference –6.1, 95% CI –11.6 to –0.6; p=0.03).

Conclusions There were no observed associations between BMI SDS and cognitive function in participants, apart from comprehension in the exploratory analyses, which may have been a random finding. Further studies need to include larger longitudinal cohorts incorporating a wider BMI range at entry to determine whether our findings persist.

Trial registration number ANZCTR12611000862943; Pre-results.

INTRODUCTION

It is recognised that obesity is associated with adverse neurocognitive outcomes in adults.¹

Strengths and limitations of this study

- This study is the first to report on any possible association between obesity and cognitive function in children and adolescents with obesity in New Zealand.
- This study used multiple assessments of executive function, in a group of children and adolescents with obesity participating in a multidisciplinary intervention, with comprehensive assessments at baseline and 12 months.
- Limitations included the heterogeneity of our sample in terms of age and high mean body mass index (BMI) standard deviation score (SDS) on entry (obese range: >98th percentile), and the mean 12 month BMI SDS remaining in the obese range.
- A potential confounder was parents/caregivers accepting assessment if there were pre-existing concerns about their child/adolescent's cognitive function.
- The study is also limited by a relatively small sample size, particularly for the stratified analyses, where we had insufficient power to draw any meaningful conclusions.

In simple terms, the relationship between obesity and brain function relates to executive function — or self-regulatory cognitive processes associated with monitoring of thought and goal-related behaviours.² These effects appear to be modifiable; a systematic review and meta-analysis of 20 studies found weight loss was associated with a significant improvement in performance across various cognitive domains in adults.³

The relationship between body mass index (BMI) and cognitive function in children and adolescents is not as well established as in adults.⁴ Cognitive skills (such as attention, working memory, flexibility and inhibition) tend to predict school achievement, and collectively these skills contribute to

executive function.⁵ Poorer educational outcomes have been found to be associated with increased weight status in American children.⁶ However, the existing data are somewhat conflicting, with a longitudinal study showing that increase in weight in American children during the first 4 years in school is a significant risk factor for adverse school outcomes for girls, but not boys.⁷ A systematic review showed that obesity is negatively associated with maths achievement in adolescent girls.⁸ Conversely, an Australian longitudinal dataset linked to assessments in maths and literacy found obesity and BMI were negatively related to school achievement for boys, but not girls.⁹ An American longitudinal study of 2–8-year-old followed for 6 years found no evidence of a causal relationship between child obesity and cognitive performance.¹⁰ Age may be a factor altering the association between weight and cognitive function, with infants with overweight/obesity showing lower cognitive and motor development when compared with normal weight peers.¹¹ Nonetheless, a further large systematic review found that overall, obesity in youth is associated with a decrease in executive function and poorer school performance in the long term.¹²

In terms of multicomponent interventions for child and adolescent obesity and the effects on cognitive function, a recent Cochrane systematic review found that in children with obesity or overweight, compared with a standard school routine, physical activity interventions can improve executive function.⁵ In children with obesity, school-based dietary interventions may benefit general school achievement.⁵ A recent study of 12-year-old Danish children who were overweight who participated in an intervention found improvements in visuospatial construction skills at 6 weeks, and emotional control and monitoring at 52 weeks.¹³ However, these findings were not reported in relation to any change in BMI standard deviation score (SDS).

Whānau Pakari is a multidisciplinary assessment and intervention programme for children and adolescents with obesity. Embedded within the service was a randomised clinical trial assessing the effects of the intervention on BMI SDS as the primary outcome measure.¹⁴ Whānau Pakari achieved a mean BMI SDS reduction across both groups of 0.10 (intervention) and 0.12 (control). Participants in the intense intervention group with attendance $\geq 70\%$ displayed a reduction in BMI SDS of 0.22.¹⁵

The purpose of this study was to determine whether BMI SDS was associated with cognitive function in a subset of the referred Whānau Pakari cohort. Further, we aimed to determine whether a reduction in BMI SDS would lead to an improvement in cognitive function (as assessed by tests of fluid reasoning, achievement, executive function and cognitive skills).

METHODS

The rationale and study design for the Whānau Pakari trial have been previously reported, as have the 12-month

outcomes of the trial.^{14 15} In brief, the unblinded randomised controlled clinical trial compared a 12-month intensive intervention with a minimal intensity control (receiving comprehensive assessments and advice), with 6 monthly follow-up for 2 years, conducted in Taranaki, New Zealand (NZ). For the purposes of this study, we enrolled participants who had consented to take part in Whānau Pakari into 'Healthy Brains', and given we were interested in BMI SDS reduction rather than the nature of the intervention, both groups (control and intervention) were eligible. Participants had to be willing to undertake cognitive function assessments. Written and verbal informed consents were obtained from all participants or their guardians.

Whānau Pakari was a novel home-based 'demedicalised' model (no hospital visits, with a comprehensive weight-related medical assessment in the home). The assessment included dietary, physical and psychological review, with assessment of readiness for change.¹⁴

The Taranaki region has a population of approximately 23 139 children aged 0–15 years, of whom 81% identify as NZ European (NZE), 28% as Māori and 1% as other ethnicity (multiple ethnicities possible).¹⁶ Eligible participants (recruited June 2013 to June 2015) were aged 5–16 years and had a BMI ≥ 98 th centile or BMI > 91 st centile,¹⁷ with weight-related comorbidities (such as obstructive sleep apnoea, type 2 diabetes, hyperlipidaemia or fatty infiltration of the liver). However, enrolment of participants who were 5 years old was deferred until 6 years due to normed scores for cognitive assessments commencing at 6 years of age. BMI percentile and BMI SDS were calculated using UK Cole normative data, using the KIGS auxology software (Pfizer Endocrine Care TM).¹⁸ Participants were referred to Whānau Pakari by a wide range of professionals. Participation in the Healthy Brains Study was offered to all participants of Whānau Pakari at baseline from June 2013. The Healthy Brains assessment occurred within 6 weeks of baseline assessment. Exclusion criteria were a pre-existing intellectual disability or global developmental delay.

Participant and public involvement

This study was designed in response to our discussions working with families, and the changes we saw in those participants who were achieving healthy lifestyle changes, such as improvements in dietary behaviour and increased physical activity. Participants were not officially involved in study design. Results will be disseminated to study participants in the form of an information leaflet after publication.

Assessment materials

Dependent variables of cognitive functioning were assessed as part of the Healthy Brains Study at baseline and 12 months. Participants were assessed in their home or at school depending on the preference of the legal guardian. All testing was individual testing; no group testing was undertaken. To obtain the best effort from the

Table 1 Baseline characteristics of the 69 Healthy Brains participants

n	69
Age (years)	11.2 (2.9)
Female	35 (50.7%)
Ethnicity*	
Māori	26 (37.7%)
NZ European	33 (47.8%)
Other	10 (14.5%)
Anthropometry	
BMI (kg/m ²)	28.9 (4.7)
BMI SDS	2.97 (0.5)
Waist to height ratio	0.57 (0.05)
Deprivation index (quintile)†	
1 (least deprived)	13 (18.8%)
2	7 (10.2%)
3	23 (33.3%)
4	13 (18.9%)
5 (most deprived)	13 (18.8%)
Accompanying adult	
Mother	52 (75.4%)
BMI (kg/m ²)‡	32.6 (6.9)
BMI ≥30 kg/m ² ‡	40 (63.5%)
Living arrangements§	
Two-parent household	31 (45.6%)
One-parent household	32 (47.1%)
Other	5 (7.4%)
Cognition (achievement)	
WRAT reading standard score	99.1 (14.2)
WRAT comprehension standard score	99.4 (13.1)
WRAT spelling standard score	95.0 (15.5)
WRAT maths standard score	85.8 (15.1)
WRAT reading comprehension standard score	98.5 (13.0)
Cognitive skills	
Raven SPM	96.6 (12.3)
WISC working memory composite score	89.4 (15.0)
WISC processing speed composite score	96.5 (12.7)

Age, anthropometry and cognitive data are means and SDs; all other data are n (%).

*Prioritised ethnicity.

†Quintiles of level of household deprivation based on the NZ Deprivation Index 2006.²⁷

‡Parameter was measured where consented to (n=63), otherwise not included. BMI ≥30 kg/m² adult cut-off for obese.

§n=68.

BMI, body mass index; NZ, New Zealand; SDS, standard deviation score; SPM, Standard Progressive Matrices; WISC, Wechsler Intelligence Scale for Children; WRAT, Wide Range Achievement Test.

participant, the test was administered in a quiet room free from distractions and disruptions. Test and retest were in the same environment (either home or school). Family members were not present during testing. Duration of

assessment was approximately 1 hour. Each assessment started with: (1) the Ravens Matrices¹⁹; (2) the Wide Range Achievement Test-fourth edition (WRAT4)²⁰ in the order: word reading, sentence comprehension, spelling and mathematics and (3) subtests from the Wechsler Intelligence Scale for Children-fourth edition (WISC-IV)²¹ provided scaled scores for working memory and processing speed.

Raven's Standard Progressive Matrices

Raven's Standard Progressive Matrices (SPM) is an instrument originally designed to measure the educative aspect of Spearman's 'g'¹⁹ and is used to provide an estimate of fluid reasoning ability. The SPM is made up of 60 questions divided into five sets of 12. Each question is made up of a pattern, which has a section missing, and the participant is required to identify the missing part from a range of options provided below the stimulus.¹⁹ Each set is designed to begin with a self-evident answer and to become more difficult. The raw scores achieved in the SPM are converted to percentile ranks.¹⁹ The age range for normed data for NZ is 8–15.5 years. The age range for the Australian normed data is 8.5–17.2 years. Both these sets of normed data are in the context of the 1979 British data.¹⁹ The British normed data ranges from 6 years 3 months to 15 years 8 months.¹⁹ The British and Australian scores were used for different age ranges within the cohort.

Wide Range Achievement Test-fourth edition

The WRAT4 is a standardised instrument that measures the basic academic skills of word reading, sentence comprehension, spelling and math computation.²⁰ These academic skills correlate with concrete academic skills expected for performance in the classroom setting.

Word reading measures letter and word decoding through letter identification and word recognition.²⁰ Sentence comprehension measures the ability to gain meaning from words and comprehend ideas and information contained in a sentence.²⁰ Spelling uses a dictated spelling format and measures an individual's ability to encode sounds into written form.²⁰ Reading composite is obtained by combining the word reading and sentence comprehension standard scores to provide a highly reliable, comprehensive measure of reading achievement.²⁰ Math computation measures an individual's ability to perform basic mathematics computation through counting, identifying numbers, solving simple oral problems and calculating written mathematics problems.²⁰

The scores on the WRAT4 are expressed as scaled scores ranging between 40 and 160 with the mean of 100. The Green WRAT forms were used for the first assessment (T=0). The Blue WRAT forms were used for the 12-month follow-up assessment (T=12).²⁰ The Blue and Green forms are able to be used interchangeably with comparable results, which allow for retesting within short periods of time without potential practice effect from repeating identical items.²⁰

Table 2 Linear associations between body mass index standard deviation score at baseline and cognitive outcomes at baseline (n=69)

	β (95% CI)	P value
Achievement		
WRAT reading standard score	-2.29 (-9.14 to 4.55)	0.51
WRAT comprehension standard score	-5.68 (-12.12 to 0.76)	0.08
WRAT spelling standard score	-3.71 (-11.21 to 3.80)	0.33
WRAT maths standard score	1.38 (-5.80 to 8.56)	0.70
WRAT reading comprehension standard score	-4.39 (-10.66 to 1.89)	0.17
Cognitive skills		
Raven SPM	1.73 (-4.37 to 7.83)	0.57
WISC working memory composite score	-4.88 (-9.45 to 5.76)	0.57
WISC processing speed composite score	-0.78 (-7.24 to 5.67)	0.81

Adjusted for level of household deprivation and whether normal development reported.

SPM, Standard Progressive Matrices; WISC, Wechsler Intelligence Scale for Children; WRAT, Wide Range Achievement Test.

Wechsler Intelligence Scale for Children-fourth edition

Executive function was assessed using four subtests from the WISC-IV.²¹ These subtests provided scaled scores on processing speed and working memory. The scaled scores range between 40 and 160 with the mean of 100.²¹

Processing speed was assessed using the digit symbol and symbol search subtests.²¹ Working memory was assessed using the digit span and letter-number sequence

Table 3 Linear associations between change in body mass index standard deviation score at 12 months and change in cognitive outcomes at 12 months (n=60)

	β (95% CI)	P value
Achievement		
WRAT reading standard score	-2.6 (-10.3 to 5.2)	0.50
WRAT comprehension standard score	-5.6 (-14.3 to 3.0)	0.20
WRAT spelling standard score	7.5 (-1.6 to 16.7)	0.11
WRAT maths standard score	-3.0 (-10.5 to 4.5)	0.43
WRAT reading comprehension standard score	-3.5 (-10.5 to 3.4)	0.32
Cognitive skills		
Raven SPM	-3.0 (-11.9 to 5.9)	0.51
WISC working memory composite score	-0.57 (-8.0 to 6.9)	0.88
WISC processing speed composite score	2.9 (-6.0 to 11.7)	0.52

Data are β coefficients and 95% CI, adjusted for level of household deprivation, whether normal development was reported, intervention group and the respective parameter at baseline. SPM, Standard Progressive Matrices; WISC Wechsler Intelligence Scale for Children; WRAT, Wide Range Achievement Test.

subtests from the WISC-IV.²¹ Both working memory and processing speed are important components of executive function in children and adolescents and together give an indication of attention.²¹ The age range for the normed data is from 6 to 16.9 years.²¹

Scoring

Scores were obtained from the administration of the Ravens, WRAT and WISC (four subsets). The raw scores were converted to standard scores.

A feedback system was used to alert the Whānau Pakari team of any concerns (psychological or health) that were noted during the assessments. Feedback was provided to parents giving their child/adolescent's results after the 12-month assessment, or earlier if there were significant concerns.

Data analyses

Linear associations between BMI SDS and parameters of cognitive function were examined using general linear mixed regression models. Models adjusted for socioeconomic deprivation and whether or not normal development was reported, while family code was included as a random factor to account for sibling clusters.

Similar models were used to examine the association between change in BMI SDS at 12 months and possible changes in cognitive outcomes, except that the trial arm was included as a factor and the respective parameter at baseline was also added as a covariate. In addition, stratified analyses were carried out comparing changes in cognition between participants who had a reduction or no change in BMI SDS compared with those with a gain in BMI SDS at 12 months.

Sensitivity analyses were carried out for the above-described models, adjusting also for either the available measure of physical fitness at baseline (time to complete 550-m walk/run) or ethnicity. Further sensitivity analyses were run, after exclusion of any potential outliers. These were identified using Tukey's method,²² with respective boundaries defined as:

$$\text{Lower boundary} = Q1 - (1.5 * IQR)$$

$$\text{Upper boundary} = Q3 + (1.5 * IQR)$$

Where, Q1 is quartile 1, Q3 is quartile 3, and IQR the interquartile range.

Statistical analyses were performed using SAS V.9.4 (SAS). All statistical tests were two-tailed and maintained at a 5% significance level.

RESULTS

A total of 69 participants were recruited for Healthy Brains from the Whānau Pakari trial. There were no exclusions for medical conditions, global developmental delay or intellectual disability. Table 1 shows the baseline characteristics of the participants.

There were no associations between baseline BMI SDS and scores of achievement and cognitive skills at baseline (table 2).

Table 4 Change in cognitive outcomes between participants who had a body mass index (BMI) standard deviation score (SDS) reduction or no change compared with those who displayed a gain in BMI SDS at 12 months

	BMI SDS loss or no change	BMI SDS increase	P value
n	36	24	
Achievement			
WRAT reading standard score	-2.0 (-5.9 to 2.0)	-3.9 (-8.1 to 0.2)	0.40
WRAT comprehension standard score	-6.3 (-11.0 to -1.6)	-12.4 (-17.9 to -7.6)	0.03
WRAT spelling standard score	2.2 (-3.2 to 7.6)	0.7 (-5.1 to 6.5)	0.65
WRAT maths standard score	-0.6 (-4.4 to 3.3)	-1.8 (-6.0 to 2.5)	0.60
WRAT reading comprehension standard score	-4.3 (-8.0 to -0.6)	-7.5 (-11.5 to -3.5)	0.15
Cognitive skills			
Raven SPM	-2.1 (-6.6 to 2.4)	-3.2 (-8.1 to 1.7)	0.69
WISC working memory composite score	0.24 (-3.7 to 4.1)	0.23 (-3.9 to 4.4)	0.99
WISC processing speed composite score	-1.2 (-5.8 to 3.4)	2.6 (-2.1 to 7.3)	0.16

Data are means and 95% CIs, adjusted for level of household deprivation, whether normal development was reported, intervention group and the respective parameter at baseline.

SPM, Standard Progressive Matrices; WISC Wechsler Intelligence Scale for Children; WRAT, Wide Range Achievement Test.

Nine participants were lost to follow-up at 12 months, so the 12-month follow-up data were obtained on 60 individuals (87% retention rate). Mean BMI SDS at 12 months was 2.89 (SD 0.61), indicating a mean reduction of 0.08 from baseline. There were no associations between change in BMI SDS at 12 months and change in cognitive outcomes at 12 months (table 3).

Exploratory analyses showed no associations of either sex or age at assessment with scores of achievement or cognitive skills at baseline or changes from baseline. In addition, changes in cognitive outcomes at 12 months were mostly similar between participants with a reduction or no change in BMI SDS compared with those with an increase in BMI SDS at 12 months (table 4). The exception was that there was a greater reduction in WRAT comprehension standard scores in participants who experienced an increase in BMI SDS (adjusted estimated difference -6.1, 95% CI -11.6 to -0.6; $p=0.03$) (table 4).

The mean change in BMI for the group showing an increase was 0.19 SDS (95% CI 0.08 to 0.29), in comparison to an average reduction of -0.22 SDS (95% CI -0.29 to -0.15) for participants with either a decrease or no change in BMI. Note that in multivariable models, the associations between socioeconomic status and cognitive outcomes were not statistically significant. In regard to development, 8 of the 60 (13%) participants with follow-up data were reported by their parent or caregiver not to have had normal development. These participants displayed a more marked reduction in WRAT comprehension standard scores after 12 months than those with normal development (-13.8, 95% CI -20.6 to -7.0 vs -3.8, 95% CI -6.5 to -1.2; $p=0.009$).

Lastly, sensitivity analyses showed that the results were largely unchanged after additional adjustment for physical fitness (550-m walk/run) at baseline (data not shown). In addition, the findings reported in tables 2-4

were unchanged following reanalyses after exclusion of possible outliers (data not shown). Further, adjustment for ethnicity in the models as well as subgroup analyses within NZE or Māori participants also mirrored the overall findings.

DISCUSSION

This study found that BMI SDS at baseline was not associated with multiple aspects of cognitive function in children with obesity. Second, we observed no associations between changes in BMI SDS and cognitive function in a group of children and adolescents with obesity participating in a multidisciplinary intervention programme. This was also the case when the subgroup with static BMI SDS or reduction were compared with those participants who had an increase in BMI SDS, apart from comprehension. Our findings are consistent with previous longitudinal data; a study using two nationally representative US cohorts found minimal evidence for a longitudinal relationship between obesity and cognitive test scores.¹⁰ However, the authors acknowledged that the low obesity prevalence in their cohort and age of the data may have impacted on their ability to detect any relationship.¹⁰ In the Healthy Brains cohort, the reduction of comprehension scores in the exploratory analyses may have been due to the degree of obesity in the participants, and the lack of shift from the obese range for any of the participants in this group at 12 months. Participants who displayed an increase in BMI SDS had a greater reduction in comprehension scores than those with no increase or a reduction in BMI SDS.

Current evidence for an association between aspects of cognitive function and obesity in childhood remains limited. A systematic review found that full IQ and performance IQ are lower in school-aged children with obesity

than normal weight counterparts.⁴ While no causal relationship is known, the authors hypothesised that individuals with obesity have regional brain volume decreases that could cause lower cognitive function and reduce IQ.⁴ However, when the authors adjusted for educational attainment, the associations between full IQ and obesity were null.⁴ In another systematic review, the majority of the evidence supported a relationship between obesity and deficits in executive functioning, attention, visuospatial skills and motor skills.¹² Nonetheless, this review acknowledged multiple studies with a lack of association between obesity and neurocognitive functioning.¹² A further systematic review reported insufficient evidence to support a direct link between obesity and lower academic performance in school-aged children.²³ However, longitudinal associations have been found between adolescent girls' achievement in maths and obesity, which were potentially influenced by weight-related bullying and executive function.⁸

Longitudinal survey of Australian children data showed on the Strengths and Difficulties Questionnaire, that emotional, peer and conduct problems are associated with obesity, after adjustment for other contributing factors, such as maternal mental health and standard child characteristics.²⁴ The authors highlight that these findings relating to emotional difficulties may affect children's general happiness and psychological resilience, and potentially, cognitive development.²⁴ This is consistent with recent findings in the Whānau Pakari cohort, in which there was low health-related quality of life and a high risk of psychological difficulties in comparison with normative population data.²⁵ If such aspects do contribute to poorer cognitive development, a potential confounder for this study was that improvements were seen in health-related quality of life and potential psychological difficulties in the participants of Whānau Pakari at 12 months.¹⁵ However, these improvements would be likely to enhance any increase in cognitive function, which we did not see.

Strengths of this study were the use of multiple assessments of executive function, in a group of children and adolescents with obesity participating in a multidisciplinary intervention, with comprehensive assessments at baseline and 12 months. Limitations included the heterogeneity of our sample in terms of age, and possible comorbidities/learning difficulties that may have impacted on cognitive function assessments. Because Healthy Brains was an opportunity to attain free cognitive function assessments, the sample may have been biased towards those families with pre-existing concerns about their child/adolescent's cognitive function, despite being open to all participants. It is possible that our null findings in terms of BMI SDS reduction were due to the small size of BMI SDS reduction, and the limited range of BMI at entry (mean BMI SDS was well above the 98th percentile, and remained above the 98th percentile at 12 months). The study is also limited by a relatively small sample size, particularly for the stratified analyses, where we had insufficient

power to draw any meaningful conclusions. Given this was a secondary analysis, the study was not powered to detect an effect in cognitive function from the outset, as the primary study aims did not include assessment and evaluation of cognitive function.

Weight loss in adults with overweight/obesity has been found in a systematic review and meta-analysis to be associated with improvements in performance across various cognitive domains.³ However, the included randomised controlled trials had an average age of 53.8 years, were predominantly female (68%), and with a mean BMI decrease of 2.5 kg/m².³ What remains unclear is the degree of weight loss or BMI SDS reduction in children with obesity who are growing that would be required to see positive effects in cognitive function, if they indeed exist. A systematic review found that multicomponent interventions led to small improvements in overall school achievement in children with overweight/obesity.²⁶ However, many of the included studies did not report BMI or BMI SDS outcomes.²⁶

In conclusion, this study found little evidence of an association between BMI SDS and cognitive function in children with obesity, apart from in comprehension scores in exploratory analyses. Further studies need to include larger longitudinal cohorts incorporating a wider BMI range at entry, with longer follow-up.

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Contributors YCA designed the study, was involved with data interpretation and drafted the manuscript. KK undertook cognitive assessments and data entry, and was involved in study design. GMSD provided psychologist oversight, and was involved in study design. TAW was involved in interpretation of data and study design. CCG is secondary supervisor for the research team and assisted with the design of the study. TLC and CEKW assisted with data entry and analysis. JGBD analysed the data. WSC contributed to study design. PLH contributed to study design and supervises the research team. All authors critically revised the manuscript, gave final approval for the version to be published and are accountable for all aspects of the work.

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Patient consent for publication Not required.

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Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Anonymised and deidentified data may be made available to other investigators on request. Interested readers should contact the senior author PLH (p.hofman@auckland.ac.nz) to obtain the data.

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