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Outcome at two years after dextrose gel prophylaxis for neonatal hypoglycemia

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Abstract

Background: Neonatal hypoglycaemia is associated with an increased risk of neurosensory impairment. Prophylactic dextrose gel reduces the risk of neonatal hypoglycaemia. The aim of this study was to determine longer term safety of prophylactic dextrose gel for prevention of neonatal hypoglycaemia.

Methods: We followed-up participants from the pre-hPOD trial (randomized to one of four dose regimes of buccal 40% dextrose gel, or equivolume placebo) at two years' corrected age. Co-primary outcomes were neurosensory impairment and executive function. Secondary outcomes were components of the primary outcomes, neurology, anthropometry and health measures.

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Contributors statement page

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

Conclusion: Prophylactic dextrose gel appears safe to two years' corrected age, but this study was underpowered to detect potentially clinically important effects on neurosensory outcomes. These results should be interpreted with caution and no change should be made to current clinical practice.

Table of contents summary:

This prospective follow-up study found that prophylactic oral dextrose gel in infants at risk of neonatal hypoglycaemia is safe up to two years of age.

Background

Neonatal hypoglycemia is common ^{1,2}. Approximately 50% of neonates born at risk of hypoglycemia have at least one episode, and 20% have a severe episode ². Hypoglycemia is associated with brain injury, seizures and poor neurodevelopmental outcomes ³⁻⁵. Even transient and treated neonatal hypoglycemia has been associated with adverse outcomes, particularly executive and visual-motor dysfunction ⁵ and poorer school performance ¹.

Buccal administration of 40% dextrose gel is an effective treatment for neonatal hypoglycemia ⁶ with no adverse effects reported up to 2 years of age ⁷, and its potential use for hypoglycemia prophylaxis is currently being trialled ⁸. We previously have reported the findings of the pre-hPOD randomized trial, designed to determine the optimal dose of 40% dextrose to prevent neonatal hypoglycemia ⁹. We found that any of the trialled doses of dextrose gel given to infants at risk reduced the incidence of hypoglycemia (RR 0.79, 95% confidence interval [CI] 0.64, 0.98, $p = 0.03$, number needed to treat 10), and that 200 mg/kg at one hour after birth was most effective with fewest limitations (RR 0.68, 95% CI 0.47, 0.99, $p=0.04$, number needed to treat 7) ⁹. In order to assess longer term safety of this approach, we now report outcomes at two years' corrected age of participants in the pre-hPOD trial.

Methods

Study design

Details of the pre-hPOD trial have been published previously ⁹. In brief, 416 infants at risk of hypoglycemia (infant of a diabetic mother, small [birthweight <2.5 kg or <10th centile], large [birthweight >4.5 kg or >90th centile] or late preterm [35 or 36 weeks]) were randomized to one of four dosage arms of 40% dextrose gel (0.5 ml/kg [200 mg/kg] once, 1 ml/kg [400 mg/kg] once, 0.5 ml/kg for four doses [total 800 mg/kg] or 1 ml/kg once

followed by 0.5 ml/kg for a further three doses [total 1,000 mg/kg] or four dosage arms of equivolume placebo gel. The primary outcome was neonatal hypoglycemia (blood glucose concentration < 47 mg/dl (2.6 mmol/l)).

Two Year Follow-up

All families who participated in the pre-hPOD dosage trial and who had consented at the time of initial recruitment to further contact were invited to participate in this follow-up study. Follow-up took place between August 2015 and February 2017 in New Zealand. Ethics approval was obtained from the Health and Disability Ethics Committees of New Zealand (13/NTA/8) and caregivers gave written informed consent at the time of assessment.

At 24 months' corrected age, children underwent a comprehensive assessment of neurodevelopment, growth and general health by doctors trained in all assessments who were unaware of the child's randomization group. Assessment included Bayley Scales of Infant Development 3rd edition ¹⁰, neurological examination, executive function (clinical assessment of inhibitory control and attentional flexibility ¹¹) and Behavior Rating Inventory of Executive Function—Preschool Version (BRIEF-P) ¹².

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

Home and health information were collected using a questionnaire. Asthma was defined as any of: diagnosis by doctor, medicine or inhaler use for wheeze or asthma in the preceding 12 months, or hospitalized for wheeze or asthma ¹³. Eczema was defined as itchy rash coming and going for 6 months ¹³ or diagnosis and treatment by doctor for eczema. Visits to a doctor for infectious illnesses were recorded.

The two pre-specified co-primary outcomes were neurosensory impairment (any of: legal blindness; sensorineural deafness requiring hearing aids; cerebral palsy; Bayley Scales of Infant Development 3rd edition [BSID-III] cognitive, language or motor score more than one standard deviation below the mean) and executive function composite z-score < -1.5, derived from standardization within the whole pre-hPOD 2-year cohort. Children unable to complete the cognitive, language or motor scales of the BSID-III because of severe delay in any of these domains were assigned scores of 49. Secondary outcomes were the components of the primary outcomes, neurology, anthropometry, and health measures. The WHO Child Growth Standards were used for calculation of z-scores, based on corrected age ¹⁴.

Statistical analysis

Analyses were performed using SAS version 9.4 (SAS Institute Inc. Cary NC). Relative risks (RR) or mean difference (MD) with 95% CI were estimated using generalized linear models, adjusted for recruitment center, socioeconomic status at birth (NZ Deprivation Index 2013 ¹⁵), gestational age and sex. These potential confounders were pre-specified with knowledge of their association with neurodevelopmental outcomes. We planned to combine

placebo groups in the analyses if there were no differences between them in the primary outcomes. We pre-specified that the primary outcomes would be compared between different dextrose gel dosage groups, between single and multiple dose groups, and between any dextrose gel dose and any placebo dose groups. Secondary analyses were pre-specified to examine any interactions between the effect of any dextrose gel versus placebo on primary outcomes and their components and the risk factor for hypoglycemia (diabetic mother versus other) and gestational age (preterm versus term), and also to determine the effect of hypoglycemia on the primary outcomes and their components and the effect of dextrose versus placebo on the primary outcomes and components in those who became hypoglycaemic. In this last subgroup, models to calculate relative risk for low motor or executive function failed to converge when fully adjusted, so the relative risks shown for these two outcomes are only adjusted for socioeconomic status, gestational age and sex.

We used two-sided statistical tests and the p value for the co-primary outcomes was divided evenly, giving a p value of 0.025 for each and maintaining the alpha error at 5%. All analyses were performed on an intention-to-treat basis. A significance level of 5% was used for each secondary outcome. Dunnett's test was used for multiple comparisons. Linear trends were tested using orthogonal contrasts. Data are presented as number (%), mean (SD), median (range), MD (95% CI), or RR (95% CI).

Results

In the pre-hPOD trial, 416 infants were randomized. One was incorrectly randomized after the trial had finished, 13 withdrew and 1 child died prior to 2 years, leaving 401 children eligible for follow-up, of whom 360 were assessed at two years (90% of those eligible, 87% of those randomized) (Figure 1). The mean age of mothers of children followed up was 33 years compared to 30 years in those not followed up, and the gestational age at birth of those followed up was 0.40 weeks less than of those not followed up (Table 1). Other maternal and infant characteristics were similar in those followed up and not followed up, and also amongst all randomization groups. Mean corrected age at follow up was ~25 months and similar in all groups.

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

Increasing cumulative dextrose dose did not alter the risk of neurosensory impairment (Table 2). Although there was a trend towards an improvement in executive function with increasing cumulative dextrose dose ($p=0.03$), this did not reach statistical significance with the split p value of 0.025 for each co-primary outcome. However, there was a trend for increasing cumulative dextrose dose to be associated with improved composite language scores ($p=0.05$) and fewer abnormalities of co-ordination or tone ($p=0.05$). There were no differences in any other secondary outcomes with increasing dose of dextrose gel.

When combined single and combined multiple doses of dextrose gel were compared with the combined placebo group, the risk of neurosensory impairment was similar amongst groups (Table 3). The multiple dextrose doses group had fewer low executive function scores compared to single or placebo groups, but this was not statistically significant ($p=0.04$) using the split p value of 0.025 for each co-primary outcome. There were no other differences in secondary outcomes between single, multiple and placebo groups.

When children who had received any dextrose dose were compared with those who received any placebo, the risk of neurosensory impairment was similar (Table 3). Although low executive function scores were less likely in the dextrose group (RR 0.48, 95% CI 0.23, 0.99), after adjustment this difference was no longer significant ($p=0.07$). Similarly, motor scores were higher in the dextrose group (mean difference 2.70, 95% CI 0.04, 5.37), but this difference was no longer significant after adjustment ($p=0.06$). There were no differences in other secondary outcomes between any dextrose and any placebo groups.

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

Discussion

In children born at risk of neonatal hypoglycemia, prophylactic dextrose gel does not alter the risk of neurosensory impairment or low executive function scores at 2 years' corrected age, regardless of the dose used. The secondary outcomes including neurology, growth, eczema, asthma and infectious illness rates were also similar in dextrose and placebo groups, providing reassurance about the safety of using oral dextrose gel prophylaxis in neonates at risk of hypoglycemia. Our results are in keeping with a previous study demonstrating similar rates of neurosensory impairment between dextrose and placebo gel groups and no adverse effects when used for treatment of neonatal hypoglycemia ⁷.

The primary aim of this study was to assess the safety of prophylactic dextrose gel; it was underpowered to detect small but clinically important differences in the primary and secondary outcomes. Nevertheless, we found several consistent trends in the data that, although not statistically significant, would be of potential importance if confirmed in a

larger study. There was a trend towards a decreased risk of low executive function with increasing cumulative doses of prophylactic oral dextrose gel, with multiple doses, or with any dextrose dose compared to placebo, and in the subgroup of infants who became hypoglycaemic. Executive function is the ability to learn using working memory, problem solving, reasoning and cognitive flexibility. Thus, subtle detrimental effects on executive function seen at two years of age may later translate into poorer academic performance. Adverse effects on later executive function have been reported in infants born moderate to late preterm^{16,17} and those born to diabetic mothers¹⁸. We observed a relationship between prophylactic dextrose gel and performance on assessed executive function tasks specifically developed for this age group¹¹, but not on the parent-reported BRIEF-P. The assessment tasks address specific components of executive function and are complementary to the manifestations of executive function in everyday behaviour assessed in the BRIEF-P. Thus, our findings may reflect improvement in specific components of executive function rather than observable effects in the child's usual environment. At 2 years of age, executive function is still developing and it is possible that further testing once the children are older may clarify the clinical significance of these observations.

We also found a trend towards fewer abnormalities of tone and co-ordination with increasing cumulative dose of dextrose and a trend towards improved motor function with any dextrose dose compared to placebo. Infants of diabetic mothers^{19,20}, moderate and late preterm infants²¹ or small for gestational term infants²² have previously been shown to have poorer motor scores compared to control infants, and poorer motor skills have been associated with neonatal hypoglycemia in infants of diabetic mothers²³ and preterm infants⁴.

There was also a trend towards higher language scores with increasing cumulative dose of dextrose and with any dextrose dose compared to placebo. The largest risk group in our study was infants of diabetic mothers. Poorer language skills have previously been documented in children of diabetic mothers²⁴ and associated with maternal glycaemic control²⁵ and in term SGA infants²⁶.

Interestingly, these possible relationships between dextrose gel prophylaxis and executive function, language, motor performance were not associated with the presence or absence of recorded hypoglycemia. The reason for this is unclear, especially as there was no dose-response observed for the effect of dextrose gel prophylaxis on the incidence or severity of neonatal hypoglycemia in the pre-hPOD trial⁹. It is possible that prophylactic dextrose gel prevented periods of hypoglycemia not detected on intermittent blood glucose monitoring. Continuous glucose monitoring has shown that up to 80% of episodes of neonatal hypoglycemia may be unrecognized using intermittent blood glucose monitoring²⁷. Further, in the CHYLD study of a cohort of children born at risk, exposure to neonatal hypoglycemia was not associated with neurosensory impairment or its components at 2 years²⁸, but at 4.5 years of age was associated with impaired executive and visual motor development in a dose dependent manner⁵, suggesting that the effects of hypoglycemia may not be evident at 2 years of age. It is also possible that the threshold we used to define hypoglycemia is not optimal for prediction of later outcomes. The threshold for defining hypoglycemia remains a topic of debate²⁹, but we used the widely used cut-off based on studies showing a

detrimental effect below 47 mg/dL (2.6 mmol/L)^{3,4}, and have not found a more discriminatory threshold to date^{5,28}.

A strength of this study is the high follow-up rate, as participants not followed up in studies are more likely to have worse outcomes than those followed up^{5,30}. In addition, this was a prospective follow-up study of participants in a blinded randomized controlled trial with similar sociodemographic characteristics across randomization groups, which should have minimized the possible effect of unrecognized confounders on the outcomes. Our assessment was comprehensive, including a standard and widely accepted assessment of early development (BSID-III), in which low scores in cognitive and language domains are predictive of later intellectual function at age 4 years^{31,32}, and also tests of more subtle neurodevelopment, and executive function; skills known to be affected by neonatal hypoglycemia¹⁸.

An important limitation of this study was that the original trial was designed to have sufficient power to compare the incidence of hypoglycemia in at-risk infants treated with prophylactic dextrose or placebo, but not differences in later developmental outcomes. Future follow-up of the 2,149 children who have now been recruited to the hPOD study⁸ of oral dextrose gel prophylaxis should help clarify if this intervention does indeed result in improvements in executive function, language and motor performance function, as suggested by the trends observed in this study. We performed multiple comparisons, since this was primarily a safety study and we wished to maximize the chance of detecting any possible adverse effects, but this leads to increased risk of a type 1 error. Thus, these findings should be interpreted with caution, pending the results of follow-up of the larger hPOD trial cohort⁸. In addition, the majority of participants in the pre-hPOD trial were infants of diabetic mothers, so our results primarily reflect the outcomes of this risk group.

The use of dextrose gel for treatment of neonatal hypoglycemia is expanding^{33–35}. Although it appears to be safe, as yet there is insufficient evidence for use of prophylactic dextrose gel in clinical practice, especially as large numbers of infants would be potentially eligible for such treatment. The follow-up of the 2,149 participants in the recently completed hPOD trial with will have much greater power to detect any effect of prophylactic dextrose gel both on short term efficacy and on later outcomes.

Conclusions

Prophylactic oral dextrose gel given to infants at risk of neonatal hypoglycemia appears to be safe to 2 years of age. It does not alter the risk of neurosensory impairment or executive function, although we observed trends in improved executive function, language and motor performance across several analyses. These results should be interpreted with caution and no change should be made to current clinical practice.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

RR	relative risk
CI	confidence interval
BSID-III	Bayley Scales of Infant Development, 3 rd edition
WHO	World Health Organization
SD	standard deviation
MD	mean difference
BRIEF-P	Behavior Rating Inventory of Executive Function—Preschool Version

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What's Known on This Subject:

Neonatal hypoglycaemia is common, with 30% of infants identified as at risk, and is associated with neurosensory impairment. Prophylactic oral dextrose gel reduces the incidence of neonatal hypoglycaemia in infants born at risk.

What This Study Adds:

In this prospective follow-up study of the pre-hPOD randomized, controlled, dosage trial of prophylactic oral dextrose gel in at risk infants, there was no difference in neurodevelopment at two years between children randomized to prophylactic dextrose or placebo.

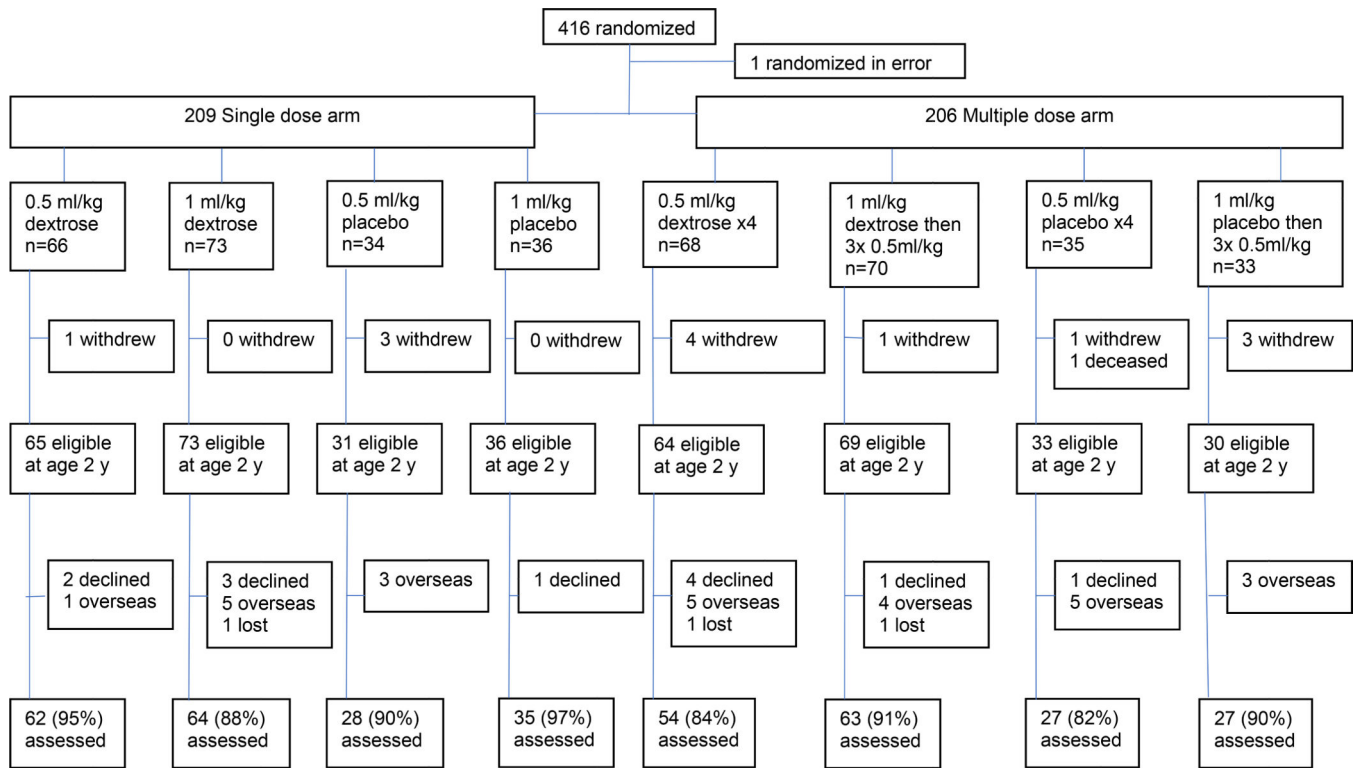


Figure 1:
Profile of participants: recruitment to two years

Table 1. Characteristics of mothers and infants who were and were not followed up at 2 years

	Not followed up		Followed up				
	Total	Total	Single placebo	Single dose Dextrose 0.5 ml/kg	Dextrose 1 ml/kg	Multiple placebo Dextrose 0.5 ml/kg × 4	Multiple dose Dextrose 1 ml/kg × 1, 0.5 ml/kg × 3
Mothers (N=403)^a	55	358	63	62	62	54	63
Age, years	30 (5)	33 (5) ^b	33 (6)	33 (5)	34 (5)	32 (6)	32 (5)
Booking BMI kg/m ² ^c	29 (9)	29 (8)	29 (8)	29 (7)	29 (8)	29 (7)	28.1 (9.2)
Caesarean section	23 (42)	176 (49)	34 (54)	33 (53)	30 (47)	31 (57)	27 (43)
Parity ^d	1 (0-5)	1 (0-8)	1 (0-8)	1 (0-6)	0 (0-4)	1 (0-4)	1 (0-7)
Diabetic ^e	41 (75)	260 (73)	45 (71)	47 (76)	44 (72)	38 (70)	44 (70)
Highest level of education ^f							
High School	NA	65 (20)	13 (24)	11 (19)	11 (20)	13 (28)	9 (18)
Tertiary	NA	253 (80)	42 (76)	47 (81)	43 (79)	33 (72)	40 (82)
Infants (N=415)	55	360	63	62	64	54	63
Female	28 (51)	174 (48)	27 (43)	33 (53)	35 (55)	26 (48)	25 (40)
Gestation, weeks	38.7 (1.1)	38.3 (1.1) ^g	38.2 (0.9)	38.3 (1.2)	38.2 (1.2)	38.4 (1.2)	38.4 (1.2)
Birthweight, grams	3217 (616)	3249 (616)	3189 (650)	3276 (618)	3261 (650)	3326 (650)	3191 (578)
Birthweight z-score	-0.07 (1.30)	0.17 (1.29)	0.05 (1.34)	0.29 (1.30)	0.24 (1.38)	0.32 (1.34)	-0.04 (1.12)
Twins	1 (2)	30 (8)	6 (10)	4 (6)	8 (13)	5 (9)	5 (8)
NZDPI	6 (1-10)	6 (1-10)	6 (1-10)	7 (1-10)	5 (1-10)	7 (1-10)	7 (1-10)
Prioritized ethnicity							
M ori	7 (12.7)	35 (9.7)	9 (14.3)	5 (8.1)	3 (4.7)	9 (16.7)	5 (9.3)
Pacific	11 (20.0)	57 (15.8)	9 (14.3)	12 (19.4)	11 (17.2)	9 (16.7)	7 (13.0)
Asian	15 (27.3)	91 (25.3)	15 (23.8)	13 (21.0)	16 (25.0)	18 (33.3)	12 (19.1)
NZ European	14 (25.5)	100 (27.8)	16 (25.4)	14 (22.6)	23 (35.9)	7 (13.0)	15 (27.8)
Other	8 (14.6)	77 (21.4)	14 (22.2)	18 (29.0)	11 (17.2)	11 (20.4)	10 (18.5)

	Not followed up		Followed up			
	Total	Single placebo	Dextrose 0.5 ml/kg	Dextrose 1 ml/kg	Multiple placebo	Multiple dose
			Dextrose 0.5 ml/kg × 4	Dextrose 1 ml/kg × 1,	Dextrose 0.5 ml/kg × 4	Dextrose 1 ml/kg × 1, 0.5 ml/kg × 3
Primary risk factor ^g						
Infant of diabetic	41 (75)	45 (71)	47 (76)	44 (69)	38 (70)	44 (70)
Preterm	3 (5)	3 (5)	4 (6)	6 (9)	3 (6)	6 (10)
Small	6 (11)	10 (16)	6 (10)	7 (11)	6 (11)	9 (14)
Large	5 (9)	5 (8)	5 (8)	7 (11)	7 (13)	4 (6)
Hypoglycemia	22 (40)	35 (56)	23 (37)	31 (48)	28 (52)	24 (38)

Data are n (%), mean (SD), or median (range)

^aThere are 12 mothers of twins, of whom 10 appear in more than one column because each twin was assigned to a different treatment group

^bp<0.05 for comparison between those who were and were not followed up

^cData missing for 12 not followed up, 10 single placebo, 7 dextrose 0.5ml/kg, 7 dextrose 1ml/kg, 6 multiple placebo, 6 dextrose 0.5ml/kg multiple, 9 dextrose 1ml/kg multiple

^dData missing for 12 not followed up, 10 single placebo, 7 dextrose 0.5ml/kg, 7 dextrose 1ml/kg, 6 multiple placebo, 6 dextrose 0.5ml/kg multiple, 9 dextrose 1ml/kg multiple

^eData missing for 1 dextrose 1ml/kg

^fData missing for 8 single placebo, 4 dextrose 0.5ml/kg, 10 dextrose 1ml/kg, 8 multiple placebo, 5 dextrose 0.5ml/kg multiple, 7 dextrose 1ml/kg multiple

NA not available

NZDPI: New Zealand Deprivation Index: a measure of socioeconomic status (1 is least deprived)

^gRisk factors prioritized in order: infant of diabetic mother, preterm, small, large

Table 2.

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

Outcome	Placebo (N=117)			Dextrose 200 mg (N=62)			Dextrose 400 mg (N=64)			Dextrose 800 mg (N=54)			Dextrose 1 g (N=63)			P Linear trend ^e			
	n (%)	n (%)	n (%)	RR or MD (95%CI)	Adjusted RR or MD (95%CI), p	n (%)	n (%)	n (%)	RR or MD (95%CI)	Adjusted RR or MD (95%CI), p	n (%)	n (%)	n (%)	RR or MD (95%CI)	Adjusted RR or MD (95%CI), p				
Neurosensory impairment	116	26 (22)	62 (16)	0.72 (0.37-1.39)	0.74 (0.32-1.68), 0.81	10 (16)	14 (22)	64 (14)	0.98 (0.55-1.73)	1.04 (0.51-2.13), 1.00	54 (6)	6 (11)	63 (17)	0.50 (0.22-1.13)	0.51 (0.18-1.43), 0.33	11 (17)	0.78 (0.41-1.47)	0.76 (0.35-1.69), 0.85	
Bayley-III cognitive score <85	116	15 (13)	62 (5)	0.37 (0.11-1.24)	0.39 (0.08-1.78), 0.39	3 (5)	9 (14)	64 (14)	1.09 (0.50-2.34)	1.17 (0.44-3.11), 0.99	54 (7)	4 (7)	63 (10)	0.57 (0.20-1.64)	0.60 (0.16-2.28), 0.80	6 (10)	0.74 (0.30-1.80)	0.73 (0.24-2.25), 0.92	
Bayley-III language score <85	116	20 (17)	62 (15)	0.84 (0.41-1.74)	0.87 (0.36-2.13), 0.99	9 (15)	10 (16)	64 (16)	0.91 (0.45-1.82)	0.96 (0.41-2.25), 1.00	54 (3)	3 (6)	63 (11)	0.32 (0.10-1.04)	0.34 (0.08-1.46), 0.22	7 (11)	0.64 (0.29-1.44)	0.62 (0.23-1.68), 0.63	
Bayley-III motor score <85	116	5 (4)	62 (1)	0.37 (0.04-3.13)	0.48 (0.04-5.21), 0.74	1 (2)	1 (2)	64 (2)	0.36 (0.04-3.04)	0.49 (0.04-5.46), 0.75	54 (0)	0	63 (0)			0		0.06	
Deaf	116	1 (1)	62 (0)			0	0	64 (0)			54 (0)	0	63 (0)			0			0
Executive function score <-1.5 SD	115	13 (11)	61 (8)	0.73 (0.27-1.94)	0.77 (0.22-2.65), 0.97 ^b	5 (8)	64 (5)	64 (8)	0.69 (0.26-1.85)	0.82 (0.24-2.85), 0.99 ^b	54 (2)	2 (4)	63 (2)	0.33 (0.08-1.40)	0.37 (0.06-2.30), 0.52 ^b	1 (2)	0.14 (0.02-1.05)	0.13 (0.01-1.75), 0.19*	0.03
Bayley-III cognitive score	116	99.6 (14.9)	62 (14.8)	0.47 (-3.96 to 4.90)	0.82 (-4.62 to 6.26), 0.99	100.1 (14.8)	100.1 (15.8)	64 (15.8)	0.47 (-3.92 to 4.85)	-0.20 (-5.59 to 5.18), 1.00	54 (11.7)	99.4 (11.7)	63 (14.1)	-0.26 (-4.90 to 4.38)	-0.63 (-6.32 to 5.06), 1.00	101.5 (14.1)	1.90 (-2.51 to 6.30)	2.23 (-3.17 to 7.62), 0.74	0.55
Bayley-III language score	116	99.7 (18.1)	62 (14.6)	1.10 (-3.99 to 6.20)	1.28 (-4.85 to 7.42), 0.97	100.8 (14.6)	104.7 (17.8)	64 (17.8)	5.00 (-0.04 to 10.04)	3.85 (-2.23 to 9.92), 0.36	54 (14.4)	103.8 (14.4)	63 (16.2)	4.12 (-1.21 to 9.46)	3.60 (-2.81 to 10.01), 0.48	103.6 (16.2)	3.90 (-1.17 to 8.97)	4.51 (-1.58 to 10.59), 0.22	0.05
Bayley-III motor score	116	102.7 (13.4)	62 (10.7)	1.55 (-2.15 to 5.26)	1.42 (-3.21 to 6.04), 0.89	104.2 (10.7)	105.6 (12.8)	64 (12.8)	2.89 (-0.78 to 6.56)	2.36 (-2.22 to 6.93), 0.56	54 (11.8)	106.6 (11.8)	63 (10.2)	3.94 (0.06 to 7.82)	3.60 (-1.24 to 8.43), 0.22	105.3 (10.2)	2.58 (-1.11 to 6.27)	2.81 (-1.77 to 7.40), 0.39	0.07

Outcome	Placebo (N=117)			Dextrose 200 mg (N=62)			Dextrose 400 mg (N=64)			Dextrose 800 mg (N=54)			Dextrose 1 g (N=63)			P Linear trend ^d	
	N	n (%) or mean (SD)	N	n (%) or mean (SD)	RR or MD (95%CI), p	n (%) or mean (SD)	RR or MD (95%CI), p	n (%) or mean (SD)	RR or MD (95%CI), p	n (%) or mean (SD)	RR or MD (95%CI), p	n (%) or mean (SD)	RR or MD (95%CI), p	n (%) or mean (SD)	RR or MD (95%CI), p		
Bayley III social emotional score	75	103.4 (13.4)	42	106.8 (16.1)	3.28 (-4.73 to 11.5)	35	111.3 (18.5)	3.49 (-0.73 to 16.5)	7.74 (-0.81 to 16.30)	0.09	32	103.6 (18.9)	0.19 (-8.70 to 9.08)	43	106.3 (15.1)	3.23 (-4.46 to 11.48)	0.69
Bayley III adaptive score	75	100.7 (16.2)	42	98.3 (12.6)	-2.34 (-9.13 to 4.44)	35	105.3 (15.1)	4.69 (-2.51 to 11.89)	3.99 (-3.06 to 11.04)	0.47	32	101.4 (12.9)	0.72 (-6.71 to 8.15)	43	102.0 (13.1)	1.39 (-5.34 to 8.15)	0.38
Executive function score	115	9.9 (4.5)	61	10.4 (4.1)	0.56 (-0.71 to 1.82)	64	10.5 (4.1)	0.66 (-0.58 to 1.91)	0.47 (-1.06 to 2.00)	0.89	54	11.1 (4.1)	1.30 (-0.02 to 2.62)	63	10.5 (3.4)	0.67 (-0.58 to 2.30)	0.15
BRIEF P GEC T-score >65	94	15 (16)	51	5 (10)	0.61 (0.24-1.59)	50	7 (14)	0.88 (0.38-2.01)	0.81 (0.30-2.24)	0.97	46	10 (22)	1.36 (0.66-2.79)	53	8 (15)	0.95 (0.43-2.17)	0.59
BRIEF P GEC T-score	94	51.5 (11.1)	51	51.3 (10.5)	-0.25 (-4.37 to 3.88)	50	50.7 (13.5)	-0.86 (-5.02 to 3.29)	-1.48 (6.47 to 3.51)	0.90	46	52.8 (13.1)	1.22 (-3.05 to 5.49)	53	52.7 (13.4)	0.14 (-2.94 to 5.56)	0.44
Abnormality of tone or coordination	115	9 (8)	62	7 (11)	1.44 (0.56-3.69)	64	4 (6)	0.80 (0.26-2.49)	0.76 (0.18-3.17)	0.98	54	2 (4)	0.47 (0.11-2.12)	63	1 (2)	0.20 (0.01-2.65)	0.05
Seizures	116	2 (2)	62	1 (2)	0.94 (0.09-10.11)	64	1 (2)	0.91 (0.08-9.80)	NC	NC	54	0		63	1 (2)	0.92 (0.09-9.96)	NC
Asthma	116	24 (21)	62	12 (19)	0.94 (0.50-1.74)	64	12 (19)	0.91 (0.49-1.69)	0.96 (0.44-2.09)	1.00	54	9 (17)	0.81 (0.40-1.61)	63	15 (24)	1.15 (0.65-2.30)	0.89
Eczema	116	42 (36)	62	28 (45)	1.25 (0.87-1.80)	64	27 (42)	1.17 (0.80-1.70)	1.15 (0.72-1.84)	0.90	54	24 (44)	1.23 (0.84-1.80)	63	27 (43)	1.18 (0.74-1.89)	0.40

Outcome	Placebo (N=117)			Dextrose 200 mg (N=62)			Dextrose 400 mg (N=64)			Dextrose 800 mg (N=54)			Dextrose 1 g (N=63)			P Linear trend ^d
	n (%) N	n (%) mean (SD)	Adjusted RR or MD (95%CI), P	n (%) N	n (%) mean (SD)	Adjusted RR or MD (95%CI), P	n (%) N	n (%) mean (SD)	Adjusted RR or MD (95%CI), P	n (%) N	n (%) mean (SD)	Adjusted RR or MD (95%CI), P	n (%) N	n (%) mean (SD)	Adjusted RR or MD (95%CI), P	
Allergy	46 (40) 116	27 (44) (1.58)	1.08 (0.69–1.71), 0.98	64 (47) 64	30 (47) (1.67)	1.18 (0.84–1.67), 0.72	54 (46) 54	25 (46) (1.68)	1.17 (0.81–1.87), 0.78	63 (52) 63	33 (52) (1.83)	1.32 (0.88–1.99), 0.29	0.10			
Doctor visits for suspected infectious illnesses	19 (16) 116	11 (18) (2.13)	1.12 (0.48–2.62), 0.99	64 (14) 64	9 (14) (1.79)	0.86 (0.41–1.79), 0.99	54 (22) 54	12 (22) (2.59)	1.36 (0.71–3.13), 0.75	63 (21) 63	13 (21) (2.38)	1.26 (0.57–2.80), 0.90	0.37			
Weight z-score	0.9 (1.3) 116	0.8 (1.2) (0.29)	-0.10 (-0.56 to 0.37), 0.97	64 (1.1) 64	0.9 (1.1) (0.34)	-0.03 (-0.40 to 0.34), 1.00	54 (1.3) 54	0.7 (1.3) (0.21)	-0.18 (-0.57 to 0.30), 0.79	63 (1.1) 63	0.7 (1.1) (0.20)	-0.17 (-0.65 to 0.28), 0.77	0.30			
Height z-score	0.3 (1.1) 115	0.2 (1.2) (0.32)	-0.05 (-0.48 to 0.38), 1.00	64 (1.2) 64	0.3 (1.2) (0.34)	0.00 (-0.34 to 0.34), 1.00	53 (1.0) 53	0.0 (1.0) (0.13)	-0.24 (-0.60 to 0.20), 0.47	63 (1.0) 63	0.0 (1.0) (0.09)	-0.25 (-0.59 to 0.17), 0.42	0.09			
Weight for height z-score	1.0 (1.3) 115	0.9 (1.2) (0.29)	-0.08 (-0.45 to 0.39), 0.98	64 (1.0) 64	0.9 (1.0) (0.33)	-0.04 (-0.40 to 0.45), 1.00	53 (1.4) 53	0.9 (1.4) (0.31)	-0.08 (-0.47 to 0.42), 0.99	63 (1.1) 63	0.9 (1.1) (0.32)	-0.05 (-0.53 to 0.40), 0.99	0.79			
Head circumference	0.8 (1.2) 115	0.8 (1.2) (0.28)	-0.06 (-0.50 to 0.39), 1.00	63 (0.9) 63	0.8 (0.9) (0.32)	-0.03 (-0.39 to 0.32), 1.00	53 (1.2) 53	0.7 (1.2) (0.21)	-0.16 (-0.54 to 0.32), 0.88	61 (1.2) 61	0.9 (1.2) (0.40)	0.04 (-0.31 to 0.46), 1.00	0.91			
Triceps skinfold z-score	0.4 (1.2) 84	0.4 (1.3) (0.55), 0.71	0.05 (-0.53 to 0.62), 1.00	45 (1.3) 45	0.4 (1.3) (0.72)	0.08 (-0.36 to 0.61), 1.00	38 (1.3) 38	0.4 (1.3) (0.46), 0.99	0.00 (-0.47 to 0.55), 1.00	41 (1.1) 41	0.2 (1.1) (0.33), 0.58	-0.13 (-0.59 to 0.41), 0.92	0.46			
Subscapular skinfold z-score	0.1 (1.3) 84	0.2 (1.3) (0.63)	0.14 (-0.45 to 0.72), 0.95	46 (1.2) 46	-0.1 (1.2) (0.25)	-0.19 (-0.62 to 0.25), 0.82	37 (1.2) 37	-0.1 (1.2) (0.34)	-0.13 (-0.60 to 0.44), 0.94	40 (1.1) 40	-0.2 (1.1) (0.18)	-0.28 (-0.86 to 0.30), 0.61	0.12			
Fat mass kg	2.8 (1.0) 88	2.7 (1.0) (0.30)	-0.07 (-0.50 to 0.37), 0.99	55 (1.1) 55	2.6 (1.1) (0.13)	-0.20 (-0.53 to 0.13), 0.74	42 (1.0) 42	2.7 (1.0) (0.28)	-0.08 (-0.44 to 0.45), 1.00**	45 (0.9) 45	2.5 (0.9) (0.12)	-0.16 (-0.59 to 0.27), 0.81**	0.55			
Fat free mass kg	10.8 (1.8) 88	10.8 (1.9) (0.63)	-0.03 (-0.59 to 0.63)	55 (1.9) 55	10.8 (1.9) (0.6)	0.06 (-0.54 to 0.6)	42 (2.0) 42	10.6 (2.0) (0.47)	-0.18 (-0.83 to 0.47)	45 (1.4) 45	10.4 (1.4) (0.30)	-0.34 (-0.98 to 0.30)	0.87			

Outcome	Dextrose 200 mg (N=62)			Dextrose 400 mg (N=64)			Dextrose 800 mg (N=54)			Dextrose 1 g (N=63)			P Linear trend ^d
	n (%) N	n (%) mean (SD)	RR or MD (95%CI), p	n (%) N	n (%) mean (SD)	RR or MD (95%CI), p	n (%) N	n (%) mean (SD)	RR or MD (95%CI), p	n (%) N	n (%) mean (SD)	RR or MD (95%CI), p	
Abdominal circumference (cm)	107 (3.9)	49.5 (4.1)	-0.15 (-1.40 to 1.10), 1.00	58	49.4 (3.5)	-0.17 (-1.39 to 1.04), 0.92	46	48.5 (4.1)	-1.07 (-2.39 to 0.24), 0.97**	58	49.3 (3.5)	-0.37 (-1.58 to 0.85), 1.00**	0.24
			0.53), 1.00			0.66), 0.92			0.69), 0.97**			0.53), 1.00**	

No children had cerebral palsy or were blind.

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

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

Fat mass and fat free mass were additionally adjusted for height

^a Adjusted for recruitment center, socioeconomic status, gestation, sex

^b Log binomial model did not converge, modified Poisson used

NC = Not calculable, model did not converge

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

Table 3.

Outcome	Placebo (N=117)		Any dextrose (N=243)		Any single dose dextrose (N=126)		Any multiple dose dextrose (N=117)					
	n	n (%) or mean, SD	n	n (%) or mean, SD	Adjusted RR or MD (95%CI), p ¹	n	n (%) or mean, SD	Adjusted RR or MD (95%CI), p ²	n	n (%) or mean, SD	Adjusted RR or MD (95%CI)	Adjusted RR or MD (95%CI), p ²
Neurosensory impairment	116	26 (22.4)	243	41 (16.9)	0.77 (0.50–1.19), 0.23	126	24 (19.1)	0.85 (0.52–1.39)	117	17 (14.5)	0.65 (0.37–1.13)	0.65 (0.35–1.21), 0.21
Bayley-III cognitive score <85	116	15 (12.9)	243	22 (9.1)	0.70 (0.38–1.30)	126	12 (9.5)	0.74 (0.36–1.51)	117	10 (8.6)	0.66 (0.31–1.41)	0.67 (0.29–1.58), 0.49
Bayley-III language score <85	116	20 (17.2)	243	29 (11.9)	0.69 (0.41–1.17)	126	19 (15.1)	0.87 (0.49–1.55)	117	10 (8.6)	0.50 (0.24–1.01)	0.49 (0.22–1.10), 0.09
Bayley-III motor score <85	116	5 (4.3)	243	2 (0.8)	0.19 (0.04–0.97)	126	2 (1.6)	0.38 (0.07–1.86)	117	0		
Deaf	116	1 (0.9)	243	0		126	0		117	0		
Executive function score < -1.5 SD	115	13 (11.3)	242	13 (5.4)	0.48 (0.23–0.99)	125	10 (8.0)	0.71 (0.32–1.55)	117	3 (2.6)	0.23 (0.07–0.78)	0.23 (0.06–0.94), 0.04 ^a
Bayley-III cognitive score	116	99.6 (14.9)	243	100.3 (14.2)	0.68 (–2.50 to 3.86)	126	100.1 (15.2)	0.47 (–3.16 to 4.09)	117	100.5 (13.0)	0.90 (–2.79 to 4.59)	0.91 (–3.14 to 4.96), 0.84
Bayley-III language score	116	99.7 (18.1)	243	103.2 (15.9)	3.53 (–0.14 to 7.19)	126	102.8 (16.4)	3.08 (–1.10 to 7.26)	117	103.7 (15.4)	4.00 (–0.25 to 8.26)	4.09 (–0.47 to 8.66), 0.09
Bayley-III motor score	116	102.7 (13.4)	243	105.4 (11.4)	2.70 (0.04 to 5.37)	126	104.9 (11.8)	2.23 (–0.80 to 5.27)	117	105.9 (10.9)	3.21 (0.12 to 6.30)	3.18 (–0.26 to 6.62), 0.08
Bayley III social emotional score	75	103.4 (17.7)	152	107.1 (17.0)	3.71 (–1.04 to 8.45)	77	108.8 (17.2)	5.43 (–0.01 to 10.9)	75	105.3 (16.8)	1.93 (–3.54 to 7.41)	2.16 (–3.96 to 8.27), 0.65
Bayley III adaptive score	75	100.7 (16.2)	152	101.6 (3.5)	0.98 (–3.00 to 4.96)	77	101.5 (14.2)	0.85 (–3.72 to 5.43)	75	101.8 (13.0)	1.11 (–3.50 to 5.72)	1.01 (–4.05 to 6.07), 0.87
Executive function score	115	9.9 (4.5)	242	10.6 (3.9)	0.78 (–0.13 to 1.69)	125	10.5 (4.1)	0.61 (–0.42 to 1.65)	117	10.8 (3.7)	0.96 (–0.09 to 2.01)	0.96 (–0.19 to 2.11), 0.12
BRIEF P GEC T- score >65	94	15 (16.0)	200	30 (15.0)	0.94 (0.53–1.66)	101	12 (11.9)	0.74 (0.37–1.51)	99	18 (18.2)	1.14 (0.61–2.13)	1.01 (0.51–2.00), 1.00
BRIEF P GEC T- score	94	51.5 (11.1)	200	51.8 (12.6)	0.30 (–2.67 to 3.27)	101	51.0 (12.0)	–0.55 (–3.95 to 2.85)	99	52.7 (13.2)	1.17 (–2.24 to 4.59)	0.60 (–3.06 to 4.27), 0.91

Outcome	Placebo (N=117)		Any dextrose (N=243)		Any single dose dextrose (N=126)		Any multiple dose dextrose (N=117)						
	n	n (%) or mean, SD	n	n (%) or mean, SD	RR or MD (95%CI)	n	n (%) or mean, SD	Adjusted RR or MD (95%CI), p ¹	Adjusted RR or MD (95%CI), p ²	n	n (%) or mean, SD	Adjusted RR or MD (95%CI), p ²	Adjusted RR or MD (95%CI), p ²
Abnormalities of tone and coordination	115	9 (7.8)	243	14 (5.8)	0.74 (0.33–1.65)	126	11 (8.7)	0.74 (0.33–1.65), 0.46 ^a	1.14 (0.45–2.93), 0.93 ^a	117	3 (2.6)	1.14 (0.45–2.93), 0.93 ^a	0.33 (0.08–1.39), 0.16 ^a
Seizures	116	2 (1.7)	243	3 (1.2)	0.72 (0.12–4.23)	126	2 (1.6)	NC	NC	117	1 (0.9)	0.50 (0.05–5.39)	NC
Asthma	116	24 (20.7)	243	48 (19.8)	0.95 (0.62–1.48)	126	24 (19.1)	0.98 (0.63–1.51), 0.92	0.96 (0.54–1.70), 0.98	117	24 (20.5)	0.99 (0.60–1.64)	1.00 (0.57–1.75), 1.00
Eczema	116	42 (36.2)	243	106 (43.6)	1.20 (0.91–1.60)	126	55 (43.7)	1.19 (0.90–1.58), 0.22	1.18 (0.83–1.67), 0.48	117	51 (43.6)	1.20 (0.88–1.65)	1.21 (0.85–1.72), 0.39
Allergy	116	46 (39.7)	243	115 (47.3)	1.19 (0.92–1.55)	126	57 (45.2)	1.20 (0.92–1.55), 0.17	1.14 (0.82–1.59), 0.57	117	58 (50.0)	1.25 (0.94–1.67)	1.26 (0.91–1.74), 0.20
Doctor visits for suspected infectious illnesses	116	19 (16.4)	243	45 (18.5)	1.13 (0.69–1.84)	126	20 (15.9)	1.15 (0.71–1.88), 0.57	0.99 (0.52–1.90), 1.00	117	25 (21.4)	1.30 (0.76–2.24)	0.32 (0.72–2.24), 0.49
Weight for age and sex z-score	116	0.9 (1.3)	243	0.8 (1.2)	-0.11 (-0.38 to 0.15)	126	0.8 (1.2)	-0.12 (-0.39 to 0.15), 0.38	-0.05 (-0.36 to 0.25)	117	0.7 (1.2)	-0.18 (-0.49 to 0.12)	-0.18 (-0.53 to 0.16), 0.39
Height for age and sex z-score	115	0.3 (1.1)	242	0.1 (1.1)	-0.12 (-0.37 to 0.12)	126	0.3 (1.2)	-0.14 (-0.39 to 0.11), 0.27	-0.01 (0.29 to 0.27)	116	0.0 (1.0)	-0.24 (-0.53 to 0.04)	-0.26 (-0.58 to 0.06), 0.14
Weight for height and sex z-score	115	1.0 (1.3)	242	0.9 (1.2)	-0.06 (-0.33 to 0.21)	126	0.9 (1.1)	-0.06 (-0.32 to 0.21), 0.68	-0.06 (-0.36 to 0.25)	116	0.9 (1.2)	-0.06 (-0.37 to 0.25)	-0.07 (-0.41 to 0.28), 0.88
Head circumference for age and sex z-score	115	0.8 (1.2)	238	0.8 (1.1)	-0.05 (-0.31 to 0.20)	124	0.8 (1.1)	-0.04 (-0.29 to 0.21), 0.76	-0.05 (-0.35 to 0.24)	114	0.8 (1.2)	-0.05 (-0.35 to 0.25)	-0.06 (-0.39 to 0.28), 0.90
Triceps skinfold z-score	84	0.4 (1.2)	163	0.4 (1.2)	0.01 (-0.31 to 0.33)	84	0.4 (1.3)	-0.02 (-0.34 to 0.30), 0.91	0.08 (-0.29 to 0.45)	79	0.3 (1.2)	0.06 (-0.36 to 0.47), 0.94	-0.09 (-0.52 to 0.32), 0.82
Subscapular skinfold z-score	84	0.1 (1.3)	162	0 (1.2)	-0.11 (-0.43 to 0.21)	85	0.0 (1.2)	-0.13 (-0.45 to 0.19), 0.43	-0.03 (-0.39 to 0.34)	77	-0.1 (1.1)	-0.05 (-0.46 to 0.37), 0.96	-0.22 (-0.65 to 0.21), 0.41
Fat mass kg	88	2.8 (1.0)	186	2.6 (1.0)	-0.15 (-0.40 to 0.10)	99	2.6 (1.1)	-0.10 (-0.34 to 0.14), 0.40	-0.14 (-0.42 to 0.15)	87	2.6 (0.9)	-0.12 (-0.43 to 0.19), 0.58	-0.08 (-0.40 to 0.24), 0.80
Fat free mass kg	88	10.8 (1.8)	186	10.7 (1.8)	-0.11 (-0.56 to 0.34)	99	10.8 (1.8)	0.06 (-0.26 to 0.37), 0.73	0.03 (-0.48 to 0.54)	87	10.5 (1.7)	0.07 (-0.33 to 0.46), 0.91	0.04 (-0.37 to 0.45), 0.96
Abdominal circumference (cm)	107	49.6 (3.9)	215	49.2 (3.8)	-0.41 (-1.30 to 0.47)	111	49.5 (3.8)	-0.45 (-1.33 to 0.43), 0.32	-0.16 (-1.18 to 0.85)	104	48.9 (3.8)	-0.18 (-1.33 to 0.96), 0.91	-0.72 (-1.87 to 0.43), 0.28

No children had cerebral palsy or were blind.

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Data are n (%); RR (95% CI), p or MD (95% CI), p¹ value for comparison with placebo group; or p² value for comparison between placebo, single and multiple groups

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

Fat mass and fat free mass were additionally adjusted for height

¹Log binomial model did not converge, modified Poisson used

NC= Not calculable