Outcomes in children of women with type 2 diabetes exposed to metformin versus placebo during pregnancy (MiTy Kids): a 24-month follow-up of the MiTy randomised controlled trial

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Summary

Background Metformin is increasingly being used during pregnancy, with potentially adverse long-term effects on children. We aimed to examine adiposity in children of women with type 2 diabetes from the Metformin in Women with Type 2 Diabetes in Pregnancy (MiTy) trial, with and without in-utero exposure to metformin, up to 24 months of age.

Methods MiTy Kids is a follow-up study that included infants of women who participated in the MiTy randomised controlled trial, receiving either oral 1000 mg metformin twice daily or placebo. Caregivers and researchers remained masked to the type of medication (metformin or placebo) mothers received during their pregnancy. Anthropometric measurements, including weight, height, and skinfold thicknesses, were taken at 3, 6, 12, 18, and 24 months. At 24 months, linear regression was used to compare the BMI Z score and sum of skinfolds in the metformin versus placebo groups, adjusted for confounders. Fractional polynomials were used to assess growth trajectories. This study is registered with ClinicalTrials.gov, NCT01832181.

Findings Of the 465 eligible children, 283 (61%) were included from 19 centres in Canada and Australia. At 24 months, there was no difference between groups in mean BMI Z score (0·84 [SD 1·52] with metformin *vs* 0·91 [1·38] with placebo; mean difference 0·07 [95% CI –0·31 to 0·45], p=0·72) or mean sum of skinfolds (23·0 mm [5·2] vs 23·8 mm [5·4]; mean difference 0·8 mm [–0·7 to 2·3], p=0·31). Metformin was not a predictor of BMI Z score at 24 months of age (mean difference –0·01 [95% CI –0·42 to 0·37], p=0·92). There was no overall difference in BMI trajectory but, in males, trajectories were significantly different by treatment (p=0·048); BMI in the metformin group was higher between 6 and 24 months. Children of women with type 2 diabetes were approximately 1 SD heavier than the WHO reference population.

Interpretation Anthropometrics were similar in children exposed and those not exposed to metformin in utero; hence, overall, data are reassuring with regard to the use of metformin during pregnancy in women with type 2 diabetes and the long-term health of their children.

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Introduction

The incidence of type 2 diabetes in pregnancy is growing at an alarming rate.[1,2] Pregnant women with type 2 diabetes are at an increased risk of adverse pregnancy outcomes, including elevated rates of preterm birth, large for gestational age, stillbirth, and perinatal mortality.[3] This population is often older, of non-European ethnicity, have increased rates of obesity and chronic hypertension, require large doses of insulin, and have high rates of social and economic deprivation.[3] Although all children of women with diabetes are at an increased risk of obesity and diabetes, children of women with type 2 diabetes are at the highest risk of these adverse outcomes.[4,5] Despite the rise in incidence and these adverse outcomes, research in the treatment of this unique group is sparse.

Metformin is increasingly being used in the management of gestational diabetes and type 2 diabetes during pregnancy. As metformin crosses the placenta,[6] this increased use is leading to a rise in fetal exposure to metformin. Although the short-term effects appear to be quite beneficial, including reduced maternal weight gain, pregnancy-induced hypertension, large for gestational age, and neonatal hypoglycaemia,[7] the long-term effects of in-utero exposure to metformin are not definitively known, with some studies indicating potential harms, including larger BMI and central adiposity at 7–9 years, as in the MiG trial,[8] and

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See Online for appendix

Research in context

Evidence before this study

Metformin is increasingly being used during pregnancy, especially in women with type 2 diabetes, but studies on its long-term effects on children of these women are sparse. Given the increasing incidence of type 2 diabetes seen in pregnancy, and the increased use of metformin, studies on the long-term effects are sorely needed. We did a literature search using the medical subject heading terms "metformin" and "randomized controlled trial" and ("pregnancy" or "in utero") and "diabetes" and ("child" or "children" or "childhood" or "infant" or "infants" or "infancy" or "offspring" or "late sequelae") for research articles published on MEDLINE between 1946 and Oct 27, 2022; Embase Classic and Embase between 1947 and Oct 28, 2022; and PsycInfo between 1806 and Oct 4, 2022. Other articles were identified based on the authors' knowledge of the field. No language restriction was applied. We found 173 articles but none that included the long-term follow-up of children of women with type 2 diabetes randomly assigned to metformin or placebo during pregnancy. We found long-term studies of children of mother with polycystic ovary syndrome and gestational diabetes that suggested potential harm with metformin exposure. In the randomised controlled trial PregMet, children of mothers with polycystic ovary syndrome exposed to metformin had a higher BMI at the age of 4 years and had a higher BMI, central adiposity, and increased risk of obesity at the ages of 5–10 years. In the randomised MiG trial, follow-up of children of women with gestational diabetes assigned to metformin or placebo at 7 years in Adelaide (SA, Australia) did not show any difference between the groups; however, children followed up at 9 years in Auckland (New Zealand), showed features of increased adiposity in the metformin group with increased BMI, waist circumference, waist-to-height ratio, fat mass, and abdominal fat volume. The authors of that study hypothesised that infants of mothers with poor glycaemic control (in Adelaide) might benefit from metformin, whereas those with tight glycaemic control (Auckland) might have increased growth and metabolic syndrome later in life. A meta-analysis of studies of children of mothers with gestational diabetes showed that birthweight was lower in the metformin group than in the placebo group but children exposed to metformin in utero showed increased weight in infancy and increased BMI at 7–9 years. A study of children of women with gestational diabetes from two randomised trials in Finland published after this meta-analysis did not find a difference in anthropometrics at the age of 9 years. We hypothesised that infants of mothers with type 2 diabetes would face overnutrition in utero and therefore might benefit from metformin in the long term.

Added value of this study

To our knowledge, this is the first long-term follow-up of children of mothers with type 2 diabetes who received metformin or placebo, added to insulin, in a randomised trial. We found that there was no difference in mean BMI Z score or mean sum of skinfolds between groups at 24 months of age. There was also no overall difference in BMI trajectory; however, in males, BMI trajectories were significantly different by treatment; the metformin group reached a higher peak mean BMI at 6 months and continued to be higher from 6 months to 24 months, at which time they were similar to the placebo group. At 24 months, metformin was not a predictor of adiposity, but several potentially modifiable risk factors were associated with child BMI Z score, including maternal pre-pregnancy BMI, low socioeconomic status, and reduced sleep time. The children of women with type 2 diabetes were approximately 1 SD heavier than the WHO reference population.

Implications of all the available evidence

Given the increasing incidence of type 2 diabetes in pregnancy and the increasing use of metformin during pregnancy, findings of this study are reassuring with regard to the use of metformin during pregnancy in women with type 2 diabetes and the long-term health of their children. Future follow-up is needed to see if such findings persist.

at 5–10 years of age, as in the PregMet follow-up study,[9] and others not finding any harms.[10] Metformin is thought to act by activation of the AMP kinase signalling pathway, leading to multiple intracellular effects, including reduction in gluconeogenesis, suppression of mitochondrial respiration, and growth inhibition.[11] It is not yet clear how these metabolic effects, when exerted in utero, affect growth and development after birth. These actions might mimic malnutrition and result in in-utero programming paradoxically leading to childhood obesity and metabolic syndrome, as has been noted in children born during times of fetal malnutrition.[12] Conversely, in an environment of overnutrition, such as the one to which offspring of women with type 2 diabetes are exposed, one might expect that metformin, by reducing insulin resistance and hyperinsulinaemia in the fetus, will improve neonatal outcomes, such as reduce large for gestational age, and in turn, improve long-term outcomes. We now have evidence from the Metformin in Women with Type 2 Diabetes in Pregnancy (MiTy) randomised controlled trial that children of metformin-exposed women with type 2 diabetes indeed have reduced extreme large for gestational age and adiposity measures at birth but are also at an increased risk of being small for gestational age.[13] These effects could lead to either benefit or harm in the long term.

Currently there is a paucity of data on the long-term effects of in-utero exposure to metformin on children, and no data in women with type 2 diabetes. We aimed to determine the effects of in-utero exposure to metformin on childhood adiposity and metabolic

syndrome up to 2 years of age in a unique cohort of children of women with type 2 diabetes who received metformin or placebo during pregnancy in the MiTy trial.

Methods

Study design and participants

MiTy Kids is a longitudinal follow-up study of children born to mothers with type 2 diabetes who participated in the MiTy trial.[13] The MiTy protocol has been published elsewhere.[14] In brief, the MiTy trial enrolled 502 women with insulin-treated type 2 diabetes in pregnancy from 25 centres in Canada and four centres in Australia. The participants were randomly assigned between 6 weeks and 22 weeks and 6 days gestation, to receive either 1 g metformin twice daily or placebo for the duration of the pregnancy. Mothers who participated in MiTy were invited to have their children enrol in MiTy Kids. Children were excluded if they had major congenital anomalies that would affect their growth or development (defined using the EUROCAT registry guidelines[15]). Caregivers and researchers remained masked to the type of medication (metformin or placebo) mothers received during their pregnancy. Ethics approval for the study was obtained from the Ethics Research Boards of each participating site. Written informed consent was obtained from children's caregivers.

Procedures

Anthropometric measurements, including weight, height and skinfold thicknesses, were taken at 6, 12, and 24 months of age at participating sites. There were also phone visits at 3 months and 18 months, during which mothers reported weights and heights from their doctors' offices and nutritional information such as breastfeeding was obtained. Mothers who could not bring in their infants were asked to sign a Release of Personal Information to allow researchers to obtain weights and heights of the children from their primary caregiver.

At the initial visit, basic demographics of the parents were obtained, including age, ethnicity, education, occupation, family arrangement, family history of diabetes, presence of major illnesses, and diabetes complications. Neonatal baseline information such as birthweight; birthweight Z score; preterm birth; respiratory distress syndrome; neonatal hypoglycaemia; small, large, and extreme large for gestational age (adjudicated using Canadian national growth curves[16] adjusted for sex and gestational age); birthweight of more than 4 kg; sum of skinfolds; body fat mass; head, chest, and abdominal circumference; and the ponderal index. For parents who agreed, children's fasting blood samples (after 8 h without food or drink) were taken for glucose, insulin, liver function, lipids, adiponectin, and leptin in red serum separator tubes, which were set aside for blood to clot for 30 min, then spun for 15 min and stored in the freezer at –80°C before shipping on dry ice to the central site for analysis.

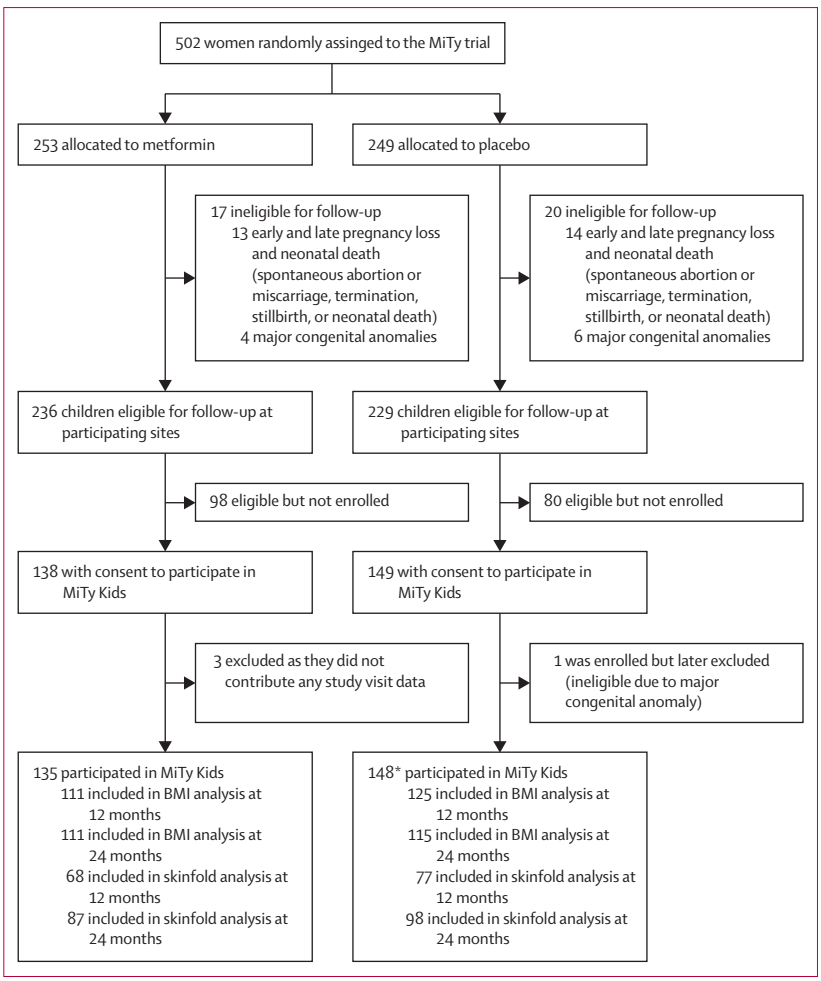

Figure 1: **Trial profile**
MiTy=Metformin in Women with Type 2 Diabetes in Pregnancy. *Although a delivery form was not completed for one participant, their data were collected and included.

Outcomes

The primary outcomes were two measures of adiposity: the mean BMI Z score and the mean sum of skinfold thicknesses of the child at 24 months of age measured using a Harpenden Caliper. If obtainable, the average of two to three measurements of infant length, weight, and skinfolds were taken using standardised anthropometric protocols.[17] Z scores were calculated using age and sex-appropriate WHO growth charts.[18] The sum of skin fold thicknesses was calculated as the sum of the thickness of the triceps, subscapular, suprailiac, and biceps skinfolds.

Secondary outcomes included BMI Z score measured at 3, 6, 12, and 18 months of age, and sum of skinfold thicknesses measured at 6 months and 12 months of age. Other secondary outcomes included BMI; weight; weight-for length percentile; and age of child when height and weight were done and were measured at 3, 6, 12, 18, and 24 months of age. Secondary outcomes such as head circumference, waist circumference, individual skinfold thicknesses (triceps, biceps,

	Participated in MiTy Kids		Did not participate in MiTy Kids	
	Metformin group (n=135)	Placebo group (n=148)	Metformin group (n=101)	Placebo group (n=81)
Maternal age at randomisation, years	35·9 (4·5)	35·3 (4·4)	33·1 (5·4)	34·4 (4·9)
Age range, years	23·6–44·4	19·4–44·9	19·1–44·2	22·7–43·0
Ethnicity				
European descent	47 (35%)	48 (32%)	26 (26%)	21 (26%)
Non-European descent	88 (65%)	100 (68%)	75 (74%)	60 (74%)
Previous pregnancies				
1–4	92/104 (88%)	103/117 (88%)	70/82 (85%)	52/65 (80%)
>4	12/104 (12%)	14/117 (12%)	12/82 (15%)	13/65 (20%)
Gestational age at randomisation, weeks	16·3 (4·0)	15·9 (3·6)	17·2 (3·8)	17·5 (3·6)
Pre-pregnancy weight*, kg	89·2 (20·0)	90·5 (22·6)	90·3 (23·0)	90·1 (20·6)
Missing	1	2	0	1
Pre-pregnancy BMI, kg/m²	33·1 (6·7)	34·1 (7·6)	33·6 (7·6)	34·1 (6·7)
Missing	1	2	0	1
Weight at randomisation, kg	93·1 (20·3)	93·7 (22·2)	94·5 (23·1)	94·4 (20·9)
BMI at randomisation, kg/m²	34·5 (6·7)	35·2 (7·3)	35·2 (7·7)	35·6 (6·8)
BMI at randomisation ≥30 kg/m²	104 (77%)	113 (76%)	75 (74%)	66 (81%)
Diagnosis of type 2 diabetes before pregnancy	112 (83%)	136 (92%)	83 (82%)	71 (88%)
Family history of type 2 diabetes	109 (81%)	127 (86%)	82 (81%)	68 (84%)
Polycystic ovary syndrome	29 (21%)	31 (21%)	12 (12%)	12 (15%)
First HbA_{1c} during this pregnancy				
mmol/mol	52·5 (15·2)	55·7 (20·2)	56·0 (19·0)	56·6 (18·6)
%	7·0% (1·4)	7·2% (1·8)	7·3% (1·7)	7·3% (1·7)
Missing	3	4	3	1
HbA_{1c} at randomisation				
mmol/mol	44·1 (9·6)	45·9 (12·5)	49·1 (16·9)	45·4 (10·5)
%	6·2% (0·9)	6·4% (1·1)	6·6% (1·5)	6·3% (1·0)
Missing	26	26	18	17
Marital status				
Single	8 (6%)	16 (11%)	13 (13%)	6 (7%)
Level of education				
Less than secondary school	7/133 (5%)	2 (1%)	9/100 (9%)	2/80 (3%)
Completed secondary school only	29/133 (22%)	34 (23%)	39/100 (39%)	31/80 (39%)
Completed post-secondary school	97/133 (73%)	112 (76%)	52/100 (52%)	47/80 (59%)
Low socioeconomic status composite†	40 (30%)	51 (34%)	57 (56%)	45 (56%)
Immigrated to current country	63/133 (47%)	71 (48%)	45 (45%)	38 (47%)
Immigrated within past 5 years‡	16/133 (12%)	16 (11%)	15 (15%)	14 (17%)
Self-reported risky behaviours§	21 (16%)	20 (14%)	19 (19%)	14 (17%)
Self-reported ever smoker	14 (10%)	13 (9%)	12 (12%)	11 (14%)
Insulin dose at randomisation, units per kg per day				
Mean	0·67 (0·54)	0·66 (0·51)	0·61 (0·49)	0·72 (0·53)
Median	0·5 (0·2–0·9)	0·5 (0·3–0·9)	0·5 (0·2–0·8)	0·7 (0·3–1·0)
Presence of diabetes complications				
Retinopathy	3 (2%)	5 (3%)	2 (2%)	3 (4%)
Nephropathy	7 (5%)	9 (6%)	4 (4%)	9 (11%)
Hypertension	30 (22%)¶	26 (18%)	13 (13%)	20 (25%)
Chronic hypertension	29/30 (97%)	26/26 (100%)	13/13 (100%)	20/20 (100%)

(Table 1 continues on next page)

subscapular, and suprailiac), Z score for tricep skinfold thickness, Z score for subscapular skinfold thickness, and central-to-peripheral adiposity by measurement of suprailiac-to-tricep skinfold ratio and the subscapular-to-tricep skinfold ratio were done at 6, 12, and 24 months of age. Intra-rater reliability of three repeated skinfold

	Participated in MiTy Kids		Did not participate in MiTy Kids	
	Metformin group (n=135)	Placebo group (n=148)	Metformin group (n=101)	Placebo group (n=81)
(Continued from previous page)				
Blood pressure				
Systolic, mm Hg	119·4 (12·6)	118·3 (12·5)	118·6 (13·8)	120·4 (14·7)
Diastolic, mm Hg	72·2 (9·6)	72·8 (9·6)	72·2 (9·3)	73·5 (9·0)
Missing	5	5	5	5
Metformin used before pregnancy within past 12 months	96/98 (98%)	109/111 (98%)	61/62 (98%)	49/50 (98%)
Metformin used during first trimester	93/95 (98%)	93/94 (99%)	55/56 (98%)	44/44 (100%)

Data are mean (SD), n (%), n/N (%), or median (IQR) unless otherwise stated. Percentages might not sum to 100 as a result of rounding. MiTy=Metformin in Women with Type 2 Diabetes in Pregnancy. *Pre-pregnancy weight was self-reported. †Met any of the following criteria: immigrated to Canada or Australia within 5 years of study entry, marital status was single, or highest attained education was secondary school or less. ‡At the time of enrolment into the MiTy trial. §Comprised smoking during pregnancy, alcohol consumption during pregnancy, or recreational drug use during pregnancy. ¶One (<1%) participant developed gestational hypertension before randomisation.

Table 1: **Maternal baseline characteristics**

measurements was quantified by the intraclass correlation coefficient. Within-child changes in BMI were calculated over specific time periods (0–6 months, 6–12 months, 12–24 months, and 0–24 months). The trajectories of weight, length, and BMI between birth and 2 years (secondary outcomes) were estimated. Measures of overweight and obesity were compared. Risk of overweight was defined as a BMI Z score at least 1 SD above the reference WHO standard growth curve. Overweight or obesity was defined as a BMI Z score at least 2 SD on the standard WHO growth curve. Obesity was defined as a BMI Z score at least 3 SD above the reference standard WHO growth curve. BMI Z score, risk of overweight and obesity, and growth trajectories were calculated for males and females. The Nutrition Screening Tool for Every Toddler (NutriSTEP)[19] was used to assess the secondary outcome of overall nutritional risk. The questions in NutriSTEP used for the obesogenic score were identified by one of the authors (JH) based on known risk factors for obesity and are listed in the appendix (p 4). The scores were added up for each individual on the basis of the answers to the selected questions, and then the mean and SD were calculated.

Statistical analysis

Baseline and end-of study variables from MiTy were tabulated for participants who did and did not proceed from MiTy into MiTy Kids. At the nominal 12-month and 24-month timepoints, mean BMI Z score and mean sum of skinfolds were compared between the metformin and placebo groups, first with Student's *t* tests, and second in a linear regression model, adjusting for the actual age at time of measurement, infant sex, maternal pre-pregnancy BMI, maternal age at randomisation, previous pregnancies, smoking during pregnancy, ethnicity, socioeconomic status, entry HbA_{1c}, obesogenic score (included only at 24 months), screen time, active time, and sleep time. These comparisons were also repeated among males and females in subanalyses. All BMI Z score measurements from birth to 24 months were included in linear mixed-effects models, which included a random effect for the individual (to handle repeated measurements) and fixed effects for the intervention group, baseline covariates (sex, maternal BMI, low socioeconomic status, maternal age at randomisation, previous pregnancies, ethnicity, exposure to maternal smoking during pregnancy, and entry HbA_{1c}), and the cumulative duration of receiving breast milk up to each assessment time. Fractional polynomials for the age at assessment were used to model growth trajectories. Interactions between treatment group and the fractional polynomial time variables were used to assess whether growth trajectories varied by treatment (details are provided in the appendix p 31). These longitudinal analyses were repeated for the actual BMI, weight, and length. Sleep time on each day was calculated as the sum of reported time sleeping and napping; screen time was calculated as the sum of reported time watching television and computer or screen time; and activity time was calculated as the sum of reported time playing in the yard or street, playing in the park, outdoor walking, and organised physical activities. The questions used to capture screen time, active time, and sleep time are listed in the appendix (p 5).[20] The weekly totals were calculated as five times the reported weekday average plus two times the reported weekend average. Multiple imputation with chained equations was used to handle all missing outcomes, with ten imputed datasets created from a model that included age at assessment and all of the covariates listed previously. Metabolic parameters measured on blood samples were compared between groups. HOMA-IR was calculated on the blood samples according to the formula: fasting insulin (μU/L) times the fasting glucose (nmol/L) divided by 22·5.[21] Details of the sample size calculations are shown in the appendix (pp 32–33). All analyses were done in R (version 4.2.1).

	Participated in MiTy Kids		Did not participate in MiTy Kids	
	Metformin group (n=135)	Placebo group (n=147)*	Metformin group (n=85)	Placebo group (n=74)
Composite primary outcome†	43 (32%)	47 (32%)	34 (40%)	30 (41%)
Livebirths	135	147	88	75
Gestational age at birth, weeks	37·7 (1·6)	37·8 (1·5)	37·5 (1·6)	37·4 (2·0)
Sex				
Male	74 (55%)	77 (52%)	41 (47%)	36 (48%)
Female	61 (45%)	70 (48%)	46 (52%)	39 (52%)
Uncertain	0	0	1 (1%)	0
Preterm birth <37 weeks of gestation	30 (22%)	28 (19%)	25 (28%)	17 (23%)
Birth injury	0	0	0	3/74 (4%)
Respiratory distress syndrome	5 (4%)	4 (3%)	5/87 (6%)	3/74 (4%)
Neonatal hypoglycaemia	16 (12%)	16 (11%)	10/87 (11%)	17/74 (23%)
NICU stay lasting >24 h	27 (20%)	26 (18%)	20/87 (23%)	17/74 (23%)
Congenital anomaly‡	1 (1%)	7 (5%)	2/85 (2%)	1/73 (1%)
Birthweight, g	3220·8 (684·6)	3371·9 (608·4)	3191·0 (654·0)	3400·1 (901·0)
Birthweight Z score	0·02 (1·39)	0·42 (1·24)	0·14 (1·52)	0·47 (1·66)
Large for gestational age (>90th percentile birthweight)§	29 (21%)	36 (24%)	21 (24%)	27 (36%)
Extreme large for gestational age (>97th percentile birthweight)§	13 (10%)	15 (10%)	7/87 (8%)	17 (23%)
Birthweight ≥4000 g	20 (15%)	23 (16%)	8 (9%)	19 (25%)
Small for gestational age (<10th percentile birthweight)§	16 (12%)	8 (5%)	12/87 (14%)	7 (9%)
Sum of skinfolds¶, mm	15·88 (5·21)	16·84 (5·77)	16·10 (4·66)	18·64 (7·21)
Missing	31	24	37	24
Neonatal body fat mass	13·43 (6·57)	14·00 (4·51)	12·66 (5·60)	16·12 (5·63)
Missing	32	24	37	23
Infants who were at ≥34 weeks of gestation within 72 h of birth	117	128	63	63
Sum of skinfolds¶ >90th percentile	15/117 (13%)	8/128 (6%)	3/51 (6%)	8/51 (16%)
Body fat mass >90th percentile	12/113 (11%)	10/128 (8%)	5/56 (9%)	9/56 (16%)
Head circumference, cm	34·29 (2·17)	34·62 (1·56)	34·31 (1·73)	34·36 (2·27)
Missing	2	0	0	1
Chest circumference, cm	32·96 (4·19)	33·68 (2·71)	33·25 (2·84)	33·83 (2·60)
Missing	7	4	11	9
Abdominal circumference, cm	32·38 (4·29)	33·08 (2·78)	31·94 (2·87)	33·12 (3·05)
Missing	8	4	11	9
Ponderal index‖, g/cm^3	27·28 (6·54)	27·40 (4·87)	26·31 (4·04)	29·31 (11·04)
Missing	2	0	1	1

Data are n (%), n, mean (SD), or n/N (%). Denominators are livebirths for all characteristics except the composite primary outcome. MiTy=Metformin in Women with Type 2 Diabetes in Pregnancy. NICU=neonatal intensive care unit. *One participant in the placebo group contributed to the maternal baseline characteristics but did not complete a delivery form in MiTy, so is not included in the neonatal baseline characteristics, but as their data were collected they are included in BMI and sum of skinfold thickness analyses. †Composite primary outcome: preterm birth, birth injury, respiratory distress syndrome, neonatal hypoglycaemia, or NICU stay lasting more than 24 h. Composite primary outcome in MiTy Kids does not include pregnancy loss. ‡The EUROCAT registry[15] of definitions was used to define infants with major congenital anomalies. §Adjudicated using Canadian national growth curves[16] adjusted for sex and gestational age. ¶Tricep, subscapular, and suprailiac skinfolds. ‖The ponderal index is the weight (grams) divided by crown–heel length (cm)^3. One baby in the MiTY and MiTy Kids trial with a weight of 2950 g and a crown–heel length of 19·5 cm was omitted, as the ponderal index was 398.

Table 2: **Neonatal baseline characteristics**

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Of the 502 women who were enrolled in MiTy, 253 were allocated to metformin and 249 to placebo (figure 1). 27 women had pregnancy losses (13 in the metformin group and 14 in the placebo group), and ten infants were excluded because they had major congenital anomalies (four in the metformin group and six in the placebo group). Of the 465 eligible children, 283 (61%) participated in MiTy Kids. Compared with mothers who did not participate in MiTy Kids, those who participated were older, were less likely to satisfy the low socioeconomic status composite, and were more likely to be European, have completed secondary

	Metformin group	Placebo group	Mean difference (95% CI)*	p value
BMI				
Children included in analysis	111	115	..	..
BMI* overall, kg/m²	16·9 (2·3)	16·9 (2·0)	0·1 (–0·5 to 0·6)	0·81
Male	16·7 (1·8)	16·9 (2·1)	0·2 (–0·5 to 0·9)	0·56
Female	17·1 (2·7)	17·0 (1·9)	–0·1 (–0·9 to 0·9)	0·84
BMI Z score*	0·84 (1·52)	0·91 (1·38)	0·07 (–0·31 to 0·45)	0·72
Male	0·66 (1·33)	0·80 (1·52)	0·14 (–0·39 to 0·66)	0·61
Female	1·04 (1·69)	1·04 (1·21)	0·00 (–0·55 to 0·55)	0·99
Weight-for-length percentile	66% (30·2)	71% (27·6)	5·0% (–2·6 to 12·6)	0·20
BMI Z score for risk of overweight (≥1 SD using WHO reference) overall	47 (42%)	54 (47%)	OR 0·83 (95% CI 0·49 to 1·4)	0·49
Male	21/57 (37%)	25/59 (42%)	OR 0·79 (95% CI 0·38 to 1·67)	0·54
Female	26/54 (48%)	29/56 (52%)	OR 0·86 (95% CI 0·41 to 1·83)	0·70
BMI Z score for overweight or obesity (≥2 SD using WHO reference) overall	22 (20%)	17 (15%)	OR 1·42 (95% CI 0·71 to 2·86)	0·32
Male	9/57 (16%)	7/59 (12%)	OR 1·39 (95% CI 0·48 to 4·03)	0·54
Female	13/54 (24%)	10/56 (18%)	OR 1·46 (95% CI 0·58 to 3·68)	0·42
BMI Z score for obesity (≥3 SD using WHO reference) overall	6 (5%)	5 (4%)	OR 1·26 (95% CI 0·37 to 4·24)	0·71
Male	1/57 (2%)	3/59 (5%)	OR 0·33 (95% CI 0·03 to 3·3)	0·35
Female	5/54 (9%)	2/56 (4%)	OR 2·76 (95% CI 0·51 to 14·85)	0·24
Anthropometric measurements				
Children included in analysis	112	120	..	..
Age of child when height done, months	25·5 (2·3)	25·4 (2·4)	–0·1 (–0·7 to 0·6)	..
Height, cm	87·7 (4·7)	88·1 (4·0)	0·4 (–0·8 to 1·5)	0·54
Age of child when weight done, months	25·3 (2·3)	25·3 (2·4)	–0·1 (–0·7 to 0·6)	..
Weight, kg	13·00 (2·18)	13·13 (1·97)	0·13 (–0·41 to 0·67)	0·64
Missing	0	3	..	..
Sum of skinfold thickness (triceps, subscapular, suprailiac), mm	23·0 (5·2)	23·8 (5·4)	0·8 (–0·7 to 2·3)	0·31
Missing	25	22	..	..
Head circumference, mm	48·5 (2·4)	48·4 (2·5)	0·0 (–0·7 to 0·7)	0·94
Missing	17	18	..	..
Waist circumference, mm	48·6 (4·6)	48·6 (3·9)	0·0 (–1·2 to 1·3)	0·93
Missing	20	21	..	..
Tricep skinfold thickness, mm	9·6 (2·4)	9·7 (2·4)	0·1 (–0·6 to 0·7)	0·81
Missing	21	20	..	..
Subscapular skinfold thickness, mm	6·7 (1·9)	6·8 (1·8)	0·1 (–0·4 to 0·6)	0·76
Missing	22	21	..	..
Suprailiac skinfold thickness, mm	6·9 (2·6)	7·3 (2·9)	0·4 (–0·4 to 1·2)	0·29
Missing	25	22	..	..
Bicep skinfold thickness, mm	6·8 (2·1)	6·5 (2·2)	–0·4 (–0·9 to 0·4)	0·40
Missing	22	21	..	..
Z score for tricep skinfold thickness for age	0·73 (0·29)	0·72 (0·28)	0·00 (–0·08 to 0·08)	0·97
Missing	21	20	..	..

(Table 3 continues next page)

school education, and have polycystic ovary syndrome (table 1). The mothers who participated had a similar weight gain to those who did not participate, but lower HbA_{1c} and lower mean glucose at the end of pregnancy, with a higher insulin dose (appendix p 6). Compared with children who did not participate, fewer of those who participated satisfied the composite adverse neonatal outcome (which included preterm birth, birth injury, respiratory distress syndrome, neonatal hypoglycaemia, and a neonatal intensive care unit stay lasting more than 24 h; table 2).

At 24 months, there was no difference between the groups in the mean BMI Z score (0·84 [SD 1·52] in the metformin group *vs* 0·91 [1·38] in the placebo group; mean difference in BMI Z score of 0·07 [95% CI –0·31 to 0·45], p=0·72) or mean sum of skinfolds (23·0 mm [5·2] *vs* 23·8 mm [5·4]; mean difference in the sum of skinfolds of 0·8 mm [–0·7 to 2·3], p=0·31; table 3).

	Metformin group	Placebo group	Mean difference (95% CI)*	p value
(Continued from previous page)				
Z score for subscapular skinfold thickness for age	0·29 (0·30)	0·29 (0·30)	0·00 (–0·08 to 0·09)	0·97
Missing	22	21	..	..
Central-to-peripheral adiposity by measurement of the ratio of suprailiac to tricep skinfolds	0·75 (0·30)	0·78 (0·33)	0·04 (–0·06 to 0·13)	0·45
Missing	25	22	..	..
Central-to-peripheral adiposity by measurement of the ratio of subscapular to tricep skinfolds	0·72 (0·20)	0·72 (0·17)	0·00 (–0·06 to 0·05)	0·91
Missing	22	21	..	..
Age of child for anthropometric measurements, months	25·6 (2·4)	25·8 (2·6)	0·2 (–0·5 to 0·9)	..
Missing	16	17	..	..

Data are mean (SD), n (%), or n/N (%) unless otherwise stated. Tests for interaction between sex and treatment with metformin were not significant at the 0·05 level for any of the outcomes. OR=odds ratio. *Unless otherwise specified.

Table 3: **BMI and anthropometrics in children at 24 months**

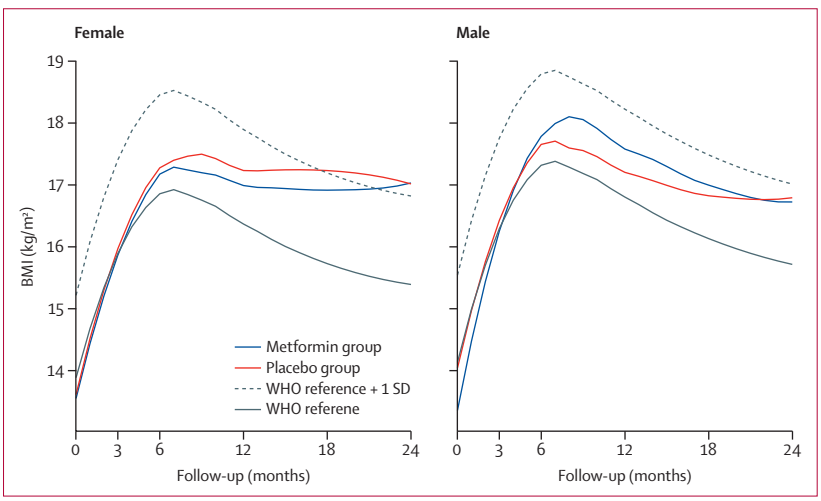

Figure 2: **BMI growth trajectories of infants up to 24 months**
The grey lines show the sex-specific WHO reference curves for the child at the mean BMI and at 1 SD above the mean BMI.

There was also no difference in weight; height; weight-for-length percentile; individual tricep, subscapular, and bicep skinfold thicknesses; Z scores for tricep and subscapular skinfolds; BMI Z scores for risk of overweight, overweight or obese, and obesity; head circumference; waist circumference; or central-to-peripheral adiposity (table 3). There were no differences in the anthropometrics of children from 3 months to 18 months (appendix pp 8–15). Within-child changes over specific time periods did not show differences overall (appendix pp 16–18), but in males exposed to metformin there was a significantly greater increase in mean BMI than in males in the placebo group (4·48 kg/m² [SD 0·29] *vs* 3·42 kg/m² [0·28], p=0·012) and mean BMI Z score (0·86 [0·23] *vs* 0·07 [0·21], p=0·014) from 0 to 12 months of age (appendix p 16), although their mean BMI Z scores were not different at 12 months. There was no difference in the overall nutritional score or obesogenic score between the metformin and placebo groups (appendix p 4). The reliability of repeated skinfold measurements was high at all sites at all times; estimated intraclass correlations were between 0·95 and 0·98 and the lowest 95% confidence limit for any estimate was 0·91 (appendix p 28).

In the linear regression models, assumptions of the models were evaluated and were met. For BMI Z scores, after inclusion of only variables with p values of less than 0·2 and metformin, we found no association between metformin and BMI Z score at 12 months of age (mean difference –0·07 [95% CI –0·41 to 0·27], p=0·68; appendix p 21) or 24 months of age (–0·01 [–0·42 to 0·37], p=0·92; appendix p 24). At 12 months, after inclusion of only variables with p values of less than 0·2 and metformin, we found that age at measurement (change per month 0·23 [95% CI 0·06 to 0·40], p=0·0084), previous pregnancies (mean difference 0·55 [0·17 to 0·94], p=0·0048, for one to four pregnancies *vs* none; mean difference 1·05 [0·43 to 1·66], p=0·0010, for more than four pregnancies *vs* none), and reduced duration of received breast milk (change per month –0·06 [–0·09 to –0·02], p=0·0030) were independently associated with child BMI Z score (appendix p 21). At 24 months, maternal pre-pregnancy BMI (change per point 0·03 kg/m² [95% CI 0·0 to 0·06], p=0·024), low socioeconomic status (mean difference –0·46 [–0·87 to –0·04], p=0·033), and reduced sleep time (change per month –0·03 [–0·05 to 0·00], p=0·021) were associated with BMI Z score (appendix p 24).

In the linear mixed-effects model, metformin was not a predictor of an overall difference in mean BMI Z score (mean difference 0·02 [95% CI –0·21 to 0·25], p=0·88; appendix p 27). After including only variables with p values of less than 0·2, maternal pre-pregnancy BMI (change per point 0·02 [95% CI 0·00 to 0·03], p=0·034) and reduced duration of received breast milk (change per month –0·03 [–0·06 to –0·01], p=0·0013) were associated with BMI Z score (appendix p 27). Because of the potential for breastfeeding to mediate the relationship between the

BMI Z score and maternal BMI, socioeconomic status, maternal age, and previous pregnancies, these models were refitted without breastfeeding duration. After running the model without breastfeeding duration, the effects of maternal BMI on BMI Z score was larger (appendix pp 20, 23, 26).

In models examining weight, length, and BMI growth trajectories by intervention and sex, there was no overall difference in the weight trajectory (p=0·87; appendix p 29), length trajectory (p=0·44; appendix p 30), or BMI growth trajectory by treatment (p=0·55; figure 2). The p value for the test of a sex-by-treatment interaction with time (ie, a differential effect of metformin on trajectories for males and females) was 0·096. However, in males, BMI trajectories were significantly different by treatment (p=0·048); the metformin group reached a higher peak mean BMI at 6 months than the placebo group that continued to be higher from 6 months to 24 months, at which time the trajectory was similar to that of the placebo group (figure 2). Children of women with type 2 diabetes were approximately 1 SD heavier than the WHO reference population (figure 2; appendix p 29).

Blood samples were taken in a subsample of 31 children at 24 months of age, 14 of whom were exposed to metformin and 17 to placebo (table 4). We found a significantly higher mean fasting glucose concentration in the metformin group than in the placebo group (4·8 mmol/L [0·7] *vs* 4·1 mmol/L [0·4]; 85·5 mg/dL [13·1] *vs* 74·6 mg/dL [7·6]), p=0·0090). There was no significant difference in fasting insulin, HOMA-IR, leptin, adiponectin, or lipids.

	Metformin group (n=14)	Placebo group (n=17)	p value
Demographics			
Birthweight, g	3238·9 (678·0)	3355·6 (586·3)	0·61
BMI, kg/m²	15·84 (1·18)	16·25 (1·51)	0·44
Missing	1	3	..
Sum of skinfolds (triceps, subscapular, suprailiac)§, mm	22·28 (4·45)	22·82 (4·13)	0·75
Missing	2	2	..
Blood work			
Leptin, pg/mL	371·2 (296·8)	498·5 (628·8)	0·49
Insulin resistance and glucose			
Missing	2*	0	..
Fasting insulin, pmol/L	23·2 (15·3)	25·2 (23·5)	0·81
Fasting glucose			
mmol/L	4·8 (0·7)	4·1 (0·4)	0·0090
mg/dL	85·5 (13·1)	74·6 (7·6)	0·0090
HOMA-IR†	0·7 (0·5)	0·7 (0·7)	0·93
Lipids			
Missing	2*	0	..
Cholesterol, mmol/L	4·5 (1·2)	3·8 (0·8)	0·077
Triglycerides, mmol/L	0·8 (0·6)	0·8 (0·5)	0·99
HDL, mmol/L	1·3 (0·2)	1·2 (0·2)	0·52
Non-HDL cholesterol, mmol/L	3·2 (1·1)	2·6 (0·7)	0·084
LDL, mmol/L	2·8 (1·0)	2·2 (0·7)	0·066
ALT, U/L	17·7 (6·2)	14·4 (4·0)	0·093
LDL:HDL, mmol/L	2·2 (0·7)	1·8 (0·6)	0·15
Adiponectin, µg/mL	79·1 (37·2)	66·0 (34·0)	0·36
Missing	3‡	2‡	..

Data are mean (SD) or n unless otherwise stated. *Two samples in the metformin group were unsuitable for testing. †HOMA-IR calculation=fasting insulin (µU/L) × fasting glucose (nmol/L)/22·5. ‡Samples were subjected to multiple freeze–thaw cycles; the results were excluded due to concerns for their validity.

Table 4: **Demographics and metabolic parameters in subsample of children with blood samples at 24 months**

Discussion

In this prospective follow-up study of a randomised trial (MiTy),[13] we found that there was no difference in BMI Z score or sum of skinfolds in the metformin-exposed infants compared with the placebo-exposed infants at 24 months of age. The 95% CIs for the between-group differences for these variables ruled out values greater than a third of a SD for BMI Z score and a half a SD for the sum of the skinfolds, which are values that are generally considered to indicate small to medium effects.[22] There was also no overall difference in the BMI growth trajectory by treatment; however, in males, the growth trajectory was significantly different by treatment such that the BMI in the metformin group was higher from 6 months to 24 months of age. At 24 months, metformin did not predict BMI Z score of the children but maternal pre-pregnancy BMI, lower socioeconomic status, and reduced sleep time were associated with increased BMI Z score. In the longitudinal model from birth to 24 months, pre-pregnancy BMI and reduced duration in which infants received breast milk were associated with an increased BMI Z score. Infants of women with type 2 diabetes were heavier than the normal reference range at 24 months of age.

In our cohort of children of women with type 2 diabetes, we found no difference in BMI Z score or sum of skinfolds at 12 months or 24 months in those exposed to metformin in utero compared with placebo. Evidence in the literature about the impact of the intrauterine exposure to metformin is conflicting. A long-term study of children of mothers with polycystic ovary syndrome whose infants were exposed to metformin in utero had a higher BMI at 4 years and at 5–11 years of age than controls.[9] A meta-analysis of follow-up studies of randomised trials of women with gestational diabetes receiving metformin or insulin found that, at mid-childhood, metformin-exposed children were heavier than those who received insulin.[23] Scientists hypothesise that metformin causes a state of intrauterine undernutrition, which then predisposes the infant to obesity and metabolic syndrome later in life. Other studies found no differences in anthropometrics.[10,24] Reassuringly, we did not find a difference in BMI in children exposed to metformin in utero and those not exposed in this cohort of women with type 2 diabetes, at 24 months of age. The

reason might be that metformin has no adverse effects in children of women with type 2 diabetes, who are generally overnourished compared with those of women with polycystic ovary syndrome or gestational diabetes. Alternatively, differences in anthropometry might only appear later in childhood.

Males exposed to metformin had a higher BMI growth trajectory from 6 months to 24 months, where they converged. Several observational studies have found that early accelerated weight gain is associated with an increase in long-term risk of obesity and non-communicable disease.[25] However, it is unclear whether this rapid weight gain is a significant contributor as some studies suggest that the rapid weight gain must occur within the first 3–6 months,[26] whereas other studies show that weight gain for up to 2 years can influence later adiposity.[27,28] Early weight gain is also affected by postnatal infant nutrition, with higher weight gain associated with formula feeding. In this study, we found that reduced duration of breast milk ingestion was associated with a higher BMI Z score. Promoting breastfeeding might help to reduce the early accelerated growth in this population.[25]

In this study, males exposed to metformin had a different growth trajectory than the male placebo group; however, we did not find a difference in the female infants. Sexual disparities in response to diabetes exposure in utero have been observed in several studies.[29,30] In a cohort study of 600 pairs of children matched 1:1 for exposure to gestational diabetes, exposure to gestational diabetes was associated with increased child overweight or obesity at 5–7 years in males only.[30] Males are hypothesised to be more insulin sensitive, making them more sensitive to maternal hyperglycaemia, which in turn might make them more sensitive to the effects of metformin. Further research is needed to see whether this sexual disparity continues in later years.

In our study, fasting glucose was significantly higher in the metformin group than in the placebo group, whereas there were no significant differences in the other parameters of the metabolic syndrome. This observation of elevated fasting glucose is similar to that found in another study of children of mothers with polycystic ovary syndrome from Norway in which the fasting glucose was higher in the metformin-exposed group (4·93 mmol/L *vs* 4·60 mmol/L, p=0·04) at 7–9 years of age.[31] By contrast, in a study of metformin-exposed children of mothers with gestational diabetes in Finland, males aged 9 years exposed to metformin in utero had a significantly lower 2 h glucose concentration than those on insulin, whereas fasting glucose was similar.[10] In the MiG TOFU follow-up trial of children aged 7–9 of women with gestational diabetes, there was no difference in any of the metabolic parameters between the metformin-exposed and non-exposed groups.[8] Although the significance and cause (or causes) of these glycaemic differences remain unknown, it should be noted that the amount of exposure to metformin, concomitant administration of insulin, rates of maternal obesity during pregnancy, and age of the children at follow-up were different. At the same time, the absence of differences in parameters associated with obesity—namely, insulin, leptin, adiponectin, and HOMA-IR—support the major finding that metformin exposure in utero did not significantly affect BMI at 2 years of age.

At 24 months of age, the children's BMI Z score was independently associated with maternal pre-pregnancy BMI, low socioeconomic status, and reduced sleep time. These findings are consistent with other studies and potentially modifiable. Several factors might play a part in the association of low socioeconomic status and childhood obesity. These include poor nutrition, such as more formula feeding in the first 6 months, introduction of solids earlier than 4 months, eating higher energy dense foods (ie, fast foods), and less access to fruits and vegetables.[32] We found that reduced sleep duration was independently associated with higher BMI Z score at 24 months of age. This finding has been noted in other studies, although the underlying aetiology is still unclear.[33] Potential mediators include the association of sleep deprivation with lower leptin and higher ghrelin concentrations leading to appetite dysregulation.

In this follow-up study, although we did not directly compare our cohort to a population-based cohort, we found that the children of the women with type 2 diabetes were approximately 1 SD heavier than the WHO reference range at 24 months of age. There is now much evidence that children of women with gestational diabetes are at an increased risk of childhood obesity, but there are few studies examining offspring of women with type 2 diabetes. Early data from the Pima indigenous population suggested that children of women with type 2 diabetes had an increased risk of obesity and type 2 diabetes, and the exposure to the in-utero environment was a significant risk factor.[5] However, data on early growth trajectories of children of women with type 2 diabetes are sparse. One study on child growth up to 14 years of age, found that children of women with type 2 diabetes had the highest growth trajectory compared with those of women with gestational diabetes and type 1 diabetes.[34] This is plausible considering the potential for more exposure to overnutrition in the intrauterine environment in offspring of women with type 2 diabetes from both hyperglycaemia and maternal obesity, although genetic factors might also play a part. More research is needed to examine the growth trajectory of children of women with type 2 diabetes and its influences.

Our study has many strengths. To our knowledge, this is the first large follow-up study of children of women with type 2 diabetes examining the growth trajectory of children exposed to metformin versus placebo. As the women included were from a randomised trial, there was less bias in choosing the intervention group.

This was an international study that included women from multiple race or ethnicity groups. Several important confounders, including age at time of measurement, infant sex, maternal pre-pregnancy BMI, maternal age at randomisation, previous pregnancies, smoking during pregnancy, ethnicity, socioeconomic status, entry HbA_{1c}, obesogenic score, screen time, active time, and sleep time, were adjusted for. However, there are some limitations. We were able to enrol only 60% of the original cohort, and women included in this cohort were mainly from Europe, had a higher socioeconomic status, and were more educated than those who were not enrolled. The number of blood samples used to examine potential metabolic differences between the groups was limited. The significant findings could have arisen by chance due to the large number of statistical tests done.

In summary, we found no difference in mean BMI Z score or mean sum of skinfolds between the children who were exposed to metformin and those exposed to placebo at 24 months of age. Given the increasing incidence of type 2 diabetes in pregnancy and the increasing use of metformin during pregnancy, we believe that these data are reassuring with regard to the use of metformin during pregnancy in women with type 2 diabetes and the long-term health of their children. Future follow-up is needed to see if such findings persist.

Contributors

DSF wrote the manuscript. ST and KM did the data cleaning. YJ and GT directly accessed and verified the underlying data reported in the manuscript and did the analysis. GT provided statistical expertise and interpretation. All authors had full access to the data and contributed to the interpretation of the data. All authors made critical revisions of the manuscript, approved the final draft of the manuscript, and accept responsibility to submit for publication. DSF is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Declaration of interests

DSF has received honoraria from Novo Nordisc for serving on an advisory board and from Sanofi for lectures, unrelated to this current work. AMH is a principal investigator for clinical trials from Levo Therapeutics and Rhythm Pharmaceuticals; is on the Pfizer Canada Somatrogon advisory board and the Rhythm Pharmaceuticals Bardet-Biedl Syndrome advisory board; and has received funding from the Canadian Institutes of Health Research and W Garfield Weston Foundation's Weston Family Microbiome Initiative for unrelated work. IGF declares grants from the Division of Endocrinology and Metabolism, McGill University. JB received honoraria for presentations from Ferring Pharmaceuticals. LL is a member of the Board of Directors of Diabetes Canada (volunteer) and receives salary support as Director of the University of Toronto Novo Nordisk Network for Healthy Populations (donation from Novo Nordisk to University of Toronto). JJS received funding from the Canadian Institutes of Health Research to support her postdoctoral fellowship salary, and grant funds were also used to attend the American Diabetes Association 2022 meeting. JH received research funding from Levo Therapeutics, SunLife, Rhythm Pharmaceuticals, Mead Johnson, Pfizer, and Foundation for Prader-Willi Research; served as a consultant for Novo Nordisk Canada; received an honoraria for speaking from Pfizer; and is the medical director for SickKids Team Obesity Management Program. All other authors declare no competing interests.

Data sharing

The datasets generated or analysed in this study are available from the corresponding author according to institutional policies and upon reasonable request by providing a detailed ethics-approved protocol for the proposed study, information about the funding, resources to carry out the study, approval by the MiTy Kids Steering Committee, and a data sharing agreement.

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