Metformin in Gestational Diabetes: The Offspring Follow-Up (MiG TOFU)

Body composition at 2 years of age

Janet A. Rowan, mbchb[1]
Elaine C. Rush, phd[2]
Victor Obolonkin, bsc[3]
Malcolm Battin, md[4]
Trecia Wouldes, phd[5]
William M. Hague, md[6]

OBJECTIVE—In women with gestational diabetes mellitus, who were randomized to metformin or insulin treatment, pregnancy outcomes were similar (Metformin in Gestational diabetes [MiG] trial). Metformin crosses the placenta, so it is important to assess potential effects on growth of the children.

RESEARCH DESIGN AND METHODS—In Auckland, New Zealand, and Adelaide, Australia, women who had participated in the MiG trial were reviewed when their children were 2 years old. Body composition was measured in 154 and 164 children whose mothers had been randomized to metformin and insulin, respectively. Children were assessed with anthropometry, bioimpedance, and dual energy X-ray absorptiometry (DEXA), using standard methods.

RESULTS—The children were similar for baseline maternal characteristics and pregnancy outcomes. In the metformin group, compared with the insulin group, children had larger mid-upper arm circumferences (17.2 ± 1.5 vs. 16.7 ± 1.5 cm; $P = 0.002$) and subscapular (6.3 ± 1.9 vs. 6.0 ± 1.7 mm; $P = 0.02$) and biceps skinfolds (6.03 ± 1.9 vs. 5.6 ± 1.7 mm; $P = 0.04$). Total fat mass and percentage body fat assessed by bioimpedance ($n = 221$) and DEXA ($n = 114$) were not different.

CONCLUSIONS—Children exposed to metformin had larger measures of subcutaneous fat, but overall body fat was the same as in children whose mothers were treated with insulin alone. Further follow-up is required to examine whether these findings persist into later life and whether children exposed to metformin will develop less visceral fat and be more insulin sensitive. If so, this would have significant implications for the current pandemic of diabetes.

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The Metformin in Gestational diabetes (MiG) trial prospectively compared pregnancy outcomes in women with gestational diabetes mellitus (GDM) randomized to either metformin (plus supplemental insulin as required) or insulin treatment. The primary outcome, a composite of neonatal complications, was not significantly different between the treatment arms (1). Secondary outcomes, including body anthropometry at birth, were also not different between the treatment arms.

Metformin crosses the placenta in significant amounts, so although neonatal outcomes are reassuring, it is important to examine longer term outcomes, such as body composition in childhood (2). It is known that offspring of women with diabetes have an increased fat mass at birth but not an increase in fat-free mass (FFM) (3). An explanation of this finding may be that because of continued exposure to nutrient excess in utero, the subcutaneous fat stores become overloaded and, thus, the fetus develops leptin and insulin resistance and deposits excess nutrients as ectopic fat (4). Reduced insulin sensitivity has been demonstrated in cord blood of infants exposed to maternal hyperglycemia (5). In a similar manner, infants of obese women, who are also exposed to nutrient excess, have an increased fat mass at birth and have been shown to be insulin resistant (6). It is possible that metformin exposure in utero might lead to improved insulin action in the fetus, resulting in a metabolically healthier pattern of growth, with more subcutaneous fat stores developing and less ectopic fat (4,7,8).

The aim of The Offspring Follow-Up (TOFU) study at 2 years of age was to compare body composition in children of women who participated in the MiG trial and, in particular, to compare measures of adiposity. Our hypothesis was that children whose mothers had been randomized to metformin treatment would have reduced central adiposity compared with children whose mothers had been randomized to insulin.

RESEARCH DESIGN AND METHODS

—In the MiG trial, 751 women with GDM who required medication to control their hyperglycemia were randomized to either metformin or insulin treatment; their pregnancy outcomes have been reported (1). From two recruiting sites in Auckland, New Zealand, and one site in Adelaide, Australia, women who had consented to further follow-up were contacted by telephone at approximately the time of the child's second birthday to explain the follow-up study and to confirm that they were still agreeable to participate. In Auckland, a home visit was arranged for the first part of the assessment during which maternal interviews and simple anthropometry measurements of the mother and child were made. A follow-up appointment was made within 1 to 2 weeks of the home visit to attend the Liggins Institute, University of Auckland, for the child to have a physical

From the [1]Department of Obstetrics, National Women's Health, Auckland, New Zealand; the [2]Centre for Child Health Research, Auckland University of Technology, Auckland, New Zealand; the [3]Department of Biological Sciences, University of Auckland, Auckland, New Zealand; the [4]Department of Pediatrics, National Women's Health, Auckland, New Zealand; the [5]Department of Psychological Medicine, University of Auckland, Auckland, New Zealand; and the [6]Department of Obstetrics, Women and Children's Hospital, University of Adelaide, Adelaide, Australia.
Corresponding author: Janet A. Rowan, janetrowan1@gmail.com.
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examination, a neurodevelopmental assessment, and a total body dual energy X-ray absorptiometry (DEXA) measurement. In Adelaide, women and their children were invited to the hospital and all the assessments were performed there. This follow-up study had ethical approval at each contributing site, and written informed consent was again obtained for each participant. The study was registered prior to its initiation under the Australian New Zealand Clinical Trials Registry (ACTRN12605000311651).

Questionnaires were completed by trained researchers, including assessment of the family's socioeconomic conditions, home environment, any drug and alcohol intake, and health of the mother and child. Diet was assessed by 24-h recall and food frequency questionnaires. Usual activity of the children was assessed by a 24-h activity diary. The child underwent a general physical examination by a pediatrician and a neurodevelopmental assessment by a psychologist. The neurodevelopmental findings and detailed diet and activity assessments will be reported separately.

Anthropometry measurements of the mother and child included weight, height, leg length, head, chest, waist, hip and mid-upper arm circumferences, and biceps, triceps, and subscapular skinfolds. Skinfolds were performed with a Holtain skinfold caliper (Holtain Ltd., Crymych, U.K.). The method for each measurement was based on those used in a New Zealand Children's Nutrition Survey (http://www.moh.govt.nz/moh.nsf/0/064234A7283A0478CC256DD60000AB4C/$File/nzfoodnzchildren.pdf) and detailed in the study manual. Training of study personnel was undertaken by a single person in Auckland to maintain consistency across sites. All measurements were repeated twice and the average calculated. A further measurement was made if the difference in measures was >0.5 cm (height and circumferences) or >0.5 mm (skinfolds), and the average of the two closest measures was calculated and used in the analysis.

Hand-to-foot single-frequency (50 kHz) bioimpedance analysis (BIA; BIM4, Impedimed, Queensland, Australia) of the child was performed with the child lying supine. Areas on the hand and foot where electrodes were to be placed were first cleaned with alcohol. The current electrodes were placed on the hand on the distal portion of the second metacarpal and on the foot over the distal portion of the second metatarsal. The sensing electrodes were placed at the anterior ankle between the tibial and fibular malleoli and at the posterior wrist between the styloid processes of the radius and ulna. The measurements were repeated up to three times until they were stable to within one ohm. The average resistance value was used in the prediction equation below. A BIA measurement was undertaken similarly in the mother, and the FFM was calculated as FFM = $-9.53 + 0.69\text{stature}^2/\text{resistance} + 0.17\text{weight} + 0.02\text{resistance}$ (9).

If consented to separately, a DEXA whole body scan of the child was performed on a Lunar Prodigy 2000 scanner (software version 4.80 × 6.50, General Electric, Madison, WI). Each scan was graded 1, 2, or 3 for quality by a single person in Auckland and a single person in Adelaide. Scans that were graded 3 (poor quality) were excluded from this analysis. As well as total fat, lean, and bone mineral content, an abdominal and thigh area for area fat content was calculated. Abdominal and thigh regions of interest were defined by the criteria of Ley et al. (10) The abdominal fat measure was obtained from analysis of a region positioned with the lower horizontal border on top of the iliac crest and the upper border approximately parallel with the junction of the T12 and L1 vertebrae. The sides of this region were adjusted to include the maximum amount of abdominal tissue. The thigh measure was obtained by analyzing an area of identical height placed over the thighs with the upper horizontal border positioned immediately below the ischial tuberosities. The lateral margins were adjusted to follow the shape of the thighs. The DEXA FFM was used as the criterion for the development of a prediction equation for bioimpedance FFM based on the following predictor values: weight, $\text{height}^2/\text{resistance}$, sex (dummy coded with girls = 0 and boys = 1), and age. The equation developed was as follows:

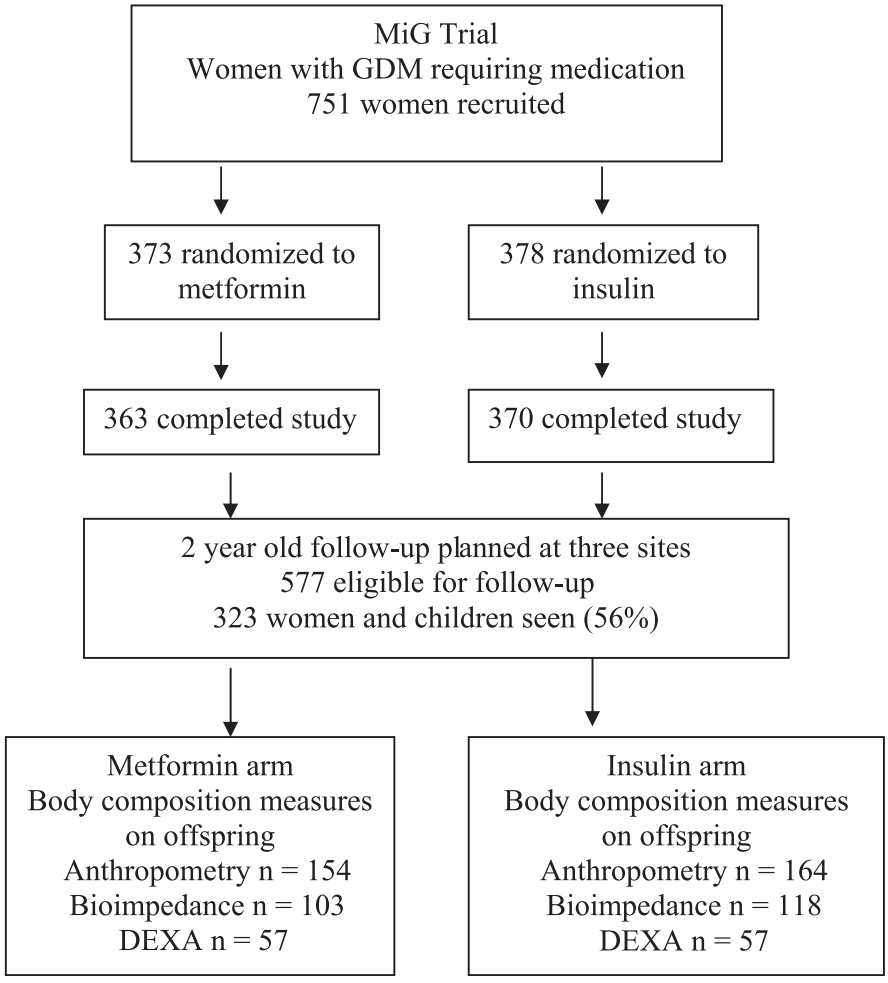

Figure 1—*Offspring followed up from the MiG trial.*

$$\text{FFM}_{\text{DEXA}}\text{kg} = 0.894 + 0.421\text{H}^2/\text{R} + 0.268\text{Wt} + 0.338\text{Sex} + 0.064\text{Age}$$

(R^2 = 0.857, SEE [standard error of the estimate] = 0.559 kg), where H is height (cm), R is resistance (Ω), Wt is weight (kg), Sex (0 = girls, 1 = boys), and Age (months) (11).

The bioimpedance and DEXA measures of the child were performed in the morning before morning tea with the child wearing a T-shirt and dry disposable nappy.

Statistical analysis

A follow-up rate of 50% was anticipated, recognizing that it might be difficult, for various social reasons, to maintain contact with the MiG trial population, as others have described and highlighted by the initial 6–8 week postpartum follow-up, which was achieved in 75%.

Power calculations. A study of 240 children (120 in each arm) would allow detection of a 2% difference in body fat percent (based on an estimated body fat of 24 ± 4%) with 97% power and, thus, allowing a clinically meaningful analysis of the groups with respect to body composition. A study of 37 children in each treatment arm would have 80% power to detect a 2% difference in body fat percent.

Continuous variables were examined for normal distribution. For all data presented, the distributions were normal. Continuous variables are presented as mean ± SD. One-way ANOVA was used to test for differences in group means, and post hoc *t* tests were used to determine which groups were different. The significance level was set at 5%. ANCOVA was used to adjust for height, weight, and age when examining differences in fat mass and FFM among ethnic groups.

RESULTS—Of the women recruited into MiG at the two Auckland sites, 189 of 282 (67%) and 33 of 114 (28.9%) were seen for follow-up. In Adelaide, 101 of 181 (55.8%) were seen, giving a total of 323 women (Fig. 1). Body composition measurements were performed in 318 children, of whom 154 mothers and 164 mothers had been randomized to metformin and insulin treatment during pregnancy, respectively. A bioimpedance measurement was performed in 103 and 118 children in the metformin and insulin arms, respectively. DEXA measurements were performed in 140 children: 114 grade 1 and 2 scans were analyzed, 57 in each treatment arm.

The children seen at 2 years of age included a smaller proportion of those of Polynesian ethnicity compared with the total MiG population (14 vs. 20%, P = 0.02). Also, children seen for follow-up had had a shorter crown-rump length at birth (33.0 vs. 33.5 cm, P = 0.005) and smaller triceps skinfolds (4.80 vs. 5.15 mm, P = 0.0002) and subscapular skinfolds (4.95 vs. 5.20 mm, P = 0.07) at birth than the total group. All other baseline characteristics of the mothers and children and trial outcome measures were not different between the follow-up group and the total MiG population (data not shown).

In the children seen at 2 years of age, there were no differences between the groups in the baseline characteristics of the mother at randomization to treatment (Table 1). There were also no differences in pregnancy outcomes between the metformin and insulin follow-up groups, including the MiG trial primary outcome composite of neonatal complications (31.2 vs. 34.7%, P = 0.97), admission to the neonatal unit (17.5 vs. 18.3%, P = 0.97), and admission for >24 h (11.7 vs. 11.6%, P = 0.98). In addition, there were no differences between the groups in measurements at birth, maternal glucose control during pregnancy, and rates of breast feeding at 6–8 weeks postpartum (Table 2). Follow-up maternal anthropometry was not different between the two groups; maternal BIA showed higher FFM in the metformin group, but percentage body fat was not different (Table 3).

Body composition measurements at 2 years of age showed three significant differences (Table 3). The upper-arm circumference was larger in the metformin group (P = 0.002), and subscapular skinfolds and biceps skinfolds were bigger (P = 0.02 and P = 0.04, respectively). These results were explored further to confirm that the differences related to treatment. After adjusting for age, sex, ethnicity, and maternal glucose control during pregnancy, the P values were: upper-arm circumference, P = 0.005; subscapular skinfold, P = 0.01; and biceps skinfold, P = 0.02. There were no differences in DEXA measures between the two groups by unadjusted and adjusted analysis. This included total and regional fat measures. Bioimpedance measures also showed no difference between the metformin and insulin group in FFM or percentage fat.

CONCLUSIONS—This study describes the body composition in a unique population of 2-year-olds whose mothers had GDM and were randomized to treatment with metformin or insulin during pregnancy. The groups were matched for baseline maternal characteristics, maternal glycemia, and pregnancy outcomes.

Our initial hypothesis was that metformin exposure in utero would be associated with less central fat and, therefore,

Table 1—*Children assessed at age 2 years: the maternal baseline characteristics at randomization to treatment in MiG*

	Metformin (n = 154)	Insulin (n = 164)	P value
Age (years)	39.4 ± 5.2	38.9 ± 5	0.32
BMI (kg/m^2)			
At booking (before 20 weeks' gestation)	31.8 ± 8.2	31.1 ± 10	0.47
At recruitment	33.4 ± 12	31.6 ± 10	0.12
Gestational age at recruitment (weeks)	30.4 ± 3.3	30.0 ± 3.3	0.58
Ethnicity (self-reported)			0.46
European/Caucasian	88 (57.1)	78 (47.6)	
Polynesian	21 (13.6)	26 (15.9)	
Indian	22 (14.3)	34 (20.7)	
Chinese and other Southeast Asian	15 (9.7)	16 (9.8)	
Other or mixed	8 (5.2)	10 (6.1)	
Tertiary education	79 (51.3)	96 (58.5)	0.24
Smoking in pregnancy	16 (10.4)	10 (6.1)	0.23
Chronic hypertension	20 (13.0)	17 (10.4)	0.58
75-g OGTT result			
Fasting plasma glucose (mmol/L)	5.5 ± 1	5.6 ± 1	0.56
2-h plasma glucose(mmol/L)	9.6 ± 2	9.5 ± 2	0.72
HbA_{1c} at recruitment (%)	5.7 ± 0.58	5.7 ± 0.67	0.96

Data expressed as mean ± SD or n (%). OGTT, oral glucose tolerance test.

Table 2—*Children assessed at age 2 years: pregnancy outcome data*

	Metformin (n = 154)	Insulin (n = 164)	P value
Neonatal			
Gestational age at birth (weeks)	38.4 ± 1.3	38.5 ± 1.2	0.32
Birth weight (g)	3,325 ± 558	3,356 ± 530	0.62
Birth weight percentile	52.8 ± 29.1	52.2 ± 30.8	0.87
Birth weight below 10th percentile	14 (9.1)	15 (9.1)	
Birth weight above 90th percentile	20 (13.0)	23 (14.0)	
Head circumference (cm)	34.8 ± 1.5	34.8 ± 1.5	0.98
Crown-heel length (cm)	50.1 ± 2.6	50.3 ± 2.4	0.60
Crown-rump length (cm)	33.0 ± 2.6	32.9 ± 2.5	0.55
Chest circumference (cm)	33.9 ± 2.4	33.9 ± 2.5	0.92
Abdominal circumference (cm)	32.8 ± 2.8	32.4 ± 3.0	0.30
Mid-upper arm circumference (cm)	11.1 ± 1.3	11.0 ± 1.3	0.63
Triceps skinfold thickness (mm)	4.77 ± 1.2	4.82 ± 1.1	0.72
Subscapular skinfold thickness (mm)	4.96 ± 1.2	4.94 ± 1.1	0.93
Ponderal index (birth weight [g] × 100/crown-heel length [cm]^3)	2.63 ± 0.3	2.63 ± 0.28	0.85
Maternal			
Glycemic control from randomization until delivery			
Mean fasting capillary glucose			0.71
Tertile 1 (mean 4.6 ± 0.3 mmol/L)	55 (35.7)	66 (40.2)	
Tertile 2 (mean 5.1 ± 0.1 mmol/L)	61 (39.6)	64 (39.0)	
Tertile 3 (mean 5.9 ± 0.6 mmol/L)	36 (23.4)	34 (20.7)	
Mean postprandial capillary glucose			0.69
Tertile 1 (mean 5.6 ± 0.2 mmol/L)	67 (43.5)	65 (39.6)	
Tertile 2 (mean 6.2 ± 0.2 mmol/L)	51 (33.1)	57 (34.8)	
Tertile 3 (mean 7.2 ± 0.7 mmol/L)	34 (22.1)	42 (25.6)	
Hypertensive complications			
Gestational hypertension	7 (4.5)	5 (3.0)	0.69
Preeclampsia	5 (3.2)	8 (4.9)	0.65
Infant feeding 6–8 weeks postpartum			0.72
Breast feeding	74 (48.1)	84 (51.2)	
Bottle feeding	30 (19.5)	35 (21.3)	
Both breast and bottle	42 (27.3)	39 (23.8)	
Not seen	8 (5.2)	6 (3.7)	

Data expressed as mean ± SD or n (%) unless otherwise detailed.

less insulin resistance in the offspring. However, we found no differences between groups in central fat measures, total fat mass, percentage body fat, or central-to-peripheral fat as measured by waist-to-hip ratio and DEXA-calculated abdominal-to-thigh fat ratios. Instead, we found that the children who were exposed to metformin in utero had larger upper-arm circumferences and bigger biceps and subscapular skinfolds. This suggests that exposure to metformin in utero has led to more fat being stored in subcutaneous sites, which may in turn mean there is less ectopic or visceral fat in these children.

These findings are important for two reasons: first, they suggest that maternal metformin treatment during pregnancy may lead to a more favorable pattern of fat distribution for exposed children; second, they suggest that simple measures of central fat may not be adequate for determining the potential effects of in utero exposure to metformin. The central fat measures used in this study provided a combined measure of subcutaneous and visceral fat, so further studies will be needed to confirm whether the children exposed to metformin have less visceral fat.

Size and location of fat cells are important predictors of insulin resistance and adverse metabolic consequences of obesity (4,8,12). Subcutaneous fat cells provide an important physiological store of extra nutrients. They have a limited capacity and are normally under homeostatic regulation, providing feedback about food intake and satiety. In situations of ongoing excessive nutrient intake, the adipocytes become large and dysfunctional and excess fat is deposited in visceral adipocyte depots, which readily release fatty acids and inflammatory adipocytokines (12). These changes are associated with insulin resistance, as opposed to insulin-sensitive obesity, which is associated with proportionally more healthy subcutaneous fat cells and less visceral fat (8,13,14). A more insulin-sensitive pattern of growth would be a plausible consequence of metformin exposure in utero, based on our understanding of metformin action (7). To examine this question further, ongoing follow-up will be important to determine whether differences persist and to measure visceral and subcutaneous fat and insulin sensitivity. Longitudinal follow-up is also important in that postnatal influences on growth may override any effect of metformin exposure during late pregnancy (15).

There are no other similar studies for comparison, so our data are novel. There are studies looking at subsequent growth of children whose mothers have had diabetes in pregnancy (16–20). Compared with children whose mothers did not have diabetes, they were more likely to be obese and have features of insulin resistance, which is felt to be the result of both genetic and intrauterine and postnatal environmental factors. It is possible that there are critical windows where intervention might improve these outcomes (21). There are two randomized trials showing that treatment of mild GDM (predominantly with diet) compared with standard pregnancy care was associated with improved pregnancy outcomes (22,23), but initial follow-up of children in one trial did not show a significant difference in BMI at 4–5 years of age (24). It is unclear whether the intervention in pregnancy was too late or inadequate or whether a difference will appear at subsequent follow-up. More detailed measures of visceral fat in those children would also be of interest. A further study has shown that treating women with GDM resulted in fewer overweight children at 5–7 years of age compared with children whose mothers had elevated glucose tolerance test results during pregnancy but did not reach the threshold for a diagnosis and treatment of GDM (25). These data also highlight the need for further studies looking at how different treatments for GDM influence long-term outcomes to better understand how to optimize the health of future generations.

The major strength of this follow-up study is that the offspring were well matched, enabling valid comparisons between treatment groups. Also, body

Table 3—*Two-year-old measurements*

	Metformin (n = 154)	Insulin (n = 164)	P value
Adjusted age (months)	28.7 ± 3.6	29.4 ± 3.8	0.08
Sex: male/female (n)	86/68	79/85	0.21
Weight (kg)	14.3 ± 2.1	14.0 ± 2.2	0.18
Height (cm)	90.7 ± 4.9	91 ± 4.8	0.68
Leg length (cm) (height minus crown to rump)	37.9 ± 3.1	38.1 ± 3.3	0.61
Head circumference (cm)	49.4 ± 1.8	49.3 ± 1.7	0.52
Chest circumference (cm)	52.1 ± 3.0	51.6 ± 3.0	0.12
Upper-arm circumference (cm)	17.2 ± 1.5	16.7 ± 1.5	0.002
Waist circumference (cm)	50.5 ± 3.5	50.1 ± 4	0.33
Hip circumference (cm)	52.1 ± 4.0	51.6 ± 4.0	0.28
Waist-to-hip ratio	0.97 ± 0.05	0.97 ± 0.05	0.95
Triceps skinfold thickness (mm)	10.1 ± 2.0	9.9 ± 2.4	0.50
Subscapular skinfold thickness (mm)	6.3 ± 1.9	6.0 ± 1.7	0.02
Biceps skinfold thickness (mm)	6.0 ± 1.9	5.6 ± 1.7	0.04
DEXA	N = 57	N = 57	
Total fat (g)	2,421 ± 1,002	2,274 ± 711	0.37
Abdominal fat (g)	132 ± 73	131 ± 60	0.92
Thigh fat (g)	266 ± 96	262 ± 86	0.83
Arm fat (g)	196 ± 104	181 ± 74	0.36
Abdominal-to-thigh fat ratio	0.48 ± 0.1	0.50 ± 0.1	0.33
Lean body mass (g)	10,756 ± 1,283	10,736 ± 1,401	0.94
Bone mineral content (g)	389 ± 69	390 ± 70	0.95
FFM	11,095 ± 1,293	11,126 ± 1,458	0.91
Total fat (%)	16.4 ± 4.9	16.9 ± 4	0.34
Abdominal fat (% of fat mass)	5.3 ± 1.3	5.6 ± 1.3	0.20
Thigh fat (% of fat mass)	11.3 ± 2.5	11.4 ± 2.5	0.73
Arm fat (% of fat mass)	7.82 ± 1.7	7.75 ± 1.6	0.81
Bioimpedance	N = 103	N = 118	
FFM (kg)	11.8 ± 1.89	11.4 ± 1.45	0.13
Total fat (%)	16.5 ± 9.07	17.1 ± 6.99	0.58
Maternal measures at 2-year assessment			
Height (cm)	163 ± 6.6	162 ± 7.4	0.06
Weight (kg)	87.7 ± 26	82.6 ± 24	0.07
BMI (kg/m^2)	32.6 ± 8.5	31.4 ± 8.2	0.19
Head circumference (cm)	57 ± 2.2	56.7 ± 2.3	0.30
Waist circumference (cm)	102 ± 18	99.4 ± 18	0.22
Upper-arm circumference (cm)	35.5 ± 6.5	34.3 ± 5.8	0.08
Hip circumference (cm)	114 ± 17	113 ± 18	0.67
Triceps skinfold thickness (mm)	27.6 ± 7.1	28.5 ± 7.6	0.32
Subscapular skinfold thickness (mm)	30.1 ± 9.1	30.5 ± 9	0.75
Biceps skinfold thickness (mm)	18.5 ± 8.7	17.3 ± 7.2	0.19
Waist-to-hip ratio	0.90 ± 0.09	0.88 ± 0.08	0.10
Bioimpedance			
FFM (kg)	51.3 ± 9.21	48.5 ± 9.09	0.01
Total fat (%)	40.1 ± 7.83	38.6 ± 7.35	0.11

composition was measured by several methods, and the differences found were consistent with a biologically plausible effect of metformin. A potential limitation is the low follow-up rate of the total MiG cohort. The follow-up group did have fewer Polynesian children, and as a group they had a shorter crown-rump length and smaller subscapular and triceps skinfolds at birth, compared with the total group. Otherwise, they were representative of the whole group and the study was adequately powered to explore differences in body composition. Also, additional analyses were performed to examine whether other potential confounders were contributing to the findings, but they confirmed that the differences related to treatment.

In conclusion, 2-year-old offspring of women with GDM, who were exposed to metformin in utero, had larger subscapular and biceps skinfolds but showed no difference in total or percentage body fat compared with children whose mothers were treated during pregnancy with insulin alone. Whether this will translate to a more insulin-sensitive pattern of growth requires further examination. The findings are reassuring for clinicians who are using metformin during pregnancy.

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