

# Childhood follow-up of the GRow randomized trial: Metformin in addition to dietary and lifestyle advice for pregnant women with overweight or obesity

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## Summary

**Background:** Metformin for women with overweight or obesity during pregnancy has been evaluated in randomized trials to reduce adverse pregnancy and birth outcomes. The effect on longer-term child health remains of interest.

**Objectives:** To evaluate the effect of in-utero exposure to metformin on child health compared with no exposure.

**Methods:** We assessed children born to 513 women who participated in the Metformin in addition to dietary and lifestyle advice for pregnant women with overweight or obesity: the GRow randomized trial, where women were randomized to receive either metformin or placebo during pregnancy. Child weight, height, anthropometry, diet, physical activity and neurodevelopment were assessed at six and 18 months and three to five years of age. The main outcome was BMI z-score > 85th centile for age and sex.

**Results:** The number of children with BMI >85th centile was similar between treatment groups at all time points. At 18 months and three to five years of age, more than half of the children had a BMI z-score > 85th centile, indicating a high risk of childhood obesity.

**Conclusions:** We did not show evidence of the benefit of metformin for children of women with overweight or obesity during pregnancy adding to the growing literature on the lack of effect of pregnancy interventions in reducing longer-term risks of childhood obesity.

## KEYWORDS

child follow-up, metformin, overweight and obesity, pregnancy intervention, randomized controlled trial

## 1 | INTRODUCTION

Oral metformin, an insulin-sensitizing agent, is commonly used during pregnancy for the management of gestational diabetes.<sup>1</sup> More recently, its use has been evaluated as a potential intervention to improve outcomes for women with overweight or obesity, either alone or as an

adjunct therapy to dietary and lifestyle advice. However, there is little evidence to suggest that the use of metformin in the setting of maternal overweight and obesity reduces either the risk of maternal adverse health outcomes or the occurrence of high infant birth weight.<sup>2</sup>

While there is some evidence that the use of metformin in pregnancy may impact pre-pubescent childhood growth measures,<sup>3</sup> the

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longer-term impact on health outcomes of children born to women with overweight or obesity remains to be determined. While some have suggested improvement in some early child cardiovascular measures following antenatal metformin,<sup>4</sup> this is not universal.<sup>5</sup> Furthermore, these follow-up studies have been limited by the relatively small numbers of participants assessed, and a lack of focus on child anthropometric measures.

The Metformin in addition to dietary and lifestyle advice for pregnant women with overweight or obesity: the GRoW randomized trial evaluated the effect of metformin as an adjuvant therapy to dietary and lifestyle advice, involving 524 pregnant women with overweight or obesity. We reported that women who received metformin in addition to dietary and lifestyle advice were at similar risk of birth of a baby with birth weight greater than 4000 g when compared with women who received the dietary and lifestyle intervention alone but had significantly lower weekly gestational weight gain.<sup>2</sup> There were no other differences identified in maternal or infant health outcomes.<sup>2</sup> We now report the follow-up of children born to women who participated in the GRoW randomized trial at six months, 18 months, and three to five years of age.

## 2 | METHODS

We have previously reported the methods and clinical outcomes of the GRoW Randomized Trial<sup>2,6</sup> (ACTRN12612001277831). Briefly, participants with a singleton pregnancy, BMI of 25 kg/m<sup>2</sup> or more, between 10 and 20 weeks gestation, were randomly allocated to daily metformin or placebo. Metformin was commenced at 500 mg and increased to 2000 mg over four weeks if tolerated. Women in the Placebo group were instructed to commence taking a single tablet, identical in taste and appearance to the metformin and increase to four tablets if tolerated. All women participating in the trial received a comprehensive dietary and lifestyle intervention as we have described previously. Approval to conduct these follow-up assessments at six months, 18 months, and three to five years of age was provided by the Human Research Ethics Committee of the Women's and Children's Health Network. GRoW participants provided informed written consent for their child's participation at each follow-up assessment. Assessments were conducted by a trained research assistant who remained blinded to the original treatment group allocation of the woman.

### 2.1 | Primary and secondary outcomes

The primary outcome for each follow-up time point was a child's BMI z-score > 85th percentile for age and sex.

A range of secondary outcomes were obtained and included:

#### 1. Infant and child Anthropometric Measurements:

We have established and validated methods of conducting anthropometric measurements in infants at six and 18 months of age, and children three to five years of age, as we have reported previously.<sup>7-9</sup> Information obtained included the infant's/child's

length/height, weight, weight-for-length, and anthropometric measurements (arm, thigh, waist and hip circumferences; biceps, triceps, sub-scapular, abdominal, supra-iliac and thigh skin-fold thickness).

Trained research assistants used Harpenden skin-fold callipers to obtain skinfold thickness measurements, and received ongoing standardized training, again as we have reported previously.<sup>10</sup>

Weight, length, BMI, weight-for-length, and head circumference measures were converted to z-scores for age and gender, using WHO standards.<sup>11,12</sup>

#### 2. Infant Neurodevelopment:

The infant's or child's primary caregiver was asked to complete a structured age-appropriate Ages and Stages Questionnaire (ASQ),<sup>13</sup> reporting five domains of development (communication, gross motor, fine motor, problem-solving, and personal-social skills), with possible responses including Yes, Sometimes, or No. A score in any one domain more than two SD below the mean was considered indicative of the need for further assessment and when identified, the primary caregiver was advised to seek additional medical advice. The ASQ has been validated against the Bayley Scales,<sup>14</sup> and in a paediatric population.<sup>15</sup>

#### 3. Infant feeding, child dietary intake and behaviour:

Six months: (breastfeeding, formula, or a combination of the two), as assessed by a questionnaire completed by the infant's primary caregiver.

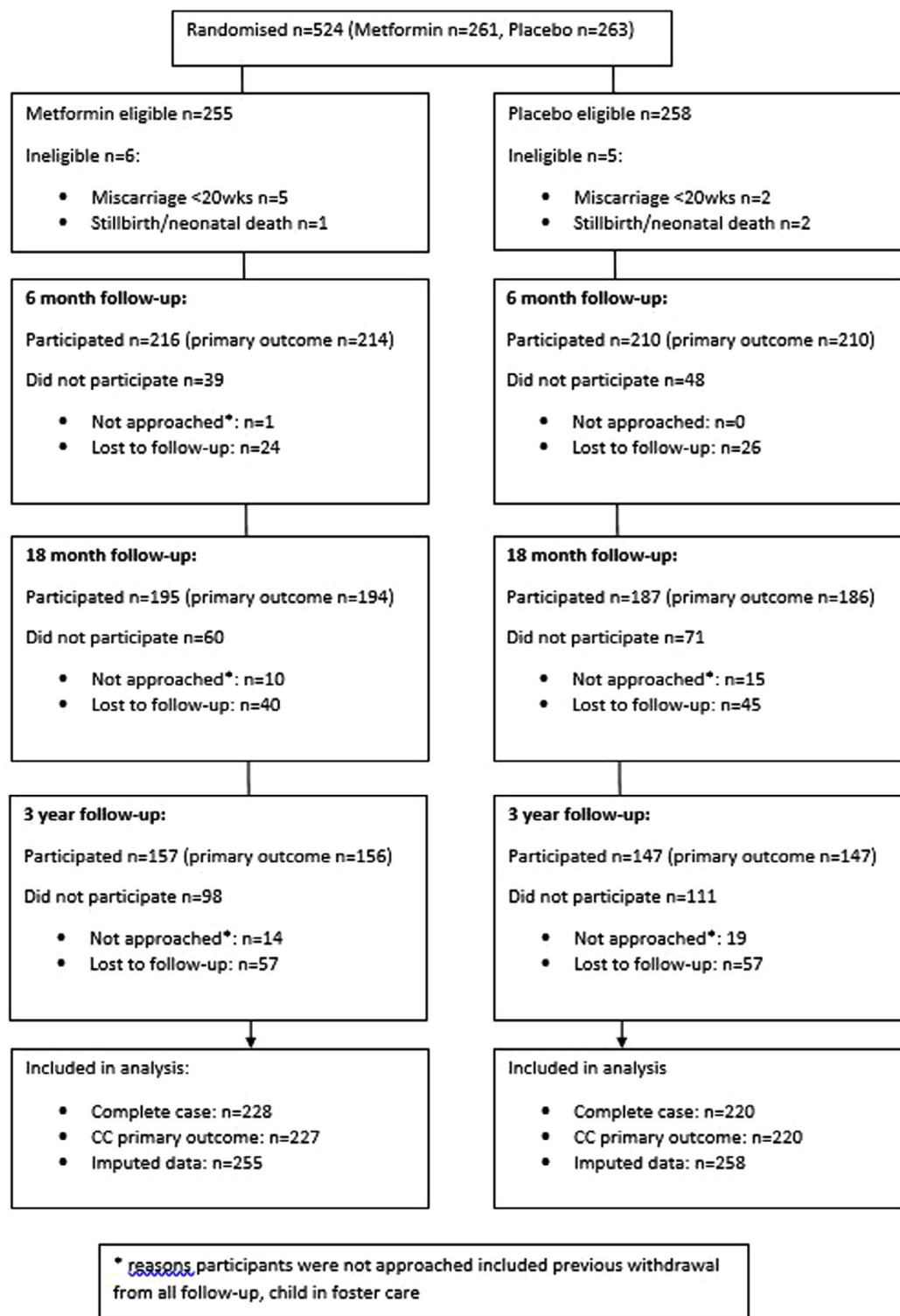
18 months based on Growing Up in Australia: the Longitudinal Study of Australian Children<sup>16</sup> and three to five years: Child dietary intake, physical activity and sedentary behaviour, as in our previous studies,<sup>7,8</sup> and included duration of breast or formula feeding; introduction of solid foods; the number of servings of fruits, vegetables, and milk consumed daily; the consumption of red meat and processed meats per week; and consumption of non-core foods, including salty snacks, fried potatoes, takeaway foods, soft drinks and other "extra" foods.<sup>16</sup> Caregivers were asked to estimate the hours per week spent playing outdoors, screen time and other sedentary behaviours, duration of overnight sleeping, and daytime sleeping.<sup>16</sup>

Family food behaviours included whether family meals were eaten together, preparation of different meals for children, use of food to encourage behaviours, and use of a bottle at bedtime.<sup>16</sup>

Three to five years: Caregivers were asked to complete the Child Eating Behaviour Questionnaire (CEBQ) to assess their child's enjoyment of food, emotional overeating, emotional undereating, satiety responsiveness, slowness in eating, desire to drink, food fussiness and food responsiveness.<sup>17</sup>

### 2.2 | Sample size

The sample size for the follow-up assessments, done at three-time points was fixed by the number of eligible women and infant pairs from the original GRoW trial, which was not designed or powered to



**FIGURE 1** Participant flow at follow-up assessments

detect differences in offspring outcomes. In the original GROW trial, 524 women were randomized (261 metformin; 263 placebos) and 514 women-infant pairs were included in the analysis (nine women experienced miscarriage or stillbirth, and one woman withdrew from the trial). One mother-infant pair included in the original analysis was not eligible for follow-up due to neonatal death. This resulted in

513 mother-infant pairs (255 metformin; 258 placebos) eligible for follow-up assessments.

The proportion of children three to five years old with BMI z-score > 85th percentile in the Lifestyle Advice group of the LIMIT study (women with BMI  $\geq 25.0$  kg/m<sup>2</sup> who received an antenatal diet and lifestyle intervention,<sup>7</sup> who were thus comparable with the

**TABLE 1** Baseline maternal characteristics include all eligible randomized women and children who participated in any of the follow-up studies

Characteristic	Metformin <i>n</i> = 228 <i>n</i> (%)	Placebo <i>n</i> = 220 <i>n</i> (%)	Overall <i>n</i> = 448 <i>n</i> (%)
Maternal age years at trial entry <sup>a</sup>	30.02 (5.51)	30.21 (5.44)	30.12 (5.47)
<i>Study centre</i>			
WCH	98 (42.98)	93 (42.27)	191 (42.63)
LMH	105 (46.05)	107 (48.64)	212 (47.32)
FMC	25 (10.96)	20 (9.09)	45 (10.04)
Primiparous at trial entry	78 (34.21)	81 (36.82)	159 (35.49)
BMI (kg/m <sup>2</sup> ) at trial entry <sup>b</sup>	32.60 (28.68, 37.58)	32.30 (29.17, 36.80)	32.40 (28.90, 37.30)
<i>BMI category</i>			
25.0–29.9	74 (32.46)	67 (30.45)	141 (31.47)
30.0–34.9	68 (29.82)	75 (34.09)	143 (31.92)
35.0–39.9	50 (21.93)	41 (18.64)	91 (20.31)
40.0+	36 (15.79)	37 (16.82)	73 (16.29)
Weight (kg) at trial entry <sup>a</sup>	92.67 (19.54)	91.98 (19.64)	92.33 (19.57)
Height (cm) at trial entry <sup>a</sup>	165.16 (6.86)	164.85 (6.74)	165.01 (6.79)
<i>Smoking</i>			
No	209 (91.67)	186 (84.55)	395 (88.17)
Yes	18 (7.89)	30 (13.64)	48 (10.71)
Missing	1 (0.44)	4 (1.82)	5 (1.12)
<i>Ethnicity</i>			
Caucasian	188 (82.46)	189 (85.91)	377 (84.15)
Asian	4 (1.75)	6 (2.73)	10 (2.23)
Aboriginal/TSI	6 (2.63)	7 (3.18)	13 (2.90)
Indian/Pak/Sri Lankan	10 (4.39)	6 (2.73)	16 (3.57)
African	6 (2.63)	0 (0.00)	6 (1.34)
Unknown	4 (1.75)	4 (1.82)	8 (1.79)
Other	10 (4.39)	8 (3.64)	18 (4.02)
<i>IRSD<sup>c</sup> Quintile</i>			
Q1 (Most Disadvantaged)	68 (29.82)	76 (34.55)	144 (32.14)
Q2	68 (29.82)	66 (30.00)	134 (29.91)
Q3	27 (11.84)	25 (11.36)	52 (11.61)
Q4	46 (20.18)	40 (18.18)	86 (19.20)
Q5 (Least Disadvantaged)	19 (8.33)	13 (5.91)	32 (7.14)
<i>Infant/child Sex</i>			
Male	120 (52.63)	131 (59.55)	251 (56.03)
Female	108 (47.37)	89 (40.45)	197 (43.97)
Age 6-month follow-up assessment <sup>b</sup>	7.13 (6.44, 7.86)	7.00 (6.34, 7.59)	7.06 (6.37, 7.72)
Age 18-month follow-up assessment <sup>b</sup>	19.18 (18.62, 19.92)	19.15 (18.54, 19.84)	19.16 (18.62, 19.87)
Age 3-year follow-up assessment <sup>b</sup>	36.85 (35.99, 38.98)	36.98 (35.93, 39.13)	36.88 (35.96, 39.02)

<sup>a</sup>Mean and standard deviation.<sup>b</sup>Median and interquartile range.<sup>c</sup>Socioeconomic index as measured by SEIFA Index of Relative Socio-economic Disadvantage (IRSD).

Placebo group of the GRow study) was 42%. With 513 children, there is 80% power (with a two-sided alpha of 0.05) to detect an absolute reduction of 17% (from 42% to 25%) in the proportion of children with BMI z-score > 85th percentile in the Metformin group compared with the Placebo group. For secondary continuous outcomes, the sample size of 513 children provides 80% power (with a two-sided alpha of 0.05) to detect differences in means between the Metformin and Placebo groups of approximately 0.24 standard deviation (SD).

## 2.3 | Statistical analysis

Data were analysed using intention to treat principles, according to the treatment group to which the woman was randomized in pregnancy. Missing data for anthropometric outcomes were imputed using the fully conditional specification (chained equations) method with data in wide form (one row per child, with repeated measures represented as separate variables). All imputation models included study

**TABLE 2** Child anthropometry outcomes at 6 months, 18 months and 3-year follow-up with time by intervention interaction term, unadjusted and adjusted treatment estimates

Outcome	Metformin	Placebo	Unadjusted estimate (95% CI)	Unadjusted p	Adjusted estimate (95% CI) <sup>c</sup>	Adjusted p
BMI z-score >85th Percentile <sup>a</sup>				0.634*		0.634*
6 Months	0.33 (0.27, 0.40)	0.28 (0.22, 0.34)	1.19 (0.90, 1.59)	0.223	1.19 (0.89, 1.58)	0.236
18 Months	0.56 (0.49, 0.63)	0.52 (0.45, 0.59)	1.08 (0.90, 1.31)	0.400	1.08 (0.89, 1.31)	0.426
3 Years	0.50 (0.43, 0.58)	0.49 (0.41, 0.57)	1.03 (0.83, 1.28)	0.795	1.03 (0.83, 1.27)	0.822
BMI z-score >90th Percentile <sup>a</sup>				0.160*		0.160*
6 Months	0.27 (0.21, 0.33)	0.20 (0.15, 0.26)	1.34 (0.95, 1.89)	0.093	1.34 (0.95, 1.89)	0.098
18 Months	0.44 (0.37, 0.51)	0.44 (0.37, 0.51)	0.99 (0.79, 1.24)	0.920	0.99 (0.78, 1.24)	0.907
3 Years	0.39 (0.31, 0.46)	0.40 (0.33, 0.48)	0.96 (0.73, 1.25)	0.740	0.95 (0.73, 1.25)	0.729
Weight z-score >85th Percentile <sup>a</sup>				0.398*		0.398*
6 Months	0.29 (0.23, 0.35)	0.24 (0.19, 0.30)	1.18 (0.86, 1.63)	0.301	1.18 (0.85, 1.62)	0.321
18 Months	0.46 (0.39, 0.53)	0.46 (0.39, 0.53)	1.00 (0.80, 1.24)	0.972	0.99 (0.80, 1.23)	0.933
3 Years	0.38 (0.31, 0.45)	0.41 (0.34, 0.49)	0.93 (0.72, 1.21)	0.592	0.93 (0.72, 1.20)	0.560
Weight z-score >90th Percentile <sup>a</sup>				0.182*		0.182*
6 Months	0.22 (0.17, 0.28)	0.16 (0.11, 0.20)	1.42 (0.95, 2.13)	0.085	1.43 (0.96, 2.15)	0.082
18 Months	0.34 (0.27, 0.41)	0.34 (0.27, 0.41)	1.00 (0.76, 1.32)	0.984	1.01 (0.76, 1.33)	0.950
3 Years	0.29 (0.23, 0.35)	0.29 (0.22, 0.36)	1.00 (0.72, 1.39)	0.991	1.01 (0.73, 1.39)	0.962
Weight (kg) <sup>b,d</sup>				0.084*		0.117*
6 Months	8.56 (8.40, 8.72)	8.31 (8.15, 8.48)	0.25 (0.02, 0.48)	0.033	0.22 (-0.00, 0.44)	0.051
18 Months	12.25 (12.06, 12.44)	12.21 (11.98, 12.44)	0.04 (-0.26, 0.33)	0.807	0.06 (-0.23, 0.35)	0.672
3 Years	16.10 (15.75, 16.45)	16.36 (15.96, 16.76)	-0.26 (-0.78, 0.27)	0.337	-0.24 (-0.74, 0.26)	0.345
Length (cm) <sup>b,d</sup>				0.667*		0.888*
6 Months	69.05 (68.62, 69.49)	68.45 (68.02, 68.89)	0.60 (-0.01, 1.21)	0.053	0.53 (-0.00, 1.06)	0.052
18 Months	83.72 (83.24, 84.20)	83.40 (82.85, 83.95)	0.32 (-0.40, 1.05)	0.385	0.42 (-0.25, 1.10)	0.220
3 Years	97.42 (96.72, 98.11)	97.13 (96.41, 97.84)	0.29 (-0.67, 1.25)	0.554	0.36 (-0.49, 1.20)	0.411
Head Circumference (cm) <sup>b,d</sup>				0.418*		0.476*
6 Months	44.32 (44.11, 44.53)	44.12 (43.90, 44.33)	0.20 (-0.09, 0.50)	0.175	0.28 (0.02, 0.55)	0.037
18 Months	48.20 (47.98, 48.41)	48.12 (47.88, 48.36)	0.07 (-0.25, 0.40)	0.649	0.18 (-0.12, 0.48)	0.245
3 Years	50.10 (49.85, 50.35)	50.11 (49.84, 50.38)	-0.01 (-0.37, 0.35)	0.965	0.09 (-0.26, 0.44)	0.618
Abdomen Circumference (cm) <sup>b,d</sup>				0.053*		0.066*
6 Months	46.71 (46.25, 47.17)	46.06 (45.53, 46.58)	0.65 (-0.04, 1.34)	0.064	0.61 (-0.07, 1.30)	0.079
18 Months	49.51 (49.01, 50.00)	49.65 (49.09, 50.21)	-0.14 (-0.88, 0.60)	0.708	-0.12 (-0.85, 0.61)	0.746
3 Years	52.00 (51.38, 52.62)	52.52 (51.77, 53.26)	-0.51 (-1.50, 0.47)	0.306	-0.51 (-1.48, 0.46)	0.306
Chest Circumference (cm) <sup>b,d</sup>				0.143*		0.180*
6 Months	45.62 (45.30, 45.94)	45.26 (44.88, 45.65)	0.35 (-0.14, 0.85)	0.163	0.38 (-0.11, 0.86)	0.132
18 Months	50.01 (49.66, 50.37)	50.06 (49.65, 50.47)	-0.04 (-0.59, 0.50)	0.875	0.03 (-0.51, 0.57)	0.908
3 Years	53.01 (52.53, 53.48)	53.33 (52.79, 53.86)	-0.32 (-1.03, 0.39)	0.373	-0.26 (-0.93, 0.42)	0.453
Arm Circumference (cm) <sup>b,d</sup>				0.012*		0.013*
6 Months	15.41 (15.24, 15.59)	15.04 (14.85, 15.24)	0.37 (0.11, 0.63)	0.006	0.37 (0.11, 0.63)	0.005
18 Months	16.45 (16.28, 16.63)	16.33 (16.13, 16.54)	0.12 (-0.15, 0.39)	0.380	0.14 (-0.13, 0.41)	0.294
3 Years	17.10 (16.89, 17.31)	17.28 (17.00, 17.56)	-0.18 (-0.53, 0.17)	0.308	-0.16 (-0.50, 0.18)	0.346

(Continues)

TABLE 2 (Continued)

Outcome	Metformin	Placebo	Unadjusted estimate (95% CI)	Unadjusted p	Adjusted estimate (95% CI) <sup>c</sup>	Adjusted p
Biceps Skin Fold (mm) <sup>b,d</sup>				0.362*		0.368*
6 Months	7.03 (6.75, 7.32)	7.05 (6.76, 7.33)	-0.01 (-0.42, 0.39)	0.949	-0.01 (-0.42, 0.39)	0.951
18 Months	6.65 (6.39, 6.91)	6.80 (6.51, 7.08)	-0.14 (-0.51, 0.23)	0.445	-0.14 (-0.51, 0.24)	0.470
3 Years	6.95 (6.55, 7.35)	7.42 (7.00, 7.84)	-0.47 (-1.04, 0.09)	0.100	-0.47 (-1.04, 0.10)	0.107
Triceps Skin Fold (mm) <sup>b,d</sup>				0.178*		0.177*
6 Months	11.82 (11.43, 12.20)	11.43 (11.05, 11.82)	0.38 (-0.15, 0.91)	0.161	0.34 (-0.20, 0.87)	0.218
18 Months	11.97 (11.49, 12.45)	12.07 (11.66, 12.48)	-0.09 (-0.73, 0.54)	0.771	-0.14 (-0.77, 0.49)	0.662
3 Years	11.61 (11.08, 12.15)	11.99 (11.39, 12.59)	-0.38 (-1.18, 0.43)	0.357	-0.42 (-1.23, 0.39)	0.304
Subscap Skin Fold (mm) <sup>b,d</sup>				0.576*		0.573*
6 Months	7.45 (7.22, 7.69)	7.42 (7.15, 7.69)	0.03 (-0.33, 0.39)	0.853	-0.00 (-0.37, 0.37)	0.992
18 Months	7.03 (6.74, 7.32)	7.03 (6.71, 7.36)	-0.01 (-0.45, 0.44)	0.978	-0.04 (-0.49, 0.40)	0.846
3 Years	6.81 (6.47, 7.15)	7.10 (6.58, 7.63)	-0.29 (-0.94, 0.35)	0.371	-0.33 (-0.97, 0.31)	0.307
Supra Skin Fold (mm) <sup>b,d</sup>				0.486*		0.513*
6 Months	8.29 (7.95, 8.64)	7.90 (7.50, 8.29)	0.40 (-0.14, 0.93)	0.148	0.31 (-0.23, 0.85)	0.254
18 Months	7.56 (7.16, 7.95)	7.53 (7.12, 7.93)	0.03 (-0.53, 0.59)	0.916	-0.04 (-0.60, 0.53)	0.896
3 Years	8.22 (7.53, 8.91)	8.29 (7.51, 9.08)	-0.07 (-1.14, 1.00)	0.892	-0.15 (-1.21, 0.91)	0.787
Abdomen Skin Fold (mm) <sup>b,d</sup>				0.133*		0.141*
6 Months	9.12 (8.77, 9.46)	8.87 (8.52, 9.21)	0.25 (-0.24, 0.74)	0.323	0.15 (-0.34, 0.65)	0.544
18 Months	8.23 (7.83, 8.63)	8.38 (7.95, 8.80)	-0.15 (-0.72, 0.42)	0.600	-0.23 (-0.81, 0.34)	0.426
3 Years	8.81 (8.30, 9.32)	9.36 (8.73, 9.99)	-0.55 (-1.37, 0.27)	0.191	-0.63 (-1.45, 0.18)	0.129
Thigh Skin Fold (mm) <sup>b,d</sup>				0.508*		0.497*
6 Months	19.79 (19.27, 20.30)	19.19 (18.64, 19.73)	0.60 (-0.15, 1.35)	0.118	0.52 (-0.22, 1.27)	0.170
18 Months	16.34 (15.77, 16.90)	16.05 (15.46, 16.65)	0.28 (-0.54, 1.10)	0.501	0.19 (-0.63, 1.02)	0.643
3 Years	15.63 (14.76, 16.49)	15.78 (14.85, 16.71)	-0.15 (-1.42, 1.12)	0.815	-0.24 (-1.50, 1.03)	0.714
BMI (kg/m <sup>2</sup> ) <sup>b,d</sup>				0.040*		0.041*
6 Months	17.92 (17.67, 18.17)	17.69 (17.45, 17.94)	0.23 (-0.12, 0.58)	0.200	0.23 (-0.12, 0.58)	0.200
18 Months	17.46 (17.25, 17.67)	17.52 (17.24, 17.79)	-0.05 (-0.39, 0.28)	0.754	-0.05 (-0.39, 0.29)	0.770
3 Years	16.93 (16.70, 17.16)	17.23 (16.91, 17.55)	-0.30 (-0.69, 0.09)	0.128	-0.30 (-0.69, 0.09)	0.134
Weight for Length ratio <sup>b,d</sup>				0.041*		0.047*
6 Months	0.12 (0.12, 0.13)	0.12 (0.12, 0.12)	0.00 (-0.00, 0.01)	0.054	0.00 (-0.00, 0.01)	0.061
18 Months	0.15 (0.14, 0.15)	0.15 (0.14, 0.15)	0.00 (-0.00, 0.00)	0.914	0.00 (-0.00, 0.00)	0.809
3 Years	0.16 (0.16, 0.17)	0.17 (0.16, 0.17)	-0.00 (-0.01, 0.00)	0.254	-0.00 (-0.01, 0.00)	0.260
Sum of Skin Fold Thickness Measures (mm) <sup>b,d</sup>				0.263*		0.264*
6 Months	63.38 (61.62, 65.13)	61.78 (59.98, 63.59)	1.59 (-0.95, 4.14)	0.221	1.28 (-1.30, 3.85)	0.331
18 Months	57.74 (55.73, 59.75)	57.73 (55.75, 59.70)	0.02 (-2.79, 2.82)	0.992	-0.29 (-3.14, 2.57)	0.844
3 Years	58.02 (54.87, 61.17)	59.98 (56.58, 63.37)	-1.95 (-6.26, 2.35)	0.373	-2.26 (-6.56, 2.04)	0.303
Fat Free Mass (kg) <sup>b,d</sup>				0.120*		0.166*
6 Months	6.06 (5.90, 6.23)	6.02 (5.84, 6.20)	0.04 (-0.21, 0.29)	0.746	0.06 (-0.18, 0.30)	0.618
18 Months	9.04 (8.74, 9.34)	9.17 (8.88, 9.46)	-0.13 (-0.54, 0.28)	0.535	-0.06 (-0.45, 0.34)	0.776
3 Years	11.82 (11.41, 12.23)	12.38 (11.94, 12.82)	-0.56 (-1.16, 0.03)	0.063	-0.50 (-1.07, 0.07)	0.086
Fat Mass (kg) <sup>b,d</sup>				0.774*		0.756*
6 Months	2.54 (2.37, 2.70)	2.36 (2.18, 2.54)	0.18 (-0.06, 0.42)	0.149	0.13 (-0.12, 0.37)	0.317

TABLE 2 (Continued)

Outcome	Metformin	Placebo	Unadjusted estimate (95% CI)	Unadjusted <i>p</i>	Adjusted estimate (95% CI) <sup>c</sup>	Adjusted <i>p</i>
18 Months	3.22 (2.98, 3.46)	2.91 (2.62, 3.20)	0.31 (−0.04, 0.65)	0.080	0.26 (−0.08, 0.61)	0.137
3 Years	4.26 (3.96, 4.56)	4.12 (3.71, 4.52)	0.14 (−0.36, 0.64)	0.582	0.10 (−0.41, 0.60)	0.706
Percentage Fat Mass <sup>b,d</sup>				0.813*		0.825*
6 Months	29.46 (27.95, 30.97)	28.03 (26.38, 29.68)	1.43 (−0.78, 3.64)	0.205	1.10 (−1.10, 3.30)	0.327
18 Months	26.34 (24.62, 28.06)	23.88 (21.92, 25.85)	2.46 (−0.13, 5.04)	0.063	2.08 (−0.48, 4.64)	0.111
3 Years	26.35 (24.79, 27.90)	24.72 (23.17, 26.28)	1.63 (−0.41, 3.67)	0.118	1.26 (−0.79, 3.31)	0.230
Length z-score <sup>b</sup>				0.413*		0.410*
6 Months	0.18 (0.03, 0.33)	−0.02 (−0.19, 0.16)	0.20 (−0.03, 0.43)	0.094	0.18 (−0.05, 0.42)	0.127
18 Months	0.26 (0.11, 0.41)	0.14 (−0.04, 0.33)	0.12 (−0.12, 0.36)	0.326	0.10 (−0.14, 0.34)	0.398
3 Years	0.10 (−0.05, 0.26)	0.05 (−0.11, 0.21)	0.05 (−0.17, 0.28)	0.647	0.04 (−0.19, 0.26)	0.751
Weight z-score <sup>b</sup>				0.003*		0.004*
6 Months	0.46 (0.33, 0.60)	0.19 (0.03, 0.36)	0.27 (0.06, 0.48)	0.012	0.25 (0.04, 0.46)	0.021
18 Months	0.93 (0.81, 1.06)	0.84 (0.68, 1.00)	0.09 (−0.10, 0.29)	0.348	0.08 (−0.12, 0.28)	0.444
3 Years	0.75 (0.61, 0.89)	0.83 (0.66, 1.01)	−0.08 (−0.31, 0.14)	0.462	−0.10 (−0.32, 0.12)	0.371
Weight for Length z-score <sup>b</sup>				0.022*		0.023*
6 Months	0.58 (0.42, 0.74)	0.39 (0.22, 0.55)	0.19 (−0.04, 0.42)	0.098	0.17 (−0.06, 0.40)	0.144
18 Months	1.06 (0.92, 1.19)	1.02 (0.85, 1.19)	0.05 (−0.16, 0.26)	0.654	0.03 (−0.18, 0.25)	0.770
3 Years	1.01 (0.84, 1.18)	1.20 (1.00, 1.41)	−0.19 (−0.46, 0.07)	0.156	−0.21 (−0.47, 0.06)	0.121
BMI z-score <sup>b</sup>				0.026*		0.028*
6 Months	0.49 (0.32, 0.65)	0.29 (0.13, 0.45)	0.20 (−0.03, 0.43)	0.096	0.18 (−0.05, 0.41)	0.125
18 Months	1.11 (0.97, 1.24)	1.08 (0.90, 1.26)	0.03 (−0.20, 0.26)	0.808	0.02 (−0.21, 0.25)	0.876
3 Years	1.02 (0.87, 1.17)	1.19 (0.99, 1.39)	−0.17 (−0.43, 0.08)	0.189	−0.18 (−0.44, 0.07)	0.160
Head Circumference z-score <sup>b</sup>				0.406*		0.395*
6 Months	0.63 (0.48, 0.77)	0.48 (0.33, 0.63)	0.15 (−0.06, 0.36)	0.158	0.16 (−0.05, 0.36)	0.140
18 Months	0.82 (0.67, 0.97)	0.73 (0.55, 0.90)	0.09 (−0.14, 0.32)	0.435	0.09 (−0.14, 0.32)	0.421
3 Years	0.64 (0.48, 0.80)	0.63 (0.45, 0.81)	0.01 (−0.23, 0.25)	0.936	0.01 (−0.23, 0.25)	0.918
Systolic Blood Pressure <sup>b,d,e</sup>	101.41 (99.76, 103.06)	100.98 (98.78, 103.18)	0.43 (−2.16, 3.02)	0.746	0.91 (−1.74, 3.56)	0.501
Diastolic Blood Pressure <sup>b,d,e</sup>	60.53 (58.86, 62.20)	61.45 (59.12, 63.77)	−0.91 (−3.84, 2.01)	0.540	−0.66 (−3.60, 2.27)	0.657

<sup>a</sup>Binary outcome; descriptives are estimated proportion and 95% CI (combined across all imputations), and estimates are relative risk (95% CI), Metformin vs. Placebo. Adjusted models used log Poisson regression with robust variance estimation as the log-binomial did not converge.

<sup>b</sup>Continuous outcomes; descriptives are estimated means and 95% CI (combined across all imputations), and estimates are differences in means (95% CI), Metformin–Placebo.

<sup>c</sup>All adjusted models included study centre, parity (0 vs. 1+), age, BMI, smoking status and quintile of relative socioeconomic disadvantage.

<sup>d</sup>Adjusted model for this outcome included child sex and actual age at follow-up in addition to other covariates.

<sup>e</sup>Measured at 3-year follow-up only; analysed using linear regression models.

\**p* value for test of treatment by time interaction.

centre, parity, maternal early pregnancy BMI (as a continuous measure), maternal age at trial entry, smoking status and quintile of relative socio-economic disadvantage. Imputation models for outcomes other than z-scores also included child sex and actual age at follow-up assessment. Birth measures were included where appropriate as auxiliary variables, as well as earlier and/or later measures of each outcome. Imputation was performed with Stata Version 17. Imputed data were analysed using appropriate methods, with effects estimated for each imputation and then combined using Rubin's Rules. Child diet, sleep and behaviour outcomes were analysed using available data

only, as there was no information available to enable sensible imputation for these outcomes.

Binary outcomes were analysed using log-binomial regression (or log Poisson regression with robust variance in the case of convergence problems), and continuous outcomes were analysed using linear regression. All models for outcomes measured at multiple time points included a time-by-treatment interaction term to test for differential treatment effects across time, and Generalized Estimating Equations were used to account for correlation due to repeated measures. Separate estimates for each time point were



**TABLE 3** Child neurodevelopment and 6 months, 18 months and 3 years of age

Outcome	Metformin	Placebo	Unadjusted estimate (95% CI)	Unadjusted <i>p</i>	Adjusted estimate (95% CI) <sup>c</sup>	Adjusted <i>p</i>
Ages & Stages in Communication <sup>b</sup>				0.635*		0.829*
6 Months	51.17 (10.36)	51.74 (8.87)	-0.64 (-2.54, 1.25)	0.507	-0.34 (-2.29, 1.60)	0.728
18 Months	41.87 (14.04)	41.79 (14.59)	-0.04 (-2.95, 2.87)	0.979	0.13 (-2.83, 3.08)	0.934
3 Years	50.17 (10.99)	51.28 (9.66)	-1.50 (-3.82, 0.82)	0.205	-0.85 (-3.24, 1.54)	0.488
Ages & Stages in Gross Motor <sup>b</sup>				0.875*		0.910*
6 Months	48.05 (11.56)	46.93 (11.60)	1.07 (-1.22, 3.36)	0.361	1.24 (-1.08, 3.56)	0.295
18 Months	57.64 (6.26)	56.09 (8.47)	1.66 (0.13, 3.19)	0.033	1.71 (0.17, 3.24)	0.029
3 Years	55.36 (7.17)	54.20 (9.48)	1.28 (-0.65, 3.21)	0.195	1.30 (-0.67, 3.27)	0.197
Ages & Stages in Fine Motor <sup>b</sup>				0.970*		0.951*
6 Months	52.41 (9.71)	51.54 (10.19)	0.80 (-1.17, 2.77)	0.427	0.76 (-1.26, 2.79)	0.459
18 Months	53.38 (7.45)	52.77 (9.14)	0.57 (-1.14, 2.29)	0.512	0.56 (-1.20, 2.33)	0.532
3 Years	42.81 (15.12)	42.59 (15.75)	0.39 (-3.10, 3.88)	0.827	0.16 (-3.42, 3.75)	0.929
Ages & Stages in Problem Solving <sup>b</sup>				0.464*		0.584*
6 Months	51.37 (9.74)	51.90 (10.23)	-0.54 (-2.51, 1.43)	0.593	-0.40 (-2.45, 1.64)	0.698
18 Months	46.51 (10.32)	45.75 (10.69)	0.71 (-1.44, 2.85)	0.519	0.82 (-1.40, 3.03)	0.471
3 Years	52.15 (10.11)	51.42 (10.43)	1.05 (-1.29, 3.40)	0.380	0.70 (-1.66, 3.07)	0.560
Ages & Stages in Personal Social <sup>b</sup>				0.280*		0.300*
6 Months	49.01 (11.07)	49.64 (11.10)	-0.58 (-2.78, 1.62)	0.605	-0.54 (-2.75, 1.68)	0.636
18 Months	50.00 (8.44)	48.66 (9.84)	1.33 (-0.54, 3.20)	0.162	1.44 (-0.51, 3.38)	0.148
3 Years	51.69 (9.02)	50.62 (9.60)	1.26 (-0.86, 3.38)	0.245	1.07 (-1.11, 3.25)	0.338
Ages & Stages in Total Score <sup>b</sup>				0.564*		0.612*
6 Months	252.01 (38.12)	251.74 (39.60)	0.01 (-7.66, 7.67)	0.998	0.72 (-7.18, 8.62)	0.859
18 Months	249.40 (31.43)	245.06 (37.41)	4.22 (-2.73, 11.17)	0.234	4.65 (-2.68, 11.97)	0.214
3 Years	252.19 (40.47)	250.11 (42.53)	2.91 (-6.41, 12.24)	0.540	2.39 (-7.32, 12.09)	0.630
Ages & Stages >1 Score Below Cutoff <sup>a</sup>				0.591*		0.620*
6 Months	11/197 (5.58)	12/192 (6.25)	0.87 (0.40, 1.92)	0.738	0.78 (0.34, 1.76)	0.543
18 Months	4/182 (2.20)	9/179 (5.03)	0.48 (0.16, 1.45)	0.194	0.42 (0.14, 1.30)	0.134
3 Years	11/151 (7.28)	16/137 (11.68)	0.60 (0.28, 1.25)	0.170	0.56 (0.27, 1.16)	0.118

<sup>a</sup>Binary outcome; descriptives are number and percentage, and estimates are relative risk (95% CI), Metformin vs. Placebo.

<sup>b</sup>Continuous outcome; descriptives are mean and standard deviation, and estimates are difference in means (95% CI), Metformin-Placebo.

<sup>c</sup>All adjusted models included study centre, parity, maternal age, early pregnancy BMI, smoking status and quintile of relative socioeconomic disadvantages as covariates.

\**p* value for test of treatment by time interaction.

derived, regardless of the significance of the interaction term. Estimates for binary outcomes are relative risks and 95% confidence intervals (Metformin vs. Placebo) at each time point, while estimates for continuous outcomes are differences in means (Metformin-Placebo) at each time point.

Both unadjusted and adjusted analyses were performed. Adjusted models included study centre, parity, maternal early pregnancy BMI, age at trial entry, smoking status and quintile of a relative socioeconomic disadvantage as covariates. Child outcomes other than z-scores also included child sex and actual age at follow-up.

Prespecified sensitivity analyses were carried out to test the robustness of the results to violations of the assumptions used in the main imputation model. Firstly, a complete case analysis (using only available data) was performed. Secondly, the primary outcome was re-imputed under a range of Missing Not At Random (MNAR)

assumptions: that having a BMI z-score >85th percentile was (a) 1.5 times as likely, (b) 2 times as likely, (c) 0.66 times as likely, or (d) 0.5 times as likely as in the observed data, in one or both treatment groups. Secondly, the imputation of repeated-measures outcomes was re-performed using the 'FCS-jomo' (a Fully Conditional Specification implementation of the Joint Multivariate-Normal method for clustered data) method, which was specifically designed for longitudinal or clustered data.

### 3 | RESULTS

There were 513 eligible children contributing data to the analyses (Figure 1). In total, 426 children (Metformin group *n* = 216; Placebo group *n* = 210) were assessed at six months of age; 382 children



TABLE 4 Child diet and behaviour

Outcome	Metformin	Placebo	Unadjusted Estimate (95% CI)	Unadjusted p	Adjusted Estimate (95% CI) <sup>f</sup>	Adjusted p
Ever Breastfed <sup>a</sup>	176/195 (90.26)	176/190 (92.63)	0.97 (0.79, 1.20)	0.807	0.97 (0.78, 1.20)	0.782
Ever Given Infant Formula <sup>a</sup>	134/181 (74.03)	139/180 (77.22)	0.96 (0.76, 1.22)	0.728	0.95 (0.75, 1.21)	0.692
Breastfeeding Duration (mths) <sup>b</sup>	8.96 (8.52)	9.21 (8.35)	-0.25 (-2.02, 1.53)	0.785	-0.15 (-1.93, 1.63)	0.869
Serves Fruit/Day <sup>c,d</sup>				0.781		0.628
18 Months	N = 180	N = 179				
Does Not Eat	2 (1.11)	0 (0.00)	1.15 (0.71, 1.86)	0.574	1.05 (0.75, 1.72)	0.842
< 1/day	7 (3.89)	12 (6.70)				
1/day	32 (17.78)	33 (18.44)				
2+/day	139 (77.22)	134 (74.86)				
3 Years	N = 146	N = 137				
Does Not Eat	0 (0.00)	3 (2.19)	1.27 (0.77, 2.10)	0.357	1.25 (0.75, 2.10)	0.392
< 1/day	10 (6.85)	9 (6.57)				
1/day	30 (20.55)	32 (23.36)				
2+/day	106 (72.60)	93 (67.88)				
Serves Vegetables/Day <sup>c,d</sup>				0.757		0.920
18 Months	N = 180	N = 179				
Does Not Eat	1 (0.56)	3 (1.68)	0.87 (0.58, 1.29)	0.482	0.83 (0.55, 1.25)	0.369
< 1/day	18 (10.00)	15 (8.38)				
1/day	63 (35.00)	56 (31.28)				
2+/day	98 (54.44)	105 (58.66)				
3 Years	N = 146	N = 137				
Does Not Eat	6 (4.11)	11 (8.03)	0.95 (0.61, 1.47)	0.820	0.85 (0.55, 1.33)	0.484
< 1/day	27 (18.49)	18 (13.14)				
1/day	56 (38.36)	52 (37.96)				
2+/day	57 (39.04)	56 (40.88)				
Times/Week Extra Foods <sup>b,d</sup>				0.992*		0.986*
18mth	6.70 (7.48)	6.76 (6.58)	-0.06 (-1.51, 1.39)	0.939	0.46 (-0.98, 1.91)	0.529
3 yr	11.83 (8.68)	11.87 (7.79)	-0.05 (-1.96, 1.87)	0.962	0.45 (-1.49, 2.38)	0.652
Hours/Week Outdoors <sup>b,d</sup>				0.437*		0.372*
18mth	5.13 (3.43)	4.71 (2.78)	0.42 (-0.23, 1.06)	0.204	0.55 (-0.13, 1.23)	0.114
3 yr	10.15 (7.51)	10.44 (8.32)	-0.30 (-2.13, 1.54)	0.753	-0.28 (-2.19, 1.62)	0.771
Hours/Week Screen Time <sup>b,d</sup>				0.164*		0.170*
18mth	0.50 (0.62)	0.50 (0.77)	-0.00 (-0.15, 0.15)	0.982	-0.02 (-0.29, 0.25)	0.901
3 yr	9.84 (7.85)	8.72 (5.65)	1.12 (-0.45, 2.68)	0.162	1.10 (-0.47, 2.67)	0.168
Total Energy (kJ) <sup>b,d,e</sup>	4277.57 (1458.78)	4351.41 (1484.86)	-73.85 (-418.38, 270.68)	0.673	11.10 (-346.78, 368.98)	0.951
Total Fat (g) <sup>b,d,e</sup>	35.27 (11.95)	36.98 (14.25)	-1.71 (-4.78, 1.36)	0.274	-0.96 (-4.13, 2.20)	0.548
Fat as % Total Energy <sup>b,d,e</sup>	31.16 (4.42)	31.75 (3.92)	-0.58 (-1.56, 0.40)	0.243	-0.52 (-1.53, 0.50)	0.314
Saturated Fat (g) <sup>b,d,e</sup>	15.48 (5.65)	16.16 (6.97)	-0.68 (-2.16, 0.80)	0.369	-0.22 (-1.75, 1.31)	0.776
Fibre (g) <sup>b,d,e</sup>	15.72 (6.87)	15.49 (5.61)	0.23 (-1.24, 1.71)	0.755	0.20 (-1.34, 1.74)	0.799
Protein (g) <sup>b,d,e</sup>	40.25 (13.70)	41.80 (15.41)	-1.54 (-4.95, 1.87)	0.374	-1.05 (-4.54, 2.44)	0.554
Glycaemic Index <sup>b,d,e</sup>	49.52 (3.91)	49.19 (4.00)	0.33 (-0.59, 1.26)	0.482	0.32 (-0.63, 1.27)	0.506

<sup>a</sup>Binary outcome; descriptives are number and percentage, and estimates are relative risk (95% CI), Metformin vs. Placebo.

<sup>b</sup>Continuous outcome; descriptives are mean and standard deviation, and estimates are difference in means (95% CI), Metformin-Placebo.

<sup>c</sup>Ordinal outcome; descriptives are numbers and percentages in each category. Estimates are Odds Ratios (95% CI) from an ordinal logistic regression model and represent the relative odds of being in a lower-ranked category vs. all higher-ranked categories, in Metformin vs. Placebo, i.e., how much more likely children from the Metformin group are of being in a higher-ranked category (lower consumption) compared to children from the Placebo group.

<sup>d</sup>Adjusted model for this outcome included child sex and actual age at follow-up in addition to other covariates.

<sup>e</sup>Measured at 3-year follow-up only; analysed using linear regression models.

<sup>f</sup>All adjusted models included study centre, parity, maternal age, early pregnancy BMI, smoking status and quintile of relative socioeconomic disadvantages as covariates.

\*p value for test of treatment by time interaction.

(Metformin group  $n = 195$ ; Placebo group  $n = 187$ ) at 18 months of age; and 304 children (Metformin group  $n = 157$ ; Placebo group  $n = 147$ ) at three to five years of age. This represents 83%, 74% and 59% of eligible children respectively. Baseline characteristics at the trial entry of women with infants and children included in this analysis were similar between treatment groups and similar to all women randomized into the study (Table 1).

Child BMI z-score > 85th centile was similar for children born to women who received metformin compared with women who received placebo at all of the time points measured, and the effect of treatment did not differ over time (Table 2). In both groups, the proportion of children with BMI z-score > 85th centile increased over time from approximately one-third of infants at six months of age, to at least half of children at 18 months, and three to five years of age.

There was a trend within the secondary anthropometric outcomes for six-month-old infants suggesting infants of women who received metformin were slightly heavier, but this was not maintained at subsequent time points assessed (Table 2). Weight, length and BMI z-scores were similar between groups and almost all greater than zero, indicating the infants of women with overweight and obesity are larger than the reference populations<sup>11</sup> (Table 2).

All other anthropometric measurements were similar between the two treatment groups at all-time points with the exception of the head and arm circumference of infants at six months of age, which were significantly larger in the infants of women who received metformin. These differences did not persist at 18 months, or three to five years of age (Table 2). Blood pressure, measured at the three to five year follow-up assessment only, was similar between the two treatment groups (Table 2).

Parent completed ASQs at six months, 18 months and three to five years of age were similar between the Metformin and Placebo groups (Table 3), across all domains with the exception of gross motor function. Infants of women who received metformin had slightly higher scores at 18 months of age compared with infants

of women who received a placebo (Table 3). Again this difference was not evident either at six months or at three to five years of age and is likely a spurious result due to the large number of comparisons made.

Breastfeeding occurrence and duration was similar for infants and children of women who received metformin compared with placebo (Table 4). The number of servings of fruit, vegetables and discretionary foods consumed was similar between treatment groups at 18 months and three to five years of age, as was the intake of energy and macronutrients (Table 4). Time spent outdoors and screen time were similar for infants and children across the two groups, at both 18 months, and three to five years of age (Table 4).

Eating behaviour as measured by the parent who completed CEBQ at three to five years of age was similar across both treatment groups for all domains except slowness of eating, where children of women who received metformin were assessed as slower at eating compared with children who received placebo (Table 5). The significance of this is unclear.

Results of sensitivity analyses were generally consistent with those of the main analysis. The estimates of treatment group comparisons in the raw data analysis, and for the primary outcome in the analysis of MNAR imputed data were consistent with the main analysis in all scenarios. The results of analyses on data imputed using 'FCS-jomo' were likewise generally consistent with the results of the main imputation, but some of the statistically significant results for secondary outcomes at six months were not statistically significant in the FCS-jomo imputed data (specifically head circumference, weight z-score, and interaction  $p$  values).

## 4 | DISCUSSION

We have previously reported that metformin as an adjuvant therapy to a dietary and lifestyle intervention reduced weekly gestational

**TABLE 5** Child eating behaviour checklist

Outcome	Metformin	Placebo	Unadjusted Estimate (95% CI)	Unadjusted $p$	Adjusted Estimate (95% CI) <sup>d</sup>	Adjusted $p$
CEBQ: Enjoyment of Food <sup>a,b,c</sup>	3.59 (0.83)	3.59 (0.89)	-0.00 (-0.20, 0.20)	0.980	-0.06 (-0.27, 0.14)	0.546
CEBQ: Emotional Over-Eating <sup>a,b,c</sup>	1.65 (0.60)	1.66 (0.55)	-0.01 (-0.14, 0.13)	0.892	-0.03 (-0.17, 0.11)	0.678
CEBQ: Emotional Under-Eating <sup>a,b,c</sup>	2.97 (0.88)	2.91 (0.96)	0.06 (-0.16, 0.27)	0.595	0.11 (-0.11, 0.34)	0.313
CEBQ: Satiety Responsiveness <sup>a,b,c</sup>	3.14 (0.57)	3.04 (0.59)	0.10 (-0.04, 0.24)	0.146	0.14 (0.00, 0.28)	0.048
CEBQ: Slowness in Eating <sup>a,b,c</sup>	3.20 (0.67)	3.04 (0.70)	0.16 (-0.00, 0.32)	0.051	0.19 (0.02, 0.36)	0.025
CEBQ: Desire to Drink <sup>a,b,c</sup>	3.03 (1.05)	2.86 (1.07)	0.17 (-0.08, 0.42)	0.173	0.20 (-0.06, 0.45)	0.126
CEBQ: Food Fussiness <sup>a,b,c</sup>	3.08 (0.88)	3.11 (1.00)	-0.03 (-0.25, 0.19)	0.808	0.03 (-0.19, 0.25)	0.795
CEBQ: Food Responsiveness <sup>a,b,c</sup>	2.41 (0.81)	2.47 (0.81)	-0.06 (-0.25, 0.13)	0.552	-0.06 (-0.26, 0.13)	0.515

<sup>a</sup>Continuous outcome; descriptives are mean and standard deviation, and estimates are difference in means (95% CI), Metformin-Placebo.

<sup>b</sup>Adjusted model for this outcome included child sex and actual age at follow-up in addition to other covariates.

<sup>c</sup>Measured at 3-year follow-up only; analysed using linear regression models.

<sup>d</sup>All adjusted models included study centre, parity, maternal age, early pregnancy BMI, smoking status and quintile of relative socioeconomic disadvantages as covariates.

weight gain compared with a dietary and lifestyle intervention alone in pregnant women with overweight and obesity (GRoW).<sup>2</sup> This modest impact on gestational weight gain did not have an effect on the proportion of infants or children with BMI >85th centile when assessed at six months, 18 months, or three to five years of age. Furthermore, we demonstrated little evidence of an effect following metformin administration during pregnancy on secondary infant and child anthropometric measurements, neurodevelopment, dietary intake, physical activity or eating behaviours. Despite the lack of differences observed between treatment groups, this cohort of children remains at high risk of overweight and obesity, with approximately half of children assessed having BMI above the 85th centile for age and sex, a figure almost double that observed in the general Australian childhood population.<sup>18</sup>

We are aware of several randomized trials, which have investigated the effect of metformin on women with overweight or obesity during pregnancy.<sup>19–23</sup> To our knowledge, two of these trials have conducted and reported follow-up of child participants at approximately three to five years of age.<sup>4,5</sup> In both of these follow-up studies, only a small proportion of eligible children were assessed (151 of 393 (40%)<sup>4</sup> and 40 of 170 (24%)<sup>5</sup>). Three trials, not reporting follow-up, report different stages of recruitment to a single trial,<sup>21–23</sup> with uncertainty regarding adjustment for interim analyses.

Yang and colleagues evaluated a small subset of children (40 in total) from the EMPOWaR randomized trial at approximately five years of age.<sup>5</sup> There were no statistically significant differences identified between children who were exposed in-utero to metformin ( $n = 19$ ) and those who were not ( $n = 21$ ) with regards to anthropometric measures. Furthermore, there were no significant differences identified in measures of cardiovascular function including blood pressure, arterial pulse wave velocity and central haemodynamics.<sup>5</sup>

In contrast, Panagiotopoulou and colleagues report findings from the follow-up of 151 children at approximately four years of age, 77 of whom were exposed to metformin during in-utero development and 77 who were exposed to placebo.<sup>4</sup> While hip circumference measures were smaller in children exposed to metformin compared with those who were not, there were no other statistically significant differences identified across a range of anthropometric measures, raising the possibility of a chance finding. Children exposed to metformin also demonstrated small differences with lower central hemodynamic and cardiac diastolic indices compared with children exposed to placebo.<sup>4</sup> While statistically significant, these differences were of small magnitude and uncertain clinical significance.

Metformin has been used in pregnancy for women with polycystic ovary syndrome<sup>24</sup> and gestational diabetes,<sup>25</sup> with both trials reporting follow-up of children after birth.<sup>3,26–28</sup> Children born to women who participated in the PREGMET Study were followed up at six months, four years, and five to 10 years of age.<sup>26,27</sup> At all-time points assessed, children exposed in-utero to metformin had higher BMI z-scores compared with children born to women who received placebo.<sup>26,27</sup>

The MIG randomized trial-compared metformin with insulin for the treatment of women with gestational diabetes.<sup>25</sup> Assessments at

two years of age identified children exposed to metformin to have larger subscapular skinfold thickness and mid-upper arm circumference measures.<sup>28</sup> While the majority of anthropometric measures at seven to nine years of age were not different between the children born to women who received metformin and those who received insulin, children exposed to metformin demonstrated higher body weight and BMI, with a suggestion of increased adiposity measured by dual-energy x-ray absorptiometry.<sup>3</sup>

Despite differences in the identified follow-up studies with regard to the initial target populations and the pregnancy intervention provided, the magnitude of the effect of metformin on childhood anthropometric measures assessed at a variety of time points, appears modest in nature. Furthermore, where studies have reported statistically significant differences in childhood skinfold thickness and body circumference measures; these are inconsistent in time and specific site of measurement, raising the possibility of spurious findings of limited clinical significance.

In the recent past, there has been considerable research on pregnancy dietary and lifestyle interventions to ameliorate the impact of overweight, obesity and excess gestational weight gain on pregnancy, birth and long-term maternal and child outcomes.<sup>29</sup> Findings from the infant and child follow-up studies of these interventional studies have shown no effect on child adiposity outcomes between infants and children exposed to intervention in-utero and those who were not.<sup>7–9,30–32</sup> The findings of these studies and studies of metformin during pregnancy highlight the likelihood that pregnancy interventions do not reduce the risk of childhood obesity and that we should focus effort on interventions prior to conception.

There are a number of strengths to our study, which to date represents the largest, most extensive, and most complete follow-up assessment of children who were exposed to metformin in-utero, at three-time points in early childhood. Our assessments included 426 (83% of those eligible) infants or children at six months, 382 (74% of those eligible) at 18 months, and 304 (59% of those eligible) at three to five years of age.

Our trial methodology was robust, with accurate measurement of early pregnancy weight, height, and BMI; detailed maternal dietary and physical activity history; and consistent provision of the dietary and lifestyle intervention to all participants. Our follow-up methods have adhered to a research quality protocol, with a standardized assessment of anthropometric measures, and consistent evaluation of childhood diet, physical activity, sedentary behaviour and sleep patterns, all of which are well-recognized early life factors contributing to childhood overweight and obesity.<sup>33</sup>

Our study does have some limitations, including that the follow-up study has a sample size fixed by the initial randomized controlled trial, which was not designed or powered to detect differences in child BMI >85th percentile. In addition, there is potential selection bias. A smaller proportion of the total eligible randomized cohort at each time point was assessed and contributed data. However, baseline and clinical characteristics of women and children for whom data were available and who participated in the follow-up study were similar

between the two randomized treatment groups at each assessment point, and similar to the full randomized GRoW cohort.

We have undertaken robust statistical methods and imputation models at each of the assessment time point to address issues related to missing data, including analyses through multiple imputations for all children eligible for three to five year follow-up. The imputation models used were robust, and additionally incorporated data available from the six and 18-month childhood assessments. We conducted sensitivity analyses using data imputed under a range of MNAR scenarios, with our results consistent under a variety of plausible assumptions about the magnitude and direction of the difference between missing and observed data. On this basis, we consider our findings robust and valid and do not consider the risk of bias to be significant.

The retrospective collection of dietary intake and habits reliant on recall of women for their children has some limitations; however, there is no reason to expect that the ability to recall would differ for women by treatment group. Whilst we would caution against accepting these data as absolute, we are confident that the between-group comparisons are robust.

Our findings show no evidence of any beneficial effects of in-utero exposure to metformin among infants and children born to women with overweight or obesity, at any of the time points assessed at follow-up. While the intervention resulted in a modest reduction in weekly gestational weight gain for women who received metformin, there was no longer-term impact on child risk of obesity. However, this group of children remains at more than double the Australian risk of overweight and obesity in early childhood. Intervention during pregnancy may be too late to change the growth trajectory to improve child health and obesity risk, with future studies required to consider interventions to improve the overall health and wellbeing of women prior to pregnancy.

## AUTHOR CONTRIBUTIONS

Jodie M. Dodd conceptualized the study with input from Andrea R. Deussen and Jennie Louise. Jennie Louise performed the statistical analysis. All authors contributed to the interpretation of the results. Andrea R. Deussen wrote the first draft. All authors contributed to critical revisions, approve the final version of the manuscript and were responsible for the decision to submit it for publication. All authors had access to the underlying data. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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## CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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