Association of Long-term Child Growth and Developmental Outcomes With Metformin vs Insulin Treatment for Gestational Diabetes

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IMPORTANCE Metformin is an emerging option for treating gestational diabetes (GDM). However, because metformin crosses the placenta, patients and clinicians are concerned with its long-term effect on child health.

OBJECTIVE To estimate the association of treating GDM with metformin vs insulin with child growth and development.

DESIGN, SETTING, AND PARTICIPANTS Population-based cohort study of New Zealand women treated with metformin or insulin for GDM from 2005 to 2012 and their children. This study linked national health care data to create a cohort of mothers and their children, including data from maternity care, pharmaceutical dispensing, hospitalizations, demographic records, and the B4 School Check (B4SC) preschool health assessment. Women treated pharmacologically with metformin or insulin during pregnancy were included. We excluded pregnancies with evidence of diabetes and deliveries prior to 2013. Liveborn infants were linked to their B4SC results. Data were analyzed between January 2017 and May 2018.

EXPOSURES Pharmacologic treatment for GDM with metformin or insulin, measured using pharmaceutical claims data.

MAIN OUTCOMES AND MEASURES Child growth (weight and height) and Strengths and Difficulties Questionnaire (SDQ) scores for behavioral development. All outcomes were derived from the B4SC screening program. Linear and log-binomial regression with inverse probability of treatment weighting was used to estimate the association of child growth and psychosocial outcomes with metformin vs insulin treatment for GDM.

RESULTS In both treatment groups, the mean (SD) maternal age was 32 (5) years. A large proportion of mothers who were treated with insulin identified as New Zealand European (867 [44.9%]) while 576 mothers who were treated with metformin (28.9%) identified as New Zealand European. Approximately one-third of mothers who were treated with metformin (n = 639) identified as Asian. We identified 3928 pregnancies treated with metformin (n = 1996) or insulin (n = 1932). After adjustment, we observed no meaningful difference in weight for height *z* scores between children exposed to metformin compared with insulin (mean difference, −0.10; 95% CI, −0.20 to 0.01). Risk of being 85th percentile or greater for weight for height was similar between treatment groups (adjusted risk ratio, 0.92; 95% CI, 0.83-1.02). Mean SDQ scores were not meaningfully different between the treatment groups, Children of metformin-treated mothers were not significantly more likely to have parent-reported SDQ scores of 14 or more (adjusted risk ratio, 1.13; 95% CI, 0.88-1.46) than those of insulin-treated mothers.

CONCLUSIONS AND RELEVANCE Our study compares long-term outcomes among school-aged children following maternal use of metformin vs insulin treatment for GDM. Children of metformin-treated mothers were indistinguishable on growth and developmental assessments from those of insulin-treated mothers. These results will help inform future GDM treatment guidelines.

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Gestational diabetes mellitus (GDM) is a common pregnancy complication, characterized by relative insulin deficiency and impaired insulin action, leading to maternal hyperglycemia.[1,2] Worldwide, an estimated 1 in 7 births are affected by GDM.[1] While many women are able to achieve adequate glycemic control through lifestyle changes, some require pharmacologic treatment to manage this condition.

Oral hypoglycemic agents, such as metformin, have emerged as a promising option for managing GDM.[3] In randomized trials comparing maternal and infant outcomes, metformin has been shown to be an effective alternative to insulin, the historical standard treatment for GDM.[4-6] In the absence of long-term data on the safety of metformin use during pregnancy, concerns remain regarding potential development effects that may only be evident later in childhood.[7] Unlike insulin, metformin has been shown to cross the placenta,[8] causing concern that metformin may affect fetal development in ways that insulin would not. Inadequate control of GDM may also increase risk of childhood overweight/obesity and altered neurodevelopment following neonatal hypoglycemia in infancy.[9,10]

To date, most studies have examined long-term outcomes following metformin vs insulin treatment during pregnancy in offspring up to age 2 years, with a 2018 study comparing outcomes in children aged 7 and 9 years.[11-15] Although these studies have suggested no clinical differences in growth or neurodevelopment among offspring of women treated with metformin vs insulin for GDM, they were limited by small sample sizes and loss to follow-up from the original, randomized study population. Thus, patients and clinicians remain concerned about the long-term effects of metformin.

To address these limitations, we conducted a retrospective cohort study in a New Zealand population of treated women linked with their child's growth and developmental data at age 4 years, taken from a preschool readiness screening program provided as routine well-child care throughout New Zealand.

Key Points

Question How do long-term child growth and development outcomes differ following prenatal exposure to metformin vs insulin when used for the treatment of gestational diabetes?

Findings In this population-based cohort study, 3928 women treated with metformin or insulin for gestational diabetes in New Zealand were linked with their children's preschool health assessments. We did not observe significant differences in child weight, weight for height, or body mass index in children of insulin-treated vs metformin-treated mothers, nor did we observe differences in results from behavioral assessments.

Meaning Children of metformin-treated mothers were indistinguishable on growth and developmental assessments from those of insulin-treated mothers.

Methods

Study Population

This study was approved by the New Zealand Health and Disability Ethics Committee and by the University of North Carolina at Chapel Hill institutional review board. As this study was conducted using previously collected health care data, informed consent was not required. Because health services in New Zealand are funded by the government, eligible persons receive free or subsidized health services including pregnancy care and prescriptions. National collections of health information are linkable through the National Health Index.[16] Infants are registered with the National Health Index at birth. We identified a cohort of pregnancies with deliveries occurring between 2005 and 2012 using the National Maternity Collection (MAT), which provides information on primary maternity services from the first prenatal encounter through the postpartum period. Mothers and their children were linked via a unique pregnancy key. Gestational age in MAT was reported as either the duration of completed weeks between a woman's self-reported last menstrual period date and her delivery date or derived from clinical assessment. While MAT excludes pregnancies lasting fewer than 20 weeks' gestation or infants weighing less than 400 g, a small number of pregnancies with these characteristics were inadvertently included in MAT and subsequently excluded from our cohort. We excluded pregnancies if the mother was younger than 15 years or older than 45 years at delivery. Finally, we excluded pregnancies missing information on gestational age. Pharmaceutical claims data from the New Zealand Pharmaceutical Management Agency (PHARMAC) are reliably available in the Pharmaceutical Claims Data Mart from 2005 onward. To observe a 6-month history of prescription use, we restricted our cohort to pregnancies with an estimated start date of June 30, 2005, or later (**Figure**).

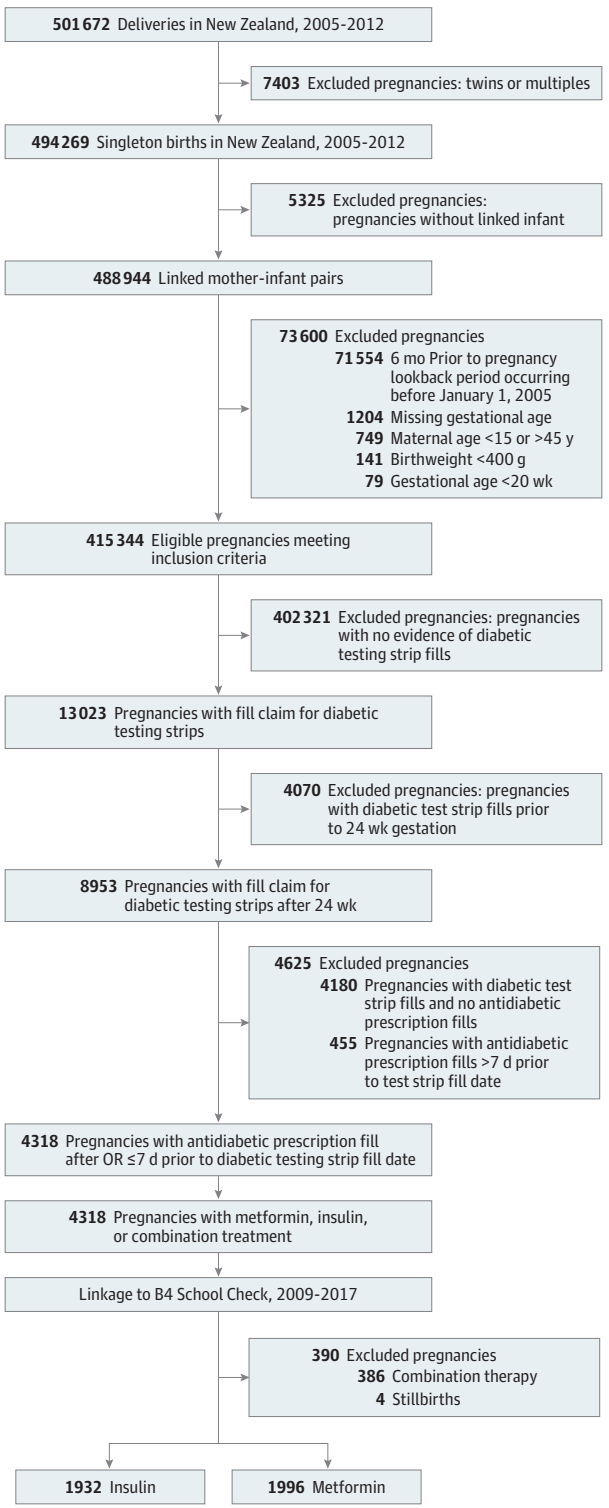
Women who receive a diagnosis of GDM in New Zealand are provided with a blood glucose meter for home-based glucose testing and given a prescription for test strips (Lesley MacLennan, Counties Manukau District Health Board, oral communication, March 21, 2017). Blood glucose test strips are subsidized, and claims are recorded in the Pharmaceutical Claims Data Mart. We considered a claim for blood glucose test strips to be evidence of a GDM diagnosis during pregnancy if the claim appeared after 24 weeks' gestation. If a test strip prescription was filled anytime between 6 months prepregnancy (3 months for closely spaced births) through 24 weeks' gestation, we considered this evidence of prior diabetes and excluded these pregnancies. We also excluded women with a claim for any antidiabetic prior to 24 weeks' gestation.

We examined health care history using data from hospitalizations, pharmaceutical claims, and maternity care from 6 months prior to the estimated start of pregnancy through start of the GDM screening and diagnosis window (24-28 weeks' gestation). Additional demographic characteristics were obtained through linkage to the NHI including region, ethnicity, and socioeconomic status via the New Zealand Deprivation Index. The New Zealand Deprivation Index is an index of social deprivation reported in deciles, where 1 represents the least and 10 represents the most deprived geographic areas of residence.[17]

Exposure Definition

After identifying pregnancies with GDM, we identified prescriptions filled after or just before (≤1 week) the first test strip

Figure. Details of Cohort Formation From Overall Population of New Zealand Pregnancies



claim. For women who received both metformin and insulin, we defined combination therapy as a dispensing for both medications within 7 days of the first claim for either. We restricted our study population to pregnancies initially treated with metformin or insulin monotherapy.

The B4 School Check (B4SC) is a universal health and development screening program offered to all children in New Zealand at age 4 years as routine well-child care prior to school entry at age 5 years.[18] This includes growth surveillance involving height and weight measurement and identification of behavioral problems using the Strengths and Difficulties Questionnaire (SDQ) for parents and teachers (SDQ-P and SDQ-T, respectively).[19,20] We linked children with B4SC results to mothers identified as initiating metformin or insulin treatment for GDM.

Growth Outcomes

We used height and weight values from the B4SC to calculate child body mass index (BMI; calculated as weight in kilograms divided by height in meters squared).[21] These values were used to estimate *z* scores and percentile-based outcomes for weight, height, weight for height (WFH), and BMI defined by the 2006 World Health Organization reference standards.[22] We used 85th and 97th percentiles to define overweight or obesity and extreme growth measurements respectively in children and created dichotomous outcomes for each. We also examined the proportion of children with weight, height, WFH, and BMI *z* scores of at least 1 or at least 2.

Strengths and Difficulties Questionnaire

The B4SC offers screening to identify children who may need help with learning and development before entering school using the SDQ,[20] which assesses the child's strengths in 5 subscales: prosocial behavior, hyperactivity, emotional symptoms, conduct, and peer problems.[20] Scores from these subscales are summed to produce a Difficulties Score ranging from 0 to 40, with higher scores indicating concern and possible need for referral.[19,21] The cutoff for a concerning score is typically 17 for SDQ-P and 16 for SDQ-T; however, a review of the SDQ in the New Zealand population found that lower cutoffs may be more appropriate (14 for SDQ-P and 11 for SDQ-T).[23,24] An additional prosocial behavior scale is scored so that an absence of prosocial behavior (eg, helping or sharing) receives a lower score.

Statistical Analysis

We identified potential confounders of the association between GDM treatment and child growth and development from relevant literature and with clinical insight. We included maternal age, race/ethnicity, socioeconomic status (New Zealand Deprivation Index), BMI, smoking status, history of GDM (treated and untreated), and timing of GDM diagnosis and treatment as potential confounders. Neonatal hypoglycemia and birthweight are independently associated with the outcomes examined in this study and likely causal intermediates.[10,25,26] We used maternity care and hospitalization data to describe these characteristics but did not adjust for them in our analyses.

Multiple imputation using chained equations was used to estimate missing covariate information.[27] We reassigned extreme BMI values (less than 14 and greater than 72) to missing. We used multiple imputation with 5 imputed data sets to estimate BMI for pregnancies with missing data, including reassigned extreme values. We similarly imputed values for

Table 1. Demographic and Clinical Characteristics of New Zealand Mothers Treated Pharmacologically for Gestational Diabetes With Metformin or Insulin, 2005-2012

Maternal Characteristic	No. (%) Metformin (n = 1996)	Insulin (n = 1932)
Age, mean (SD)	32.1 (5.5)	32.4 (5.6)
BMI, mean (SD)	29.6 (7.7)	29.5 (9.4)
Gestational week of diagnosis, mean (SD)	30.6 (2.9)	30.3 (2.8)
Gestational week of treatment, mean (SD)	32.0 (3.0)	31.8 (2.9)
Age categories, y		
15-20	37 (1.9)	42 (2.2)
21-25	209 (10.5)	195 (10.1)
26-30	536 (26.9)	441 (22.8)
31-35	633 (31.7)	638 (33.0)
36-40	463 (23.2)	499 (25.8)
41-45	118 (5.9)	117 (6.1)
Geographic region		
Northern	1331 (66.7)	548 (28.4)
Midland	139 (7.0)	456 (23.6)
Central	274 (13.7)	418 (21.6)
South Island	252 (12.6)	510 (26.4)
Maternal ethnicity (prioritized)[a]		
European	576 (28.9)	867 (44.9)
Māori	290 (14.5)	360 (18.7)
Pacific Peoples	435 (21.8)	243 (12.6)
Asian	639 (32.0)	408 (21.1)
Other	55 (2.8)	52 (2.7)
Maternal ethnicity (any, yes)[a,b]		
European	843 (42.2)	1143 (59.2)
Māori	290 (14.5)	360 (18.6)
Pacific Peoples	474 (23.8)	274 (14.2)
Asian	736 (36.9)	460 (23.8)
Other	75 (3.8)	62 (3.2)
New Zealand Deprivation Index Deciles		
1 (Least deprived)	89 (4.5)	129 (6.7)
2	111 (5.6)	132 (6.8)
3	148 (7.4)	133 (6.9)
4	136 (6.8)	166 (8.6)
5	154 (7.7)	168 (8.7)
6	195 (9.8)	188 (9.7)
7	224 (11.2)	239 (12.4)
8	207 (10.4)	271 (14.0)
9	362 (18.1)	293 (15.2)
10 (Most deprived)	370 (18.5)	213 (11.0)
Delivery year		
2006	20 (1.0)	174 (9.0)
2007	9 (0.5)	270 (14.0)
2008	143 (7.2)	287 (14.9)
2009	336 (16.8)	266 (13.8)
2010	412 (20.6)	249 (12.9)
2011	540 (27.1)	332 (17.2)
2012	536 (26.9)	354 (18.3)
New Zealand resident, yes[c]	1797 (90.5)	1794 (93.2)
Parity[d]		
0 (primipara)	627 (38.0)	645 (38.3)
1	536 (32.5)	545 (32.3)
2	256 (15.5)	273 (16.2)
3 or more	231 (14.0)	222 (13.2)
Trimester of maternity care registration[e]		
First	1056 (58.8)	980 (54.0)
Second	583 (32.5)	710 (39.1)
Third	157 (8.7)	125 (6.9)
Smoker at first visit, yes[f]	114 (6.6)	151 (10.9)
BMI categories[g]		
Underweight (<18.5)	16 (0.8)	25 (1.3)
Normal (18.5-24.9)	442 (22.1)	376 (19.5)
Overweight (25-29.9)	431 (21.6)	340 (17.6)
Obese (≥30)	640 (32.1)	553 (28.6)
Prior GDM, yes	112 (5.6)	135 (7.0)
Prior treated GDM, yes	56 (2.8)	84 (4.4)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); GDM, gestational diabetes.

[a] Maternal ethnicity was missing for 3 women (0.1%).

[b] This includes any mention of a given ethnicity reported in first, second, or third ethnicity codes. Because multiple ethnicities can be reported, proportions do not add up to 1. The category of "other" ethnicity includes Middle Eastern, Latin American/Hispanic, African, and other unspecified ethnicities.

[c] New Zealand resident status was missing for 18 women (0.5%).

[d] Parity information was missing for 593 women (15.1%).

[e] Trimester of maternity care registration was missing for 317 women (8.1%).

[f] Smoking status was missing for 814 women (20.7%).

[g] BMI values are recorded at the first prenatal care encounter. These values reflect BMI recorded prior to metformin or insulin initiation. Body mass index values were missing for 1105 women (28.1%).

maternal ethnicity, smoking status (yes/no), and parity (0, 1, 2, or 3 or more prior births) at first LMC encounter.

To control for potential confounding, we estimated propensity scores for each pregnancy, calculated as the estimated probability of treatment with metformin based on measured covariates using logistic regression. We used these values to estimate inverse probability of treatment weights (IPTW), calculated as the inverse of the probability of receiving the treatment actually received. We assessed balance of covariates preweighting and postweighting by calculating standardized mean differences for individual covariates for comparison and defined balance as standardized mean difference of 0.05 or less.

For continuous outcomes (eg, weight z scores), we used linear regression to compare mean differences in outcomes between children of metformin-treated and insulin-treated pregnancies. Log-binomial regression was used to estimate risk ratios and 95% confidence intervals for binary outcomes (eg, weight greater than the 97th percentile for age). Because some women contributed multiple pregnancies, we used generalized estimating equations with an independent working correlation structure for repeated measures to control for within-woman correlations.[28] We also included geographic region as a covariate in outcome models.

We estimated propensity score and outcome models stratified by child sex to explore potential sex differences.[29] We performed a sensitivity analysis restricted to mothers who

Table 2. Unadjusted and Adjusted Estimates From Linear Regression Models Comparing Child Health Outcomes Between Children Exposed in Utero to Metformin vs Insulin for Treatment of Gestational Diabetes, 2005-2012

Outcomes	Mean (SD)		Difference (95% CI)[a]	
	Metformin (N = 1996)	Insulin (N = 1932)	Unadjusted	Adjusted[b]
Child growth outcomes				
Weight *z* score[c,d]	0.7 (1.1)	0.7 (1.2)	0.01 (−0.07 to 0.10)	−0.03 (−0.13 to 0.07)
Height *z* score[d,e]	0.4 (1.1)	0.3 (1.1)	0.12 (0.04 to 0.19)	0.05 (−0.03 to 0.14)
Weight for height *z* score[f,d]	0.7 (1.3)	0.9 (1.3)	−0.11 (−0.20 to −0.02)	−0.10 (−0.20 to 0.01)
BMI *z* score[f]	0.8 (1.4)	0.9 (1.3)	−0.10 (−0.19 to 0.00)	−0.10 (−0.20 to 0.01)
Strengths and Difficulties Questionnaire				
SDQ-P difficulties score[g,h]	6.7 (4.7)	6.5 (4.9)	0.20 (−0.14 to 0.54)	0.12 (−0.27 to 0.51)
SDQ-T difficulties score[g,i]	4.0 (4.4)	3.7 (4.5)	0.35 (−0.08 to 0.77)	0.25 (−0.24 to 0.74)
SDQ-P prosocial behavior score[h]	8.5 (1.7)	8.5 (1.7)	−0.03 (−0.15 to 0.09)	−0.02 (−0.15 to 0.12)
SDQ-T prosocial behavior score[i]	8.0 (2.3)	8.2 (2.3)	−0.25 (−0.47 to −0.03)	−0.18 (−0.43 to 0.06)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); GDM, gestational diabetes; IPTW, inverse probability of treatment weight; SDQ-P, Strengths and Difficulties Questionnaire for Parents; SDQ-T, Strengths and Difficulties Questionnaire for Teachers.

[a] This estimate represents the mean difference in outcomes between metformin-exposed and insulin-exposed children from linear regression models.

[b] IPTWs were estimated using a propensity score model containing the following covariates: maternal age, maternal ethnicity, maternal New Zealand deprivation decile score, parity, BMI prior to prescription initiation, smoking status, timing of GDM diagnosis and treatment, history of GDM, and history of GDM treatment. The IPTW adjusted model uses imputed values for parity, BMI, and smoking status. These models are also adjusted for geographic region.

[c] Weight was available for 3156 children (80.4%). Weight measurements were missing for 21.5% of insulin-exposed children and 17.9% of metformin-exposed children.

[d] *z* Scores and percentiles were calculated based on a World Health Organization 2006 reference standard.

[e] Height was available for 3154 children (80.3%). Height measurements were missing for 21.5% of insulin-exposed children and 17.9% of metformin-exposed children.

[f] Weight for height and BMI measurements were calculated for children with nonmissing weight and height (3154; 80.3%). Height was rounded to the nearest 0.5 for determining weight for height percentiles.

[g] SDQ difficulties scores were calculated by summing scores from 4 scales: emotional problems, conduct problems, hyperactivity/inattention, and peer relationship problems.

[h] SDQ-P values were available for 3129 children (79.7%). Scores could not be calculated for 22.3% of children exposed to insulin and 18.4% of children exposed to metformin.

[i] SDQ-T values were available for 1681 children (42.8%). Scores could not be calculated for 53.0% of children exposed to insulin and 61.3% of children exposed to metformin.

received only 1 medication (metformin or insulin alone). Additionally, we identified a subgroup of children born to women with laboratory results available from the TestSafe laboratory repository in the Northern region. We included laboratory values from maternal diagnostic tests for GDM (2-hour and fasting glucose tests) as a covariate in sensitivity analyses. This includes laboratory data from the Auckland region, which is home to approximately one-third of NZ's total population.

Results

We identified 501 672 deliveries in New Zealand and recorded in MAT between 2005 and 2012 (Figure). Of 8953 pregnancies identified with GDM, 4318 (48.2%) initiated a prescription for metformin or insulin after or shortly prior to obtaining diabetic test strips. We excluded 386 pregnancies in which metformin and insulin were initiated concomitantly. The final cohort included 1996 pregnancies initially treated with metformin and 1932 pregnancies initially treated with insulin. Among metformin initiators, 417 (20.9%) subsequently filled a prescription for insulin. Conversely, 22 (1.1%) of insulin initiators later received metformin.

Overall, women treated with either metformin or insulin were similar with respect to age, BMI, and timing of GDM diagnosis and treatment initiation (**Table 1**). However, we observed strong differences by region and delivery year. More than half of metformin use (1331 [66.7%]) was among women residing in the Northern region, including Auckland. We also observed differences in treatment initiation by ethnicity and the New Zealand Deprivation Index. After weighting, treatment groups were well balanced on measured covariates, reducing potential bias from confounding (eFigure 1 in the Supplement).

Children from both treatment groups were similar with respect to mean gestational age at birth (38.2 weeks for metformin-treated and 38.0 weeks for insulin-treated pregnancies) and mean birthweight (3362 g for metformin-treated and 3437 g for insulin-treated pregnancies). Children of women treated with metformin were less likely to have experienced neonatal hypoglycemia (273 [14%]) at birth compared with children of women treated with insulin (445 [23%]).

In adjusted models, we did not observe significant differences in child growth outcomes in the 2 groups (**Table 2**). The average weight *z* score for both groups was 0.7. and we observed no differences in the adjusted linear regression model (mean difference, −0.03; 95% CI, −0.13 to 0.07). Similarly, we observed no meaningful difference in WFH *z* scores (mean difference = -0.10, 95% CI −0.20 to 0.01). We also found no significant differences in the proportion of children with weights, heights, WFH, and BMI values at or greater than the 85th percentile and in risk of these outcomes (**Table 3**). Children of metformin-treated mothers were not significantly more likely to be at or greater than 85th percentile for weight (adjusted risk ratio [aRR], 1.04; 95% CI, 0.93-1.16) or WFH (aRR, 0.92; 95% CI, 0.83-1.02) than children of insulin-treated mothers. Effect

Table 3. Unadjusted and Adjusted Risk Ratio Estimates Comparing Child Health Outcomes Between Children Exposed in Utero to Metformin vs Insulin for Treatment of Gestational Diabetes, 2005-2012

Outcome	No. (%)		Risk Ratio (95% CI)	
	Metformin (n = 1996)	Insulin (n = 1932)	Unadjusted	Adjusted[a]
Child growth outcomes				
Weight ≥85th percentile	600 (36.6)	520 (34.3)	1.07 (0.98-1.18)	1.04 (0.93-1.16)
Weight ≥97th percentile	235 (14.4)	202 (13.3)	1.08 (0.90-1.28)	0.93 (0.76-1.13)
Weight *z* score ≥1 SD	616 (37.6)	549 (36.2)	1.04 (0.95-1.14)	1.01 (0.91-1.12)
Weight *z* score ≥2 SD	207 (12.6)	172 (11.4)	1.13 (0.94-1.37)	0.94 (0.76-1.18)
Height ≥85th percentile	441 (26.9)	341 (22.5)	1.19 (1.05-1.34)	1.06 (0.92-1.22)
Height ≥97th percentile	136 (8.3)	95 (6.3)	1.32 (1.03-1.70)	1.08 (0.81-1.43)
Height *z* score ≥1 SD	450 (27.5)	355 (23.4)	1.17 (1.03-1.31)	1.05 (0.91-1.20)
Height *z* score ≥2 SD	116 (7.1)	76 (5.0)	1.41 (1.07-1.87)	1.13 (0.82-1.54)
Weight for height ≥85th percentile	600 (36.6)	612 (40.4)	0.91 (0.83-0.99)	0.92 (0.83-1.02)
Weight for height ≥97th percentile	252 (15.4)	244 (16.1)	0.96 (0.82-1.13)	0.91 (0.75-1.09)
Weight for height *z* score ≥1 SD	599 (36.8)	614 (40.6)	0.91 (0.83-0.99)	0.91 (0.83-1.01)
Weight for height *z* score ≥2 SD	219 (13.4)	210 (13.9)	0.97 (0.82-1.16)	0.89 (0.73-1.09)
BMI ≥85th percentile	605 (36.9)	618 (40.8)	0.91 (0.83-0.99)	0.92 (0.83-1.01)
BMI ≥97th percentile	267 (16.3)	256 (16.9)	1.01 (0.86-1.18)	0.92 (0.77-1.11)
BMI *z* score ≥1 SD	622 (38.0)	641 (42.3)	0.90 (0.83-0.98)	0.91 (0.83-1.00)
BMI *z* score ≥2 SD	233 (14.2)	220 (14.5)	0.99 (0.83-1.17)	0.89 (0.73-1.08)
BMI ≥21	59 (3.6)	51 (3.4)	1.07 (0.74-1.55)	0.81 (0.53-1.22)
Strengths and Difficulties Questionnaire				
Concerning SDQ-P difficulties score (≥14)[f]	152 (9.3)	137 (9.1)	1.03 (0.83-1.28)	1.13 (0.88-1.46)
Concerning SDQ-T difficulties score (≥11)[g]	73 (9.5)	74 (8.1)	1.16 (0.85-1.58)	1.21 (0.85-1.71)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); IPTW, inverse probability of treatment weight; SDQ-P, Strengths and Difficulties Questionnaire for Parents; SDQ-T, Strengths and Difficulties Questionnaire for Teachers.

[a] IPTWs were estimated using a propensity score model containing the following covariates: maternal age, maternal ethnicity, maternal New Zealand deprivation decile score, parity, BMI prior to prescription initiation, smoking status, timing of GDM diagnosis and treatment, history of GDM, and history of GDM treatment. The IPTW adjusted model uses imputed values for parity, BMI, and smoking status. These models are also adjusted for geographic region.

[b] Weight was available for 3156 children (80.4%). Weight measurements were missing for 21.5% of insulin-exposed children and 17.9% of metformin-exposed children.

[c] *z* Scores and percentiles were calculated based on a World Health Organization 2006 reference standard for children aged 0 to 5 years. One child was measured at 62 months and excluded from these calculations.

[d] Height was available for 3154 children (80.3%). Height measurements were missing for 21.5% of insulin-exposed children and 17.9% of metformin-exposed children.

[e] Weight for height and BMI measurements were calculated for children with nonmissing weight and height (n = 3154; 80.3%). Height was rounded to the nearest 0.5 for determining weight for height percentiles.

[f] SDQ-P Difficulties Scores were calculated by summing scores from 4 scales: emotional problems, conduct problems, hyperactivity/inattention, and peer relationship problems. The SDQ-P values were available for 3129 children (79.7%). The SDQ-P difficulties score could not be calculated for 22.3% of children exposed to insulin and 18.4% of children exposed to metformin.

[g] SDQ-T difficulties scores were calculated by summing scores from 4 scales: emotional problems, conduct problems, hyperactivity/inattention, and peer relationship problems. The SDQ-T values were available for 1681 children (42.8%). The SDQ-T difficulties score could not be calculated for 53.0% of children exposed to insulin and 61.3% of children exposed to metformin.

estimates were similar after restricting to mothers with a single medication (n = 3489) (eTable 1 in the Supplement).

Children born to metformin-treated and insulin-treated mothers had similar mean SDQ-P and SDQ-T Difficulties Scores (Table 2). More than half of the children were missing SDQ-T scores owing to not having a completed questionnaire (756 [19.3%]), caregiver declining consent to complete the SDQ-T (838 [21.3%]), or not being enrolled in Early Childhood Education (653 [16.6%]). Approximately 3129 (80%) had a completed SDQ-P. On average, children with missing SDQ-T results had higher SDQ-P difficulties scores (mean, 7.0) compared with those with results from both questionnaires (mean, 6.3). We observed no meaningful difference in adjusted mean SDQ-P (mean difference, 0.12; 95% CI, −0.27 to 0.51) or SDQ-T difficulties scores (mean difference, 0.25, 95% CI, −0.24 to 0.74). After weighting, children born to metformin-treated women were not at significantly increased risk of having a concerning SDQ-P (aRR, 1.13; 95% CI, 0.88-1.46) or SDQ-T difficulties score (aRR, 1.21; 95% CI, 0.85-1.71).

In sex-specific models, we observed differences in adjusted models for selected growth outcomes between boys and girls. Among boys, risk of having an extreme weight for height *z* score (≥2) was lower among those exposed to metformin compared with insulin (aRR, 0.77; 95% CI, 0.59-1.00). For girls, risk was similar in the 2 treatment groups (aRR, 1.08, 95% CI, 0.78-1.49) (**Table 4**; eFigure 2 in the Supplement). The risk of having a concerning SDQ-P difficulties score was not significantly different between treatment groups in either boys or girls (aRR for girls, 0.98; 95% CI, 0.61-1.56; aRR for boys, 1.20; 95% CI, 0.89-1.63) (Table 4).

Among 1598 mothers with laboratory results available from the Northern District Health Boards, we observed and excluded 8 pregnancies (0.5%) with hemoglobin A_{1c} values indicative of preexisting diabetes and 145 pregnancies (9.1%) missing values for fasting or 2-hour glucose tolerance tests used for GDM diagnosis, resulting in a sample size of 1445 children born to women treated with metformin (n = 1053) or insulin (n = 392). In this subgroup, mothers initiating insulin had higher

Table 4. Sex-Specific Adjusted Risk Ratio Estimates Comparing Child Growth and Development Outcomes Between Children Born to Women Treated With Metformin vs Insulin for Gestational Diabetes

Outcome	Boys			Girls		
	No. (%)		Adjusted Risk Ratio (95% CI)[a]	No. (%)		Adjusted Risk Ratio (95% CI)[a]
	Metformin (n = 1082)	Insulin (n = 1044)		Metformin (n = 914)	Insulin (n = 888)	
Child growth outcomes						
Weight ≥85th percentile[b,c]	354 (39.8)	311 (38.2)	1.01 (0.88-1.16)	246 (32.9)	209 (29.8)	1.05 (0.89-1.25)
Weight ≥97th percentile	149 (16.7)	120 (14.7)	0.94 (0.72-1.22)	86 (11.5)	82 (11.7)	0.88 (0.64-1.21)
Weight *z* score ≥1 SD	361 (40.6)	329 (40.4)	0.98 (0.86-1.11)	255 (34.1)	220 (31.4)	1.03 (0.87-1.22)
Weight *z* score ≥2 SD	132 (14.8)	107 (13.1)	0.90 (0.68-1.19)	75 (10.0)	65 (9.3)	0.98 (0.69-1.39)
Height ≥85th percentile[c,d]	257 (28.9)	203 (24.9)	1.00 (0.84-1.21)	184 (24.6)	138 (19.7)	1.12 (0.89-1.39)
Height ≥97th percentile	84 (9.4)	57 (7.0)	1.05 (0.72-1.52)	52 (7.0)	38 (5.4)	1.12 (0.72-1.76)
Height *z* score ≥1 SD	260 (29.3)	211 (25.9)	0.98 (0.82-1.17)	190 (25.4)	144 (20.5)	1.12 (0.90-1.38)
Height *z* score ≥2 SD	73 (8.2)	47 (5.8)	1.11 (0.74-1.67)	43 (5.8)	29 (4.1)	1.11 (0.66-1.87)
Weight for height ≥85th percentile[c,e]	339 (38.1)	345 (42.4)	0.91 (0.79-1.03)	261 (34.9)	267 (38.0)	0.92 (0.78-1.07)
Weight for height ≥97th percentile	149 (16.7)	146 (17.9)	0.83 (0.65-1.05)	103 (13.8)	98 (14.)	1.01 (0.75-1.35)
Weight for height *z* score ≥1 SD	338 (38.2)	347 (42.7)	0.89 (0.78-1.01)	261 (35.1)	267 (38.1)	0.92 (0.79-1.08)
Weight for height *z* score ≥2 SD	128 (14.4)	129 (15.9)	0.77 (0.59-1.00)	91 (12.2)	81 (11.5)	1.08 (0.78-1.49)
BMI ≥85th percentile[c,e]	344 (38.7)	352 (43.2)	0.89 (0.79-1.02)	261 (34.9)	266 (38.0)	0.92 (0.79-1.08)
BMI ≥97th percentile	164 (18.4)	162 (19.9)	0.85 (0.67-1.06)	103 (13.8)	94 (13.4)	1.02 (0.76-1.38)
BMI *z* score ≥1 SD	356 (40.0)	367 (45.1)	0.89 (0.79-1.01)	266 (35.6)	274 (39.1)	0.91 (0.78-1.07)
BMI *z* score ≥2 SD	141 (15.8)	142 (17.4)	0.78 (0.61-0.99)	92 (12.3)	78 (11.1)	1.08 (0.78-1.50)
BMI ≥21	33 (3.7)	26 (3.2)	0.81 (0.44-1.46)	26 (3.5)	25 (3.6)	0.73 (0.40-1.34)
Strengths and Difficulties Questionnaire						
Concerning SDQ-P difficulties score (≥14)[f,g]	103 (11.6)	86 (10.7)	1.20 (0.89-1.63)	49 (6.6)	51 (7.3)	0.98 (0.61-1.56)
Concerning SDQ-T difficulties score (≥11)[f,h]	53 (5.9)	51 (6.2)	1.24 (0.82-1.88)	20 (5.6)	23 (5.3)	1.24 (0.68-2.25)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); IPTW, inverse probability of treatment weight; SDQ-P, Strengths and Difficulties Questionnaire for Parents; SDQ-T, Strengths and Difficulties Questionnaire for Teachers.

[a] IPTWs were estimated using sex-specific propensity score models containing the following covariates: maternal age, maternal ethnicity, maternal NZ deprivation decile score, parity, BMI prior to prescription initiation, smoking status, timing of GDM diagnosis and treatment, history of GDM, and history of GDM treatment. The IPTW-adjusted model uses imputed values for parity, BMI, and smoking status. These models are also adjusted for geographic region.

[b] Weight was available for 3156 children (80.4%). Weight measurements were missing for 21.5% of insulin-exposed children and 17.9% of metformin-exposed children. Weight was missing for 421 boys (19.8%) and 351 girls (19.5%).

[c] *z* Scores and percentiles were calculated based on a World Health Organization 2006 reference standard.

[d] Height was available for 3154 children (80.3%). Height measurements were missing for 21.5% of insulin-exposed children and 17.9% of metformin-exposed children. Height was missing for 422 boys (19.9%) and 352 girls (19.5%).

[e] Weight for height and BMI measurements were calculated for children with nonmissing weight and height (n = 3154, 80.3%). Height was rounded to the nearest 0.5 for determining weight for height percentiles.

[f] SDQ difficulties scores were calculated by summing scores from 4 scales: emotional problems, conduct problems, hyperactivity/inattention, and peer relationship problems.

[g] SDQ-P values were available for 3129 children (79.7%) (79.6% of boys and 79.7% of girls). The SDQ-P Difficulties Score could not be calculated for 22.3% of children exposed to insulin and 18.4% of children exposed to metformin.

[h] SDQ-T values were available for 1681 children (42.8%) (41.8% of boys and 44.0% of girls). The SDQ-T difficulties score could not be calculated for 53.0% of children exposed to insulin and 61.3% of children exposed to metformin.

mean values for fasting (mean [SD], 100.8 [21.6] mg/dL) and 2-hour glucose tests (mean [SD], 175.0 [43.2] mg/dL, SD = 2.4) than those initiating metformin (fasting mean [SD], 91.8 [14.4]; 2-hour glucose mean [SD], 167.4 [28.8]). After controlling for differences in diagnostic results, effect estimates were largely unchanged from crude results in this population. Consistent with the overall cohort, we observed no meaningful difference in risk of having a WFH (aRR, 0.93; 95% CI, 0.75-1.14) or BMI (aRR, 0.91; 95% CI, 0.74-1.12) at or greater than the 85th percentile among children exposed to metformin compared with insulin, but this was not significant (eTable 2 in the Supplement). While we observed a mean of higher SDQ-T difficulties scores among children exposed to metformin vs insulin, more than 70% of children were missing this assessment.

Discussion

In a population-based cohort of children born to women treated with metformin or insulin for GDM in New Zealand, we did not observe meaningful differences in child growth outcomes at age 4 years. Children whose mothers were treated initially with metformin vs insulin to treat GDM were similar with respect to weight, WFH, and BMI, and we did not observe statistically or clinically significant differences in growth outcomes after adjusting for measured covariates. We observed variation in estimates by child sex; however, we did not conduct formal tests to determine whether these differences were statistically significant. In mouse models of prenatal exposure to

metformin, researchers observed a more prominent protective effect for metabolic outcomes among female offspring,[30] although this is not consistently observed in humans.[31] Further research on sex-specific effects is needed. Mean SDQ-P and SDQ-T difficulties and prosocial behavior scores were similar between the 2 groups. Metformin-exposed children were not statistically at greater risk of having a concerning SDQ-P or SDQ-T difficulties score; however, the confidence intervals were wide and could not exclude potentially increased risk associated with metformin vs insulin treatment.

Our findings are consistent with prior studies focused on child health outcomes at younger ages. A follow-up study of offspring born to women enrolled in the Metformin in Gestational Diabetes trial[12] (N = 323) found that children who had been prenatally exposed to metformin did not differ from children exposed to insulin with regard to weight, height, or abdominal fat at age 2 years.[12] Results published in 2018 from this trial's follow-up at age 7 years (n = 109) and age 9 year (n = 99) showed no differences in body fat or metabolic measures between children exposed to metformin compared with those exposed to insulin.[15] At age 9 years, children exposed to metformin were consistently larger than those exposed to insulin, although these estimates are imprecise due to a substantially reduced sample size. At 18 months after randomization, Ijäs et al[11] reported increased risks of having a height or weight at or greater than the 95th percentile for metformin-exposed children, but the sample was similarly small (n = 93), making it impossible to rule out a large range of possible effect sizes. Previous follow-up studies have also found no differences between children born to mothers treated with metformin vs insulin with respect to neurodevelopmental outcomes and were similarly limited by small samples.[11,13,14]

Limitations

This study had some limitations, primarily stemming from missing data. Outcome measurements were missing for approximately 20% of children. More than half the cohort was missing teacher-reported SDQ results. Parent-reported SDQ results differed between children with and without recorded SDQ-T results. In the New Zealand Children with Hypoglycaemia and Their Later Development (CHYLD) study, researchers compared SDQ-P difficulties scores from the study's assessments with B4SC results and found higher SDQ-P difficulties scores among enrolled children without a complete B4SC,[32] suggesting that children who do not complete the B4SC may differ meaningfully from those who do. We were also missing covariate data for some mothers (BMI, smoking status, and parity). Using a state-of-the-art approach to missing covariate data, multiple imputation, we augmented these data but did not impute outcomes. We were limited to follow-up at age 4 years, and differences in child growth may not fully appear until late childhood.[33,34] However, GDM has been associated with increased risk of overweight in children at age 3 years.[9] Despite missing data, our study was able to examine outcomes in more than 3000 children, resulting in more precise estimates to reduce uncertainty surrounding metformin's effect on child development when used to treat GDM.

It is possible that there may be residual confounding related to disease severity owing to the observational nature of this study. However, the mothers included in this study were similar with respect to important indicators of GDM severity such as BMI and timing of diagnosis. The new-user, active comparator study design helped reduce residual and unmeasured confounding by including exclusively women with the indication for treatment and comparing 2 likely first-line therapies.[35] This is a major strength of our methods. Finally, our subgroup analysis adjusting for diagnostic laboratory results for GDM did not change our conclusions.

Conclusions

To our knowledge, this study is the largest to examine long-term outcomes in a real-world setting in children born to women treated with metformin vs insulin for GDM. We observed no meaningful differences in growth or behavioral and emotional development between treatment groups. This will provide clinicians and patients with important information concerning long-term outcomes following treatment with metformin vs insulin when making treatment decisions.

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Concept and design: Landi, Engel, Boggess, Sturmer, Jonsson Funk.
Acquisition, analysis, or interpretation of data: Landi, Radke, Engel, Boggess, Howe, Jonsson Funk.
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Administrative, technical, or material support: Landi, Radke, Boggess, Howe, Jonsson Funk.
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