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# Is the Association Between Pregnancy Weight Gain and Fetal Size Causal?

## *A Re-examination Using a Sibling Comparison Design*

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**Background:** Observational cohort studies have consistently shown that maternal weight gain in pregnancy is positively associated with fetal size, but it is unknown whether the association is causal. This study investigated the effect of pregnancy weight gain on fetal growth using a sibling comparison design to control for unmeasured confounding by genetic and shared environmental factors.

**Methods:** Our study population included 44,457 infants (21,680 women) with electronic medical records in the Stockholm–Gotland Obstetrical Database, 2008–2014. We standardized pregnancy weight gain into gestational age-specific *z*-scores. Fetal size was classified as birthweight (gram), and as small- and large-for-gestational-age birth (birthweight <10th or >90th percentiles, respectively). Our sibling comparison analyses used multivariable linear fixed effects models for birthweight and hybrid logistic fixed effects models for small- and large-for-gestational-age birth (SGA and LGA). We repeated analyses using conventional (unmatched) regression models.

**Results:** Sibling comparison analyses showed a clinically meaningful association between weight gain and fetal size (e.g., adjusted difference of +89 g birthweight [95% CI = 82, 95 g]; adjusted risk ratios [aRR] for SGA of 0.80 [95% CI = 0.75, 0.86] per 1 *z*-score increase in weight gain for a woman of body mass index [BMI] = 25). These findings were consistent across the range of BMI. Estimates were only modestly attenuated compared with conventional approach (+97 g [95% CI = 92, 102 g], aRR for SGA of 0.70 [95% CI = 0.67, 0.73] per 1 *z*-score increase in weight gain).

**Conclusion:** The positive association between pregnancy weight gain and fetal size we found using a sibling comparison design suggests that this relation has minimal confounding by familial factors that remain constant between pregnancies.

**Keywords:** Birthweight; Fetal growth; Gestational weight gain; Large-for-gestational-age; Pregnancy; Sibling analysis; Small-for-gestational-age

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Numerous studies have shown a strong, positive association between pregnancy weight gain and infant size at birth.[1,2] However, this evidence is largely based on observational cohort studies comparing effects of weight gain on infant size between different women, and observed effects may be confounded by underlying genetic or lifestyle factors. In their 2009 pregnancy weight gain recommendations, the Institute of Medicine Committee concluded that "In summary, the issue of whether the association between gestational weight gain and fetal growth is causal cannot be answered with certainty based on the available evidence".[1] (p.208)

Sibling comparisons provide an alternative approach for estimating the causal effect of prenatal risk factors on child health.[3] Because siblings are typically exposed to similar genetic and environmental factors, the sibling comparison design can reduce confounding by unmeasured or poorly

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The data from this study cannot be made publicly available for legal reasons. According to Swedish law and the Stockholm Regional Ethical Review Board, it is prohibited to publicly share data with personal information. Statistical code is available in eAppendix; http://links.lww.com/EDE/B447.

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measured risk factors that remain relatively constant between a woman's pregnancies (such as socioeconomic status, lifestyle, environmental toxins, or maternal genotype). Use of the sibling comparison design to understand the effect of pregnancy weight gain on offspring birthweight is limited and has produced conflicting results.[4,5] A smaller study of mothers with gestational diabetes found that a positive association between pregnancy weight gain and birthweight disappeared in the sibling comparison analysis, suggesting that the effects of pregnancy weight gain may be confounded by shared genetic and/or environmental factors.[4] In contrast, a large study based on vital statistics data from Michigan/New Jersey found that among term infants, an association remained between pregnancy weight gain and birthweight using a sibling analysis.[5] However, this study did not control for prepregnancy BMI, an important determinant of birthweight that can vary between a woman's pregnancies, creating the potential for confounding.

The objective of this study was to investigate the effect of pregnancy weight gain on infant size at birth using a sibling comparison design to help control for unmeasured confounding by genetic and time-invariant shared environmental or lifestyle factors in a large, population-based cohort with detailed clinical data.

## METHODS

### Study Population

Our study population included all singleton pregnancies delivered in the counties of Stockholm and Gotland, Sweden from January 2008 to October 2014 (n = 175,522). In these counties, demographic, obstetrical, and neonatal electronic medical record data from all pregnancy-related visits and admissions (antenatal clinic, delivery, and postpartum) are forwarded daily into the Stockholm–Gotland Obstetrical database.[6] The study was approved by the Stockholm regional ethics committee, and all included clinics consented to medical record access.

We excluded women with a missing or implausible weight (<30 or >350 kg), no early pregnancy weight measurement (<14 weeks), last measured weight more than 31 days before delivery, implausible weight gain measurements (>4 SD or <−4 SD), and infants with missing or implausible gestational age, sex, or birthweight *z*-scores (>4 SD or <−4 SD). Our primary analyses were restricted to women with two or more deliveries during the study period.

### Weight Measurements

Early pregnancy body mass index (BMI) was calculated as the first weight (<14 weeks' gestation) in kilograms divided by height in meters squared. Total pregnancy weight gain was calculated as the last measured weight before delivery minus early pregnancy weight (<14 weeks') and standardized into a BMI- and gestational age–specific *z*-score using a weight-gain-for-gestational-age chart derived in our population.[7] The pregnancy weight measurements in the electronic medical record were obtained from measured weights on a scale (generally, wearing light clothing) during routine antenatal care at each clinic.

### Fetal Growth

Our primary outcome examined birthweight (gram) as a continuous variable. Our secondary outcomes were small- and large-for-gestational-age birth, defined as birthweight <10th and >90th percentile for sex and gestational age, based on the Swedish ultrasound fetal growth chart.[8] Gestational age (in days) was based on ultrasound or embryo transfer dating in 99% of the cohort.

### Covariates

We considered potential confounders of delivery date (day/month/year), parity (0 vs. 1, 2+), maternal height (cm), maternal age (years), smoking during pregnancy (nonsmoker vs. smoked, quit during pregnancy), prepregnancy diabetes (International Classification of Diseases 10 codes O24.0–O24.3, E10–E14), prepregnancy hypertension (International Classification of Diseases 10 codes O10, I10–I15 or chronic hypertension in the electronic medical record), and cohabitation status (yes/no). We did not adjust for gestational diabetes or pre-eclampsia as we hypothesized that these conditions were downstream consequences of maternal weight gain (i.e., potentially mediators), and we were interested in estimating the total effect of pregnancy weight gain on fetal size, but controlled for a history of gestational diabetes (International Classification of Diseases 10 code O24.4) or pre-eclampsia (International Classification of Diseases 10 code O14–O15) in a prior pregnancy (both coded as yes/no based on observed status in prior pregnancy).[9]

### Statistical Analysis

Our sibling comparison design estimated the effect of pregnancy weight gain on fetal size using a multivariable linear fixed effects model (for birthweight) and a hybrid logistic fixed effects model (for small- and large-for-gestational-age birth).[10] The fixed effects models (xtreg, fe option in Stata) estimated the expected difference in fetal size between siblings based on the differences in pregnancy weight gain experienced by their mother in each of her pregnancies. The hybrid fixed effects model controls for differences in time-invariant factors between woman by including cluster (mother)-level mean values as a covariate (in Stata, creating a new variable containing each woman's mean weight gain and including this variable as a covariate in subsequent xtlogit models).[10] We used this hybrid method rather than a logistic fixed effect model to generate an estimate for weight gain that accounted for the component terms of weight as a main effect and the interaction term between weight gain and early pregnancy BMI through postestimation commands.

For each outcome, we built a simple model that included weight gain *z*-score, early pregnancy BMI, and an interaction term between weight gain *z*-score and early pregnancy BMI.

The simple model for birthweight additionally controlled for sex and gestational age, modeled using a restricted cubic spline with five knots to allow a nonlinear pattern of fetal growth throughout gestation.[11] Models for small- and large-for-gestational-age birth were not adjusted for sex or gestational age. We included an interaction term between early pregnancy BMI and pregnancy weight gain *z*-score based on previous knowledge demonstrating that the effect of pregnancy weight gain on adverse pregnancy outcomes differs according to prepregnancy BMI status.[1] Because of this interaction term, we used the "margins" command in Stata (College Station, TX) to obtain estimates of the effect of weight gain on fetal size that accounted for the contribution of the weight gain–BMI interaction term. We also used this command to obtain risk ratios instead of odds ratio as our outcomes of small- and large-for-gestational-age birth were not rare. Stata code is provided in eAppendix 1; http://links.lww.com/EDE/B447.

Adjusted models further controlled for delivery date, parity, maternal height (between-women analysis only), maternal age, smoking during pregnancy, prepregnancy diabetes, prepregnancy hypertension, previous gestational diabetes, previous pre-eclampsia, and cohabitation status. We confirmed the linearity of the weight gain–fetal growth association by regressing birthweight against quintiles of weight gain and plotting the resulting coefficients and 95% confidence intervals.

We also estimated the association between pregnancy weight gain and fetal size using a conventional population approach based on multivariable linear and logistic regression (i.e., estimating how differences in weight gain between different women were associated with differences in infant birthweights). In these models, we accounted for the correlation in birthweight between siblings using a Huber–White sandwich estimator.[12] We conducted this latter analysis to facilitate comparison with previous research on pregnancy weight gain and fetal size. The interpretation of the sibling comparison and the conventional population models differ, which limits the value of direct comparisons. That is, the conditional approach of the sibling comparison design produces subject-specific estimates that describe the change in the expected change in fetal size for an individual woman if she gains 1 *z*-score of weight gain, whereas the conventional population approach produces population average estimates, which reflect the difference in fetal size in the overall population of women with a weight gain *z*-score of 0 compared with women with a *z*-score of 1.

We conducted several sensitivity analyses to support the validity of the sibling comparison design. First, we assessed the potential for selection bias in our analytic sample that was restricted to women with more than one pregnancy during the study period by comparing the coefficients obtained from conventional linear and logistic regression models in our analytic sample to those obtained using similar models in the entire population (i.e., including women with only one birth during the study period who could not be included in the sibling comparison analyses). Second, we tested for birth order effects by including an interaction term between parity and weight gain. That is, we tested whether the effect of weight gain on fetal growth differed by birth order, which would imply that sibling pregnancies are not interchangeable.

## RESULTS

There were 175,522 deliveries in Stockholm–Gotland counties, 2008–2014. After excluding pregnancies with missing or implausible values for weight, weight gain, birthweight, gestational age, or fetal sex, there were 126,309 eligible pregnancies (Figure 1). Of these, there were 44,457 infants (to 21,680 women) who had one or more sibling in our cohort. As shown in Table 1, the characteristics of our sibling cohort were largely similar to the characteristics of the population of all pregnancies in Stockholm–Gotland counties. However, pregnancies in the sibling cohort were more likely to be multiparous and living with a partner. In the sibling cohort, 67%

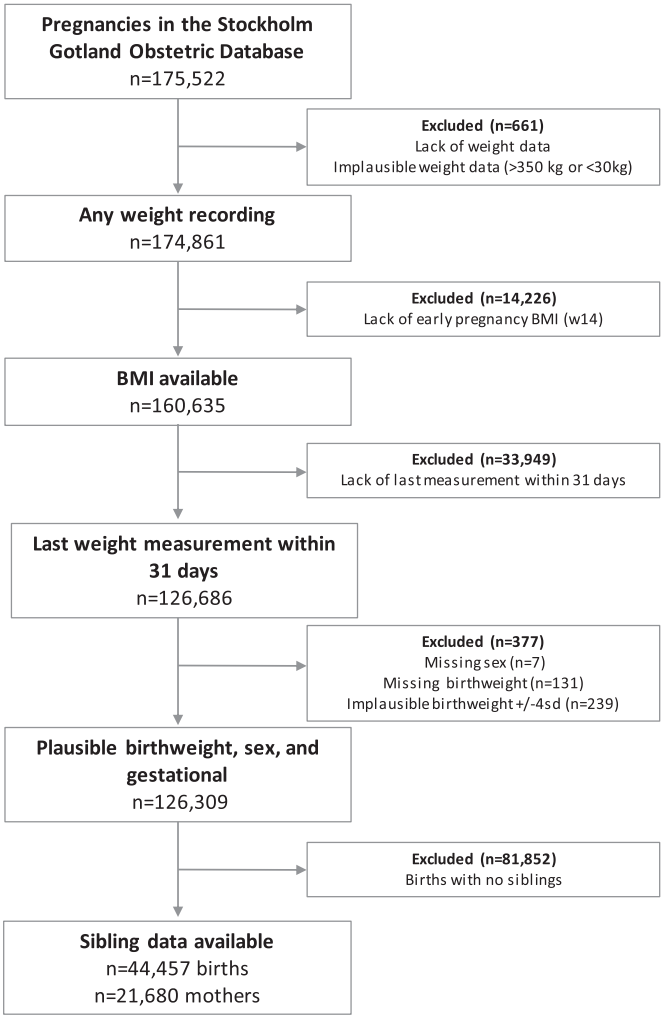


**FIGURE 1.** Flow chart of the sibling cohort (n = 44,457) in the Stockholm–Gotland counties in Sweden between 2008 and 2014.

**TABLE 1.** Maternal and Pregnancy Characteristics Among 126,309 Births in the Stockholm–Gotland Region in Sweden Between 2008 and 2014

| | Births in Stockholm–Gotland, 2008–2014 (n = 126,309) | Sibling Cohort (44,457 Infants to 21,680 Mothers) |
|---|---|---|
| Gestational weight gain[a] | | |
| Kg, mean (SD) | 13.5 (4.8) | 13.4 (4.7) |
| *z*-score, mean (SD) | 0.007 (0.93) | −0.029 (0.95) |
| No. weight measurements, median (IQR) | 5 (4–7) | 5 (4–7) |
| Gestational age (days), mean (SD) | 278.6 (11.2) | 278.6 (10.7) |
| BMI in early pregnancy (kg/m$^2$) | | |
| Underweight (<18.5), no. (%) | 3,882 (3.1) | 1,405 (3.2) |
| Normal weight (18.5–24.9), no. (%) | 84,299 (66.7) | 29,876 (67.2) |
| Overweight (25.0–29.9), no. (%) | 27,179 (21.5) | 9,408 (21.2) |
| Obese class I (30.0–34.9), no. (%) | 8,048 (6.4%) | 2,802 (6.3%) |
| Obese class II (35.0–39.9), no. (%) | 2,231 (1.8) | 752 (1.7) |
| Obese class III (≥40.0), no. (%) | 670 (0.5) | 214 (0.5) |
| Maternal age (year), mean (SD) | 31.4 (5.1) | 30.9 (4.7) |
| Maternal height (cm), mean (SD) | 166 (6.5) | 166 (6.5) |
| Living with partner, no. (%) | 118,253 (93.6) | 42,553 (95.7) |
| Nulliparous, no. (%) | 58,063 (46.0) | 17,225 (38.7) |
| Prepregnancy hypertension, no. (%) | 1,144 (0.9) | 360 (0.8) |
| Prepregnancy diabetes, no. (%) | 666 (0.5) | 171 (0.4) |
| Early pregnancy smoking status | | |
| Nonsmoker, no. (%) | 120,089 (95.0) | 42,623 (95.9) |
| 1–9 cigarettes/day, no. (%) | 4,302 (3.4) | 1,274 (2.9) |
| ≥10 cigarettes/day, no. (%) | 1,036 (0.8) | 304 (0.7) |
| Missing, no. (%) | 882 (0.7) | 256 (0.6) |

[a]Based on last measurement before delivery.

of women had a normal BMI in early pregnancy and gained an average of 13.4 kg. The average interpregnancy interval was 2.5 ± 0.9 years.

As expected, early pregnancy BMI in our sibling cohort was higher in second compared with first pregnancies (+0.5 kg/m$^2$), while total pregnancy weight gain was approximately 1 kg less in second pregnancies (Table 2). Risk of small-for-gestational-age birth was lower in second births, while the risk of large-for-gestational-age birth was increased. For 52% of women in the sibling cohort, weight gain between pregnancies differed by more than 2 kg, and more than 4 kg for 33% of women. Weight gain differences within women were balanced across birth order (i.e., the proportion of women experiencing higher weight gain in their first pregnancy was comparable to the proportion experiencing higher weight gain in their second pregnancy).

## Birthweight

Figure 2 shows the estimated effect of each 1 *z*-score increase in pregnancy weight gain on fetal size using the sibling comparison and conventional regression (between pregnancies) approaches (values provided in eAppendix 2; http://links.lww.com/EDE/B447). In the simple sibling comparison model, birthweight was an average 66 g (95% CI = 60, 73 g) higher for every 1 *z*-score change in pregnancy weight gain for a woman with a BMI of 25. After adjusting for confounders, associations became more pronounced (e.g., 89 g [95% CI = 82, 95 g] for a woman with a BMI of 25). The changes between the crude and adjusted estimates were driven primarily by the adjustment for parity. In the conventional analysis, the simple model estimated that for every 1 *z*-score difference in pregnancy weight gain, birthweight was 97 g higher (95% CI = 92, 102 g). This estimate was similar across different BMI values, and adjustment for confounders had little impact.

## Small- and Large-for-gestational-age Birth

Similar findings were observed when we examined the risks of small- and large-for-gestational-age birth (Figures 3 and 4, eAppendix 2; http://links.lww.com/EDE/B447). For small-for-gestational-age birth, the simple sibling comparison models yielded null effects at all BMI values except 18.5 kg/m$^2$. After adjustment for time-varying factors, point estimates across the BMI categories suggested risk ratios for small-for-gestational-age birth of 0.80 (95% CI = 0.75, 0.86) to 0.85 (95% CI = 0.74, 0.95) per 1 *z*-score change in pregnancy weight gain. The conventional between-pregnancies analysis estimated that for every 1 *z*-score difference in pregnancy weight gain, the risk ratio for small-for-gestational-age birth was approximately 0.70 across all BMI categories, in both simple and adjusted models (e.g., adjusted risk ratio at BMI of 25 of 0.70 [95% CI = 0.67, 0.73]).

The adjusted sibling comparison model found a positive association between pregnancy weight gain and large-for-gestational-age birth, but the strength of association varied by early pregnancy BMI. The effect of pregnancy weight gain became weaker with increasing early pregnancy BMI, with an estimated 1.58-fold (95% CI = 1.45, 1.71) increase in risk at a BMI of 18.5 compared with an estimated 1.32-fold (95% CI = 1.23, 1.41) increase in risk at a BMI of 35. A similar trend was seen in the adjusted between-pregnancies analysis, with an estimated 1.76-fold (95% CI = 1.66, 1.87) increase in risk of large-for-gestational-age birth per 1 *z*-score difference in weight gain at a BMI of 18.5, decreasing to a 1.43-fold (95% CI = 1.34, 1.52) increase in risk at a BMI of 35.

## Sensitivity Analyses

Our sensitivity analyses supported the validity of our sibling comparison models. As shown in eAppendix 3; http://links.lww.com/EDE/B447, the associations between pregnancy weight gain and fetal size estimated in our sibling cohort were similar to those estimated using the total population of Stockholm–Gotland births. This reduces the potential for selection bias introduced by systematic differences between women who do versus do not have more than one offspring.

Additionally, in our model assessing the potential for carryover effects, the coefficient for the interaction term

**TABLE 2.** Maternal and Infant Characteristic in First Versus Second Pregnancy in the Sibling Cohort (n = 44,457) in the Stockholm–Gotland Region in Sweden Between 2008 and 2014

| | Pregnancy 1 (n = 21,680) | Pregnancy 2 (n = 21,680) | Pregnancy 3 (n = 1,072) | Pregnancy 4 (n = 25) |
|---|---|---|---|---|
| Pregnancy weight gain[a] (kg), mean (SD) | 13.9 (4.8) | 12.8 (4.6) | 12.1 (4.7) | 9.2 (4.1) |
| Pregnancy weight gain *z*-score,[a] mean (SD) | 0.08 (0.95) | −0.13 (0.93) | −0.24 (0.97) | −0.73 (0.90) |
| Early pregnancy BMI (kg/m$^2$), mean (SD) | 23.5 (3.9) | 24.1 (4.3) | 24.8 (4.8) | 24.9 (5.3) |
| Underweight, no. (%) | 743 (3.4) | 625 (2.9) | 33 (3.1) | 4 (16.0) |
| Normal weight, no. (%) | 15,236 (70.3) | 14,020 (64.7) | 612 (57.1) | 8 (32.0) |
| Overweight, no. (%) | 4,168 (19.2) | 4,952 (22.8) | 280 (26.1) | 8 (32.0) |
| Obese, no. (%) | 1,479 (6.8) | 2,083 (9.6) | 147 (13.7) | 5 (20.0) |
| Infant birthweight (gram), mean (SD) | 3,473 (519) | 3,608 (496) | 3,611 (496) | 3,361 (465) |
| Infant birthweight *z*-score, mean (SD) | −0.16 (0.98) | 0.19 (0.99) | 0.25 (1.00) | −0.05 (1.00) |
| SGA birth (<10th percentile), no. (%) | 2,394 (11.1) | 1,237 (5.7) | 56 (5.2) | 4 (16) |
| LGA birth (>90th percentile), no. (%) | 1,447 (6.7) | 2,649 (12.2) | 154 (14.4) | 2 (8.0) |

[a]Based on last measurement before delivery.
LGA indicates large for gestational age; SGA, small for gestational age.

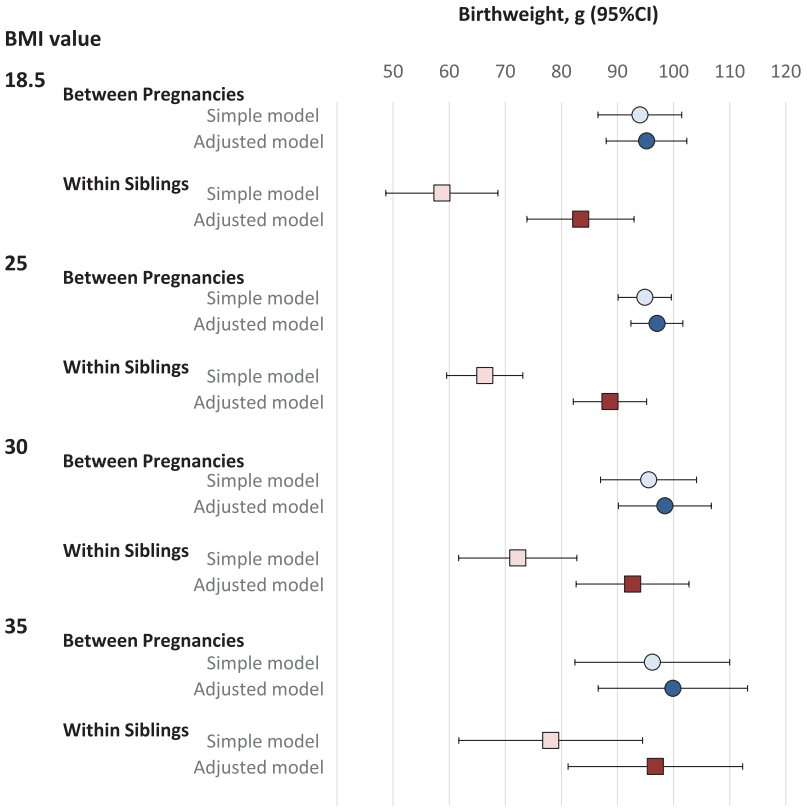


**FIGURE 2.** Estimated effect of pregnancy weight gain *z*-score on birthweight in grams at different prepregnancy BMI values among 44,457 siblings. The simple model was adjusted for sex, gestational age, and early-pregnancy BMI as well as an interaction term between early-pregnancy BMI and weight gain *z*-score. The adjusted model was further adjusted for delivery date, parity, maternal height (between-mothers model only), smoking, prepregnancy diabetes, prepregnancy hypertension, previous gestational diabetes, previous preeclampsia, and cohabitation status.

between birth order and weight gain was not clinically meaningful in magnitude (7.2 g [95% CI = −0.4, 14.7]).

## DISCUSSION

### Main Findings

In this population-based sibling comparison study of 44,457 infants, we found positive, clinically meaningful associations between pregnancy weight gain and fetal size. This suggests that previously observed associations between pregnancy weight gain and fetal size are not primarily attributable to confounding by unmeasured genetic, environmental, or lifestyle factors that remain constant between a woman's pregnancies.

### Comparison with the Literature

Available studies using a sibling comparison design for causal inference on pregnancy weight gain and birthweight

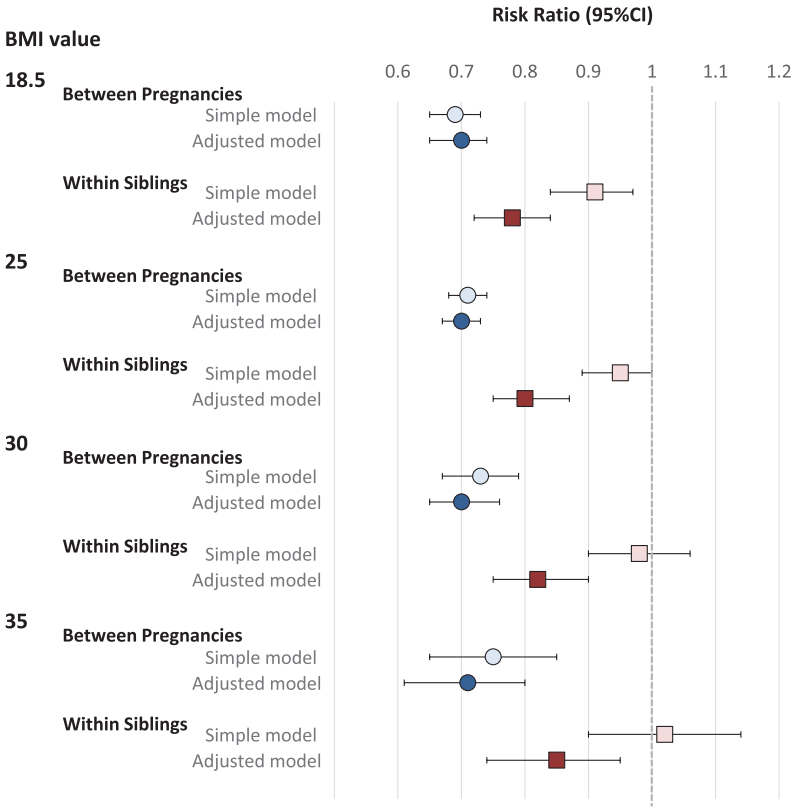


**FIGURE 3.** Estimated effect of pregnancy weight gain *z*-score on risk of small-for-gestational-age birth at different prepregnancy BMI values among 44,457 siblings. The simple model was adjusted for early-pregnancy BMI and an interaction term between early-pregnancy BMI and weight gain *z*-score. The adjusted model was further adjusted for delivery date, parity, maternal height (between-mothers model only), smoking, prepregnancy diabetes, prepregnancy hypertension, previous gestational diabetes, previous preeclampsia, and cohabitation status.

have produced conflicting results.[4,5] A small study of 90 women with at least two pregnancies complicated by gestational diabetes found that an association between pregnancy weight gain and infant birthweight from the conventional population analysis (24.8 g per 1 kg pregnancy weight gain [95% CI = 7.6, 42.0]) was attenuated in the sibling comparison analysis (13.7 g [95% CI = −0.6, 27.9]). This suggested that the apparent effect of pregnancy weight gain on birthweight may be primarily due to shared environmental or genetic factors rather than causal, at least in the setting of gestational diabetes.[4] In contrast, a large study of birth certificate data from 513,501 term sibling groups in New Jersey and Michigan (1989–2003) found a linear association between maternal weight gain and infant birthweight (7.35 g per 1 kg maternal weight gain [95% CI = 7.10, 7.59]). However, data on prepregnancy BMI were unavailable in this study. As prepregnancy BMI is a known determinant of pregnancy weight gain and birthweight,[1] and can vary between a woman's pregnancies (especially given high weight gain in an earlier pregnancy), the study estimates were likely biased by some degree of confounding.

Sibling comparison studies of pregnancy weight gain and longer term offspring size have likewise produced conflicting findings.[13–15] A study of 2,758 sibling groups in the Collaborative Perinatal Project found a positive association between gestational weight gain and child BMI at 4 years using the conventional between-women analyses (0.07 *z*-score increase per 1 kg increase in total pregnancy weight gain [95% CI = 0.04, 0.11]), which was attenuated in the sibling comparison design (0.03 [95% CI = −0.02, 0.08]). This led the authors to conclude that the association between pregnancy weight gain and child size may be explained by shared family characteristics rather than a causal effect of the intrauterine environment.[15] In contrast, a study of administrative data from 42,133 women in Arkansas found that an association remained between pregnancy weight gain and childhood obesity using a sibling analysis, suggesting that maternal weight gain in pregnancy has a causal influence on child anthropometry.[14] Finally, a sibling analysis using the Swedish Medical Birth Register was used to examine pregnancy weight gain and offspring adiposity at the time of conscription at age 18 in 46,066 male sibling groups.[13] The study found that the effect of pregnancy weight gain and offspring adiposity observed in conventional population analyses disappeared in the sibling analyses among normal weight women, but remained in overweight and obese women. However, pregnancy weight gain data were missing in more than 60% of the original cohort, as the Swedish Medical Birth Register is based on information from the delivery admission, and women in Sweden are not routinely weighed at delivery (whereas our cohort included weight measurements from antenatal care).[16] As a result, the generalizability of the study findings is unclear.

Our study overcame the concerns of small sample size, selection bias, or confounding of previous sibling comparison studies by using a large, population-based obstetrical cohort with detailed clinical data including early pregnancy BMI. We also accounted for effect modification by early pregnancy

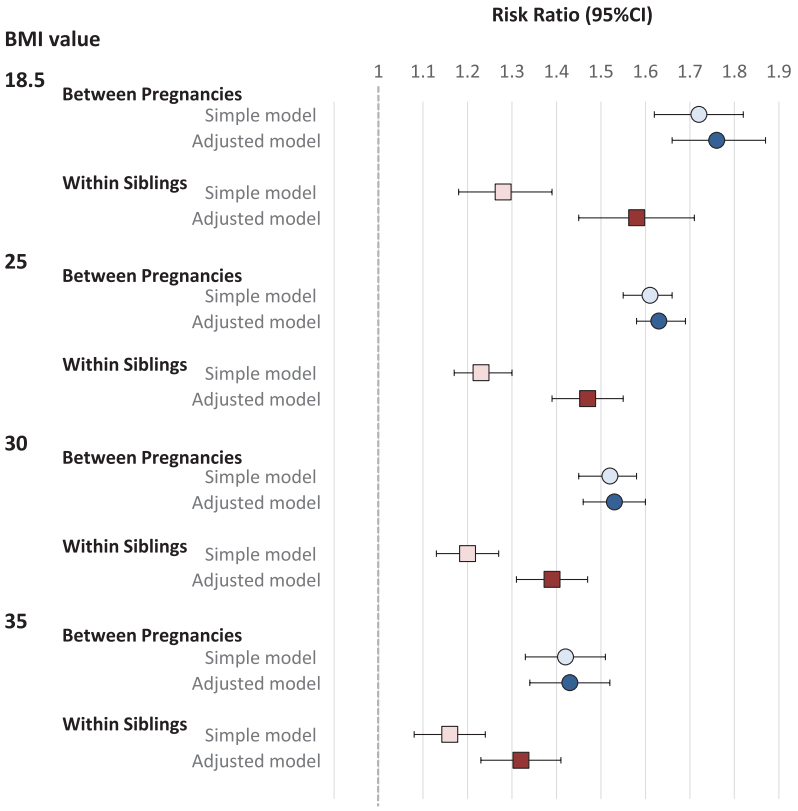


**FIGURE 4.** Estimated effect of pregnancy weight gain *z*-score on risk of large-for-gestational-age birth at different prepregnancy BMI values among 44,457 siblings. The simple model was adjusted for early-pregnancy BMI and an interaction term between early-pregnancy BMI and weight gain *z*-score. The adjusted model was further adjusted for delivery date, parity, maternal height (between-mothers model only), smoking, prepregnancy diabetes, prepregnancy hypertension, previous gestational diabetes, previous preeclampsia, and cohabitation status.

BMI, which makes our findings easier to interpret in the context of BMI-specific pregnancy weight gain recommendations. Our results provide robust evidence that pregnancy weight gain has an effect on fetal growth, when shared genetic and time-invariant environmental factors between siblings are taken into account. For Swedish women of normal early pregnancy BMI, one pregnancy weight gain *z*-score corresponds to approximately 5.2 kg at 40 weeks.[7] Thus, our findings suggest that each 1 kg increase in weight gain would correspond to a 17.2 g increase in birthweight (=5.2 kg/89.51 g per 1 *z*-score of weight gain at BMI = 25 kg/m$^2$). Potential biologic mechanisms linking gestational weight gain and fetal size could include altered availability of metabolites that cross the placenta such as fatty acids, glucose, and lactate in the maternal blood stream used for fetal fat deposition, or increases in adipokines released by maternal adipose tissues crossing the placenta and altering fetal metabolism.[17] Translating these findings into public health pregnancy weight gain recommendations will require identifying the weight gain range that best balances the risks of small- and large-for-gestational-age birth, while simultaneously considering other important maternal and child health outcomes that also differ in the direction of their association with pregnancy weight gain. These include maternal and child obesity, cesarean delivery, preterm birth, and infant death.[1]

Alternative strategies exist for estimating the causal effects of pregnancy exposures. In the Mendelian randomization design, genome-wide association studies are used to identify genotypes that are robustly associated with an exposure of interest. The genes can then be used as an instrumental variable to establish the effects of the exposure on a health outcome of interest.[18] A Mendelian randomization design was recently used to demonstrate that prepregnancy obesity has a causal effect on birthweight,[19] but we are unaware of a Mendelian randomization study examining weight gain in pregnancy. This research would provide valuable insights to confirm or refute the findings from sibling comparison studies.

Randomized trials of interventions aiming to influence pregnancy weight gain through diet or physical activity can also provide high-quality evidence on the effect of weight gain on infant birthweight. Two systematic reviews with meta-analyses have summarized the effects of such interventions.[20,21] Both found that dietary or lifestyle interventions can modify pregnancy weight gain, but neither found differences between groups in birthweight, small- or large-for-gestational-age birth. However, the mean differences in weight gain between intervention and control arms were generally very modest (1.42 kg [95% CI = 0.95, 1.89] in the meta-analysis that reported a summary of the average weight gain difference between groups[20]). This could explain the lack of differences in fetal size.

## Strengths and Limitations

The validity of our findings is supported by our use of a large, population-based cohort. The quality-controlled electronic medical record data provided a high degree of clinical

detail, including measured early pregnancy weights and day-specific, ultrasound-confirmed estimates of gestational age. Unlike the Swedish Medical Birth Register, the Stockholm–Gotland Obstetrical database contains weight gain measurements for most women because it contains antenatal clinic data in addition to information from the delivery admission. By modeling early pregnancy BMI and pregnancy weight gain as continuous variables (rather than BMI categories of underweight, normal weight, overweight, and obese and/or weight gain adequacy categories), our analyses reduced the potential for residual confounding. By using the continuous measure of birthweight as our primary outcome, we avoided the reduction in effective sample size to discordant pairs only that occurs when a binary outcome is used. This helped maintain the generalizability of our findings.

The sibling comparison design is dependent on several assumptions.[22] First, the design assumes that there are no carryover effects between pregnancies; i.e., the conditions of the first pregnancy cannot affect the exposure–outcome association in subsequent pregnancies. The findings from our sensitivity analysis to determine whether the weight gain–fetal size association differed between a woman's first and second pregnancy were consistent with the conclusion that any carryover effects were likely negligible. Second, the sibling comparison design only controls for confounding that is invariant between siblings and does not control for factors such as differences in child genotype (including change in paternity), or changes in home environmental, lifestyle, or other factors. As a result, we cannot rule out potential confounding due to these additional factors. Nevertheless, we speculate that variation within women in characteristics such as socioeconomic status, lifestyle, or environmental toxins is likely smaller in magnitude compared with the total variation in these risk factors across a population, resulting in greater internal validity in our approach. This speculation is consistent with previously observed differences in BMI and socioeconomic position between a woman's successive pregnancies versus across populations of pregnant women.[23,24]

We used early pregnancy BMI as a proxy for prepregnancy BMI. Although weight gain in the first trimester is negligible,[1] it is likely that pregnancy weight gain in our cohort was underestimated to a small degree. However, this would have affected both our sibling design and conventional analyses equally, so would be unlikely to have had a meaningful impact on our comparisons of the two approaches. Also, we used a primary outcome of birthweight for sex and gestational age rather than birthweight *z*-score to increase clinical interpretability of our model estimates. However, this approach could have introduced bias if gestational age at delivery is systematically different according to gestation weight gain (as this would be analogous to use a reference chart derived from birthweights rather than estimated fetal weights at preterm ages). As recent estimates suggest that the association between pregnancy weight gain and preterm birth is modest at best,[25] this reduced the likelihood of bias. Our outcomes of small- and large-for-gestational-age birth were not prone to this bias as they were derived using a reference chart derived from intrauterine estimated fetal weights; however, the clinical importance of these outcomes is unclear as a birthweight in the smallest (or largest) 10% of the population may reflect constitutional smallness rather than an underlying pathological process.[26]

Finally, our conclusion that these findings lend support to a causal effect of pregnancy weight gain on fetal growth assumes that the manner in which a woman achieved her total gestational weight gain does not influence its relation with the outcome (fetal size). There are multiple ways to arrive at the same total weight gain: e.g., through different longitudinal weight gain patterns across pregnancy (e.g., steady weight gain throughout, low weight gain in early pregnancy with later catch-up gain), through different distributions of fat mass, fat-free mass, and water, and following different biological mechanisms (e.g., hyperemesis causing low gain vs. dietary restriction). However, the extent to which these differences in how total weight gain was reached translate into different exposure–outcome associations is unclear. Although pregnancy weight gain is used in clinical practice because it is a reliable, inexpensive, and simple monitoring tool, further research using an exposure definition that more closely mirrors a well-defined intervention would be valuable.

## Implications

Our results provide evidence consistent with the hypothesis that pregnancy weight gain has an effect on fetal growth, independent of shared genetic, lifestyle, or environmental factors that remain constant across a woman's pregnancies. The current Institute of Medicine gestational weight gain guidelines were established assuming that fetal size is influenced by pregnancy weight gain, despite the acknowledged absence of clear evidence on causality.[1] Our findings lend support to including fetal size as a consequence of inadequate or excess weight gain when establishing optimal pregnancy weight gain ranges.

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