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Original Contribution

Maternal and Early Childhood Determinants of Women's Body Size in Midlife: Overall Cohort and Sibling Analyses

Wietske A. Ester, Lauren C. Houghton, L. H. Lumey, Karin B. Michels, Hans W. Hoek, Ying Wei, Ezra S. Susser, Barbara A. Cohn, and Mary Beth Terry*

* Correspondence to Dr. Mary Beth Terry, Department of Epidemiology, Mailman School of Public Health, Columbia University, 722 West 168th Street, New York, NY 10032 (e-mail: mt146@columbia.edu).

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Observational evidence suggests that adult body size has its roots earlier in life, yet few life-course studies have data on siblings with which to control for family-level confounding. Using prospective data from the Early Determinants of Mammographic Density Study (n = 1,108; 1959–2008), we examined the association of maternal prepregnancy body mass index (BMI; weight (kg)/height (m)^2), gestational weight gain (GWG), birth size, and childhood growth factors with adult BMI in daughters at midlife using quantile, linear, and logistic regression models. We compared overall cohort findings (n = 1,108) with sibling differences (n = 246 sibling sets). Results derived by all 3 regression methods supported positive and independent associations of prepregnancy BMI, GWG, and percentile change in early childhood growth with BMI in daughters at midlife. Sibling analyses demonstrated that higher GWG was independently related to a higher adult BMI in daughters, particularly for the highest 90th quantile of adult BMI ($\beta = 0.64$ (standard error, 0.26) BMI units). Greater increases in weight percentiles between 1 and 4 years of age within siblings were also associated with higher adult BMI in the 75th quantile ($\beta = 0.06$ (standard error, 0.03) kg). Thus, even after consideration of the role of family-level fixed effects, maternal GWG and childhood weight gain are associated with adult body size in midlife.

body mass index; catch-up growth; gestational weight gain; life course; obesity

Abbreviations: BMI, body mass index; CHDS, Childhood Health and Development Study; CPP, Collaborative Perinatal Project; EDMD, Early Determinants of Mammographic Density; GWG, gestational weight gain; SE, standard error.

Body size in midlife is associated with many chronic conditions, including cardiovascular diseases (1) and cancers (2, 3). Body mass index (BMI; weight (kg)/height (m)^2) has increased dramatically over the past several decades (4–6). For example, 60.7% of US women aged 35–44 years are now overweight (BMI ≥25) or obese (BMI ≥30), as compared with 38.2% in the 1970s (7).

Many studies have demonstrated a positive association between maternal conditions, such as prepregnancy BMI and gestational weight gain (GWG), and offspring BMI across the life course, either at birth (8), in childhood (9), or in early adulthood (8, 10–13). The studies that have collected data on BMI through adulthood suggest that the effects of maternal conditions persist into adulthood, even after childhood growth is considered (9, 14–16). Although the data are now considerable in quantity, a lingering critique is that the associations between maternal factors and offspring BMI in adulthood may be confounded by characteristics shared between mother and child (17). The tracking of BMI across generations in mother-offspring pairs may be explained by shared genetics and a shared social environment (9, 10, 18). Sibling study designs address this legitimate concern by considering shared fixed family factors (19). Thus, unmeasured family-level confounding is reduced with the use of this design. For example, Terry et al. (20) showed that prepregnancy BMI and GWG were associated with childhood BMI at age 7 years in both unrelated persons and related individuals. Specifically, using data from 1,222 same-sex sibling sets, a sibling was more likely to be overweight at age 7 years if the mother's GWG was higher than her GWG with the lighter-weight sibling (20).

GWG is modifiable, as evidenced by the 29% increase in the percentage of US women who gained more than 18 kg during pregnancy between 1990 and 2005 (21). Because GWG has been linked with offspring BMI at earlier stages in the life course, we hypothesized that maternal GWG, independent of childhood growth, would be associated with women's BMI in midlife, both in a birth cohort and in a subcohort of same-sex siblings.

METHODS

Study design and participants

We examined the associations of maternal (prepregnancy BMI, GWG), infant, and childhood factors with body size later in life among 1,108 adult daughters as part of the Early Determinants of Mammographic Density (EDMD) Study (22). The EDMD Study is comprised of subsets of 2 birth cohort studies, the Childhood Health and Development Study (CHDS) (23) and the Collaborative Perinatal Project (CPP) (24). Between 1959 and 1966, the CHDS was conducted in California and the CPP was conducted at a dozen university hospitals across the United States.

We used a subset of the CHDS and CPP data sets (the Boston, Massachusetts, and Providence, Rhode Island, sites—also known as the New England Family Study) based on adult female follow-up eligibility (22). In brief, study criteria for the EDMD Study were: 1) singleton birth, 2) survived to last childhood follow-up, 3) birth size recorded at birth, 4) childhood growth measures for at least 2 time points, 5) third-trimester serum available, and 6) at least 1 sister in the original cohort meeting the same criteria. Based on the EDMD Study criteria, the CPP and CHDS cohorts had 2,423 eligible women and 1,163 sibling sets (22). The sibling sample was extended by an extra sample of women who also met the same 5 inclusion criteria but did not have a sibling who fulfilled these 5 criteria. Thus, 3,256 women in total were eligible for the EDMD Study. Because of resource constraints, we were only able to contact part of the eligible cohort; therefore, we randomly selected 1,925 (59.1%) of the 3,256 eligible women to approach for participation. We successfully traced 1,314 women, of whom 1,134 (86.3%) participated. Tracing rates were higher for the CHDS cohort than for the New England Family Study (CPP) cohort (80.2% vs. 59.1%); however, participation rates were very similar across the CHDS and New England Family Study cohorts once the women were successfully traced (85% and 88%, respectively). Of these women, 1,108 (97.7% of the 1,134 women) who had complete data on adult BMI were included in this study, including 246 sibling sets. The institutional review boards at Columbia University Medical Center, Kaiser Permanente, Brigham and Women's Hospital, and Brown University approved the EDMD Study protocol.

Baseline maternal data

The mothers were enrolled in the cohorts and were followed prospectively throughout pregnancy. At the clinic visits, study staff collected information on prepregnancy BMI, smoking during pregnancy, and maternal education at registration. Information on GWG was abstracted from the records of prenatal visits and was determined as the difference between the last predelivery maternal weight and the first recorded maternal weight (23, 24). At the time of delivery, birth weight and length were measured using standardized scales maintained by the study staff. Gestational age was calculated by subtracting the date of the last menstrual period from the date of delivery.

Childhood growth data

We assessed growth in terms of height and weight measurements taken at 4 months, 1 year, and 4 years of age, because these were the common time points between the 2 cohorts at which children were measured. In the CHDS, serial growth measurements were abstracted from medical records (23). In the CPP, trained clinical staff measured childhood height and weight at 8 months or 12 months of age and at 4 years or 7 years of age (24). Because the actual dates of the clinic visits differed by individual and did not correspond to exactly 4 months, 1 year, and 4 years, we performed interpolations of height and weight measurements using individual cubic interpolation splines (19). Using the interpolated growth variables, we assessed growth in 2 ways. Firstly, standard childhood growth analysis is based on within-cohort percentile changes regarding weight and height between birth and age 4 months, ages 4 months and 1 year, and ages 1 year and 4 years. Secondly, we examined 3 patterns of weight change—rapid, stable, and slow—between birth and 4 years of age, based on the Centers for Disease Control and Prevention's growth chart reference percentiles (5th, 10th, 25th, 50th, 75th, and 95th) (22). We defined rapid weight change as a within-cohort percentile rank increase of at least 2 major reference percentiles of weight from birth to 4 years of age. Stable weight was defined as a rank that remained within 2 major percentiles; these children formed the reference group. We defined slow weight change as a within-cohort percentile rank decrease of at least 2 major percentiles.

Data collected during adult daughter interview

We calculated current BMI from self-reported height and weight, obtained from a telephone interview with daughters carried out when they were adults. A subgroup of the women participating in the EDMD Study ($n = 190$) also participated in the Early Determinants of Adult Health Study, for which adult height and weight were measured clinically (25, 26).

Statistical analysis

Regression models. We used quantile regression (15, 22, 27) to investigate the associations of maternal and childhood factors with different quantiles of adult BMI. Unlike linear regression, which models the mean value, quantile regression assesses the effect of a factor X across the full distribution of another factor Y. We estimated quantile-specific associations at the 10th, 25th, 50th, 75th, and 90th percentiles. We compared

these results with those of linear and logistic regression (with the cutpoint of adult BMI ≥ 25).

Overall cohort. We compared progressive models examining the associations of maternal and child factors with BMI in daughters at midlife by considering the temporal aspect of each construct. For example, first we examined the association of prepregnancy maternal variables (model 1: prepregnancy BMI, race, education, and geographic site) with BMI in daughters. Second, we added pregnancy-specific maternal variables (model 2: model 1 + pregnancy weight gain and smoking) to understand whether the inclusion of these pregnancy-specific variables added to the prediction of the outcome. In a similar manner, we then went on to examine daughter birth measurements (model 3: model 2 + gestational age, birth weight, and birth length) and childhood growth variables (model 4: model 3 + percentile weight and height changes for each of the 3 childhood time periods). Each model was nested within the previous model so we could examine changes in the magnitude of the estimates after incorporating the additional variables for events that occurred later in the life course. We further assessed whether birth order or maternal age added to the overall fit of the final model.

We tested for potential interactions of race and site with prepregnancy BMI and GWG separately by introducing cross-product terms, for a total of 4 tests of interaction. We also tested for interactions between birth weight and childhood growth between birth and age 4 months, ages 4 months and 1 year, and ages 1 year and 4 years.

Sibling analysis. We also used quantile regression to perform sibling analysis to investigate whether associations between maternal and childhood factors remained after consideration of shared familial-level confounders. The exposure and outcome variables for these models were created by subtracting the values of the variables for the lighter adult sibling from those for the heavier adult sibling. For the sibling analyses, we constructed 3 models that were analogous to models 2–4 in the full-cohort analysis. Model A included only GWG, because siblings did not differ according to the other maternal factors. Model B additionally adjusted for birth measurements (model A + gestational age, birth weight, and birth length), and model C additionally adjusted for childhood growth variables (model B + percentile weight changes for each of the 3 childhood time periods and height).

RESULTS

The median prepregnancy BMI and GWG were 22.4 units and 9.3 kg, respectively. Table 1 shows additional descriptive characteristics of the eligible cohort ($n = 1{,}108$) for nonoverweight (BMI <25) and overweight/obese (BMI ≥25) women in midlife. Mothers of overweight/obese women had a 5.5% higher prepregnancy BMI and a 4.8% higher GWG than mothers of nonoverweight women. Gestational lengths were similar between the 2 groups (40 weeks). Overweight/obese women had higher weights and heights than nonoverweight women at ages 1 and 4 years but not between birth and 4 months of age. Table 1 also shows baseline data for the sibling subset. Prepregnancy BMI was highly correlated between siblings ($r = 0.90$), whereas the sibling correlation in GWG was 0.48. The sibling correlations of childhood growth variables ranged from 0.29 to 0.66.

Table 2 shows the associations of maternal, infant, and childhood factors with 3 percentiles (10th, 50th and 90th) of midlife BMI for 4 progressive models (models 1–4; see Methods section). For example, for each unit increase in prepregnancy BMI, the BMI in midlife was 0.20 (standard error (SE), 0.05) units higher at the 10th percentile, 0.47 (SE, 0.06) units higher at the 50th percentile, and 0.59 (SE, 0.17) units higher at the 90th percentile. Within each quantile, the consistency in parameter estimates across the 4 models suggested that prepregnancy BMI remains associated with BMI at midlife in daughters even after adjustment for both infant and childhood growth factors. GWG was associated with BMI in midlife at the 50th percentile in all models. Percentile change in childhood weight but not percentile change in height was also associated with BMI in midlife across all percentiles. Birth weight became associated with BMI in midlife in the 10th and 50th quantiles after addition of childhood growth to the model; however, there were no statistically significant interactions between birth weight and child growth. We tested whether adjusting for other potential covariates affected the point estimates within each percentile. With few exceptions (e.g., maternal age for the 10th quantile and birth order for the 90th quantile), no other covariates changed the estimates for the relationship between GWG and adult BMI by more than 10%.

Table 3 presents results from the full multivariable regression models for the quantile regression model (columns 2–6), the linear regression model (column 7), and the logistic regression model (column 8). Results from all 3 regression methods supported positive, independent associations of prepregnancy BMI, GWG, and percentile change in weight with BMI in midlife for all 3 time periods (birth–age 4 months, ages 4 months–1 year, and ages 1–4 years). The standardized effect sizes from the linear models for prepregnancy BMI, GWG, birth weight, and childhood growth from birth to age 4 months, age 4 months to 1 year, and ages 1 year to 4 years were 8.2, 4.0, 2.1, 4.0, 6.0, and 7.0, respectively.

There were statistically significant interactions between prepregnancy BMI and site (P-interaction = 0.013) and race (P-interaction = 0.006) only in the 75th percentile. When the model for the 75th percentile stratified results by site, the corresponding β coefficients for prepregnancy BMI were 0.31 (SE, 0.11) and 0.68 (SE, 0.14) in the CPP and the CHDS, respectively. When the models for the 75th percentile were stratified by race, the corresponding β coefficients for prepregnancy BMI were 0.35 (SE, 0.09) and 0.59 (SE, 0.31) among white women and black women, respectively. There were no differences in the overall findings for GWG and BMI in midlife across sites or races (data not shown).

The estimates of the association of percentile weight change with midlife BMI for each of the childhood time periods were similar in magnitude, so we further examined whether these estimates differed when accounting for pattern of weight change from birth to age 4 years (Table 3). Results from all 3 regression models (quantile, linear, and logistic)

Table 1. Characteristics of Participants in the Early Determinants of Mammographic Density Study From Prepregnancy in Mothers to Midlife in Offspring, 1959–2008

Characteristic	Daughter's BMI[a] in Midlife (Age 40 Years)					Sibling Study					
	BMI <25 (n = 486)		BMI ≥25 (n = 622)		*P* Value[b]	Lighter Adult Sibling (n = 246)		Heavier Adult Sibling (n = 246)		r[c]	*P* Value
	Median (IQR)	%	Median (IQR)	%		Median (IQR)	%	Median (IQR)	%		
Maternal factors											
Prepregnancy BMI	21.75 (3.32)		23.02 (4.92)		<0.001	22.13 (3.63)		21.95 (3.77)		0.90	0.15
Gestational weight gain, kg	9.07 (4.54)		9.53 (4.54)		0.02	8.57 (4.15)		9.19 (4.00)		0.48	0.01
Smoking during pregnancy		39		42	0.26		41		44	0.71	0.40
Infant characteristics											
Gestational age, weeks	40 (2)		40 (2)		0.63	40 (2)		40 (2)		0.22	0.17
Birth weight, g	3,430 (766)		3,459 (822)		0.39	3.29 (0.57)		3.26 (0.57)		0.48	0.29
Birth length, cm	51.00 (3.81)		51.00 (3.81)		0.79	50.80 (2.54)		50.80 (3.07)		0.29	0.90
Childhood growth											
Weight, g											
At age 4 months	6,413 (999)		6,430 (1,070)		0.23	6,268 (988)		6,190 (913)		0.49	0.09
At age 1 year	9,531 (1,536)		9,752 (1,620)		<0.01	9,503 (1,598)		9,429 (1,559)		0.47	0.67
At age 4 years	15,884 (2,556)		16,830 (2,839)		<0.0001	15,843 (2,576)		16,278 (2,669)		0.58	0.09
Height, m											
At age 4 months	62.39 (3.37)		62.38 (3.51)		0.68	61.78 (3.28)		61.63 (2.96)		0.38	0.71
At age 1 year	73.60 (3.58)		74.19 (4.22)		0.01	73.51 (3.85)		73.81 (3.46)		0.44	0.81
At age 4 years	99.58 (6.57)		101.00 (6.00)		<0.001	100.06 (6.31)		99.67 (6.90)		0.66	0.65
Demographic characteristics											
Race/ethnicity (black or other)		12		21	<0.001						
Maternal education (less than high school)		20		29	<0.001						
Geographic site (Boston, Massachusetts)		50		50	0.81						
Midlife characteristics											
Age at follow-up, years	44 (2.7)		44.2 (2.5)		0.28	44 (2.8)		43.9 (2.9)		0.16	0.71
Mean BMI at follow-up	22.1 (3.0)		29.6 (7.0)		<0.001	23.6 (5.8)		28.8 (8.6)		0.67	<0.001
Daughter's education (high school diploma or less)		14		23	<0.001		16		15	0.27	0.68
Daughter's parity (parous)		86		88	0.31		88		85	0.15	0.12

Abbreviations: BMI, body mass index; IQR, interquartile range.
[a] Weight (kg)/height (m)^2.
[b] Midlife BMI groups were compared using the Kruskal-Wallis test.
[c] Pearson correlation coefficient, except for ranked variables, for which the Spearman correlation coefficient is presented.

demonstrated positive associations between rapid childhood growth and BMI in midlife. For example, rapid weight change (catch-up growth) from birth to age 4 years was associated with an increase in BMI of 1.7–3 units across percentiles (last row in Table 3) and a nearly 2-fold increase in the probability of being overweight in midlife (odds ratio = 1.87, 95% confidence interval: 1.20, 2.92), relative to stable growth.

In a series of sensitivity analyses, the results shown in Table 3 did not differ in mothers with and without sibling pairs, in daughters who were and were not firstborn, and in daughters who were nulliparous or parous.

Table 4 presents the results from the sibling analyses. Given the high correlation of maternal prepregnancy BMI between siblings (see Table 1), we limited the sibling analysis to associations of GWG and childhood growth differences with BMI in midlife. The unadjusted parameter estimates for GWG ranged from 0.06 (SE, 0.05) in the 10th percentile and 0.08 (SE, 0.06) in the 50th percentile to 0.65 (SE, 0.27) in the 90th percentile. Additional adjustment for infant weight characteristics (model B) did not affect the association between GWG and the difference in midlife BMI among siblings in the 90th percentile (β = 0.64 (SE, 0.26).

Table 2. Associations of Maternal, Infant, and Childhood Growth Factors With Offspring Body Mass Index in Midlife (β (Standard Error)) in the Early Determinants of Mammographic Density Study (Quantile Regression), 1959–2008

Variable	Change in Daughter's BMI[a] in Midlife (Age 40 Years)											
	10th Percentile				50th Percentile				90th Percentile			
	Model 1[b]	Model 2[c]	Model 3[d]	Model 4[e]	Model 1	Model 2	Model 3	Model 4	Model 1	Model 2	Model 3	Model 4
Maternal factors												
Prepregnancy BMI	0.20 (0.05)[f]	0.22 (0.06)[f]	0.20 (0.06)[f]	0.21 (0.08)[f]	0.47 (0.06)[f]	0.51 (0.06)[f]	0.52 (0.07)[f]	0.45 (0.08)[f]	0.59 (0.17)[f]	0.47 (0.15)[f]	0.47 (0.20)[f]	0.40 (0.15)[f]
Maternal weight gain, kg		0.09 (0.04)	0.06 (0.04)[f]	0.09 (0.04)		0.22 (0.07)[f]	0.26 (0.07)[f]	0.24 (0.04)[f]		0.34 (0.14)[f]	0.32 (0.14)[f]	0.22 (0.15)
Maternal smoking, ever vs. never		0.16 (0.33)	0.15 (0.38)	0.16 (0.52)		0.51 (0.37)	0.43 (0.33)	−0.02 (0.34)		2.57 (1.09)[f]	2.09 (1.02)	1.61 (1.73)
Infant characteristics												
Birth weight, kg			0.66 (0.33)[f]	1.77 (0.64)[f]			−0.26 (0.54)	1.49 (0.83)[f]			−1.35 (0.90)	1.05 (1.32)
Birth length, cm			0.01 (0.07)	−0.11 (0.15)			−0.06 (0.09)	−0.21 (0.17)			0.15 (0.24)	−0.12 (0.29)
Gestational age, weeks			0.07 (0.10)	0.07 (0.13)			−0.06 (0.11)	−0.03 (0.12)			0.06 (0.16)	0.11 (0.24)
Childhood growth												
Weight percentile change												
Birth–age 4 months				0.03 (0.01)[f]				0.04 (0.01)[f]				0.07 (0.03)[f]
Ages 4 months–1 year				0.03 (0.01)[f]				0.06 (0.02)[f]				0.09 (0.04)[f]
Ages 1 year–4 years				0.04 (0.01)[f]				0.06 (0.01)[f]				0.12 (0.04)[f]
Height percentile change												
Birth–age 4 months				−0.01 (0.01)				−0.02 (0.01)				−0.04 (0.03)
Ages 4 months–1 year				0.00 (0.01)				−0.02 (0.01)				−0.03 (0.03)
Ages 1 year–4 years				−0.02 (0.01)[f]				−0.02 (0.02)				−0.05 (0.04)

Abbreviation: BMI, body mass index.
[a] Weight (kg)/height $(m)^2$.
[b] Model 1: prepregnancy BMI, geographic site, race, and maternal education ($n = 1,030$).
[c] Model 2: model 1 + pregnancy weight gain and smoking ($n = 993$).
[d] Model 3: model 2 + gestational age, birth weight, and birth length ($n = 986$).
[e] Model 4: model 3 + percentile weight and height changes for each of the 3 childhood time periods ($n = 929$).
[f] $P < 0.05$.

Further adjustment for childhood growth, including height (model C), reduced some of the association between GWG and midlife BMI in the 90th percentile ($\beta = 0.50$ (SE, 0.30)).

Differences in childhood growth in weight were also associated with differences in midlife BMI between siblings. For example, for each increment of change in weight percentile between 1 and 4 years of age, the midlife BMI of the heavier sibling was 0.03 units higher in the 50th percentile, 0.06 units higher in the 75th percentile, and 0.09 units higher in the 90th percentile, compared with the lighter sibling.

DISCUSSION

In our overall cohort and sibling analyses, we observed that higher GWG was independently associated with BMI in daughters at midlife. This suggests that GWG remains related to the next generation's BMI in adulthood even after accounting for shared family factors, which might include diet and exercise.

Few studies have used a sibling design to address this question, and those that have done so have not followed body size to midlife. For example, investigators in 3 cohort studies evaluated GWG and birth outcomes (28, 29), one at either 4 years (30), 7 years (22), or 18 years (11, 31) of age. These studies had findings that were mostly consistent with our results in that GWG was associated with higher body size in offspring, except for the study by Branum et al. (30). In their CPP subsample of 2,758 sibling groups, GWG and prepregnancy BMI were associated with offspring BMI at age 4 years, but the association was not seen between siblings (30). In contrast, in another CPP subsample of 1,222 sibling groups, Terry et al. (20) found that GWG was independently associated with BMI at age 7 years. The 2 CPP studies focused on outcomes at different ages, one after the adiposity rebound, but the other likely reason for the difference lies in how the authors modeled BMI: Branum et al. (30) studied the mean BMIs of siblings, whereas Terry et al. (20) examined quantiles of BMI. Similarly to the latter study, our study demonstrates that higher GWG has the strongest association with offspring BMI in the higher quantiles. Stronger associations between risk factors and the upper percentiles of BMI may mean that these risk factors are associated with differences in fat mass as opposed to lean body mass.

Our consistent findings between the overall cohort and the sibling subcohort suggest that there may have been minimal family-level confounding in previous nonsibling studies that demonstrated a positive association between GWG and offspring BMI (32–34). Both sibling and overall cohort analyses supported the hypothesis that higher GWG is associated with BMI in daughters at midlife; as in the full cohort, the sibling analyses demonstrated that increases in childhood growth between birth and 4 years of age were also strongly and independently associated with a higher BMI at midlife. The association between GWG and BMI in midlife diminished when childhood changes in weight were added to the model. In another prospectively followed growth cohort born during a time period similar to ours, Rooney et al. (33) found that greater GWG was associated with an increased BMI from childhood through adulthood and that approximately 50% of the association with adult BMI was mediated by birth weight and childhood BMI. The extent of attenuation was less in our sibling study, suggesting that the role of childhood adiposity in midlife BMI is not due to family-level confounding.

In addition to GWG and childhood growth, prepregnancy BMI and birth weight were also associated with BMI in daughters at midlife, with corresponding standardized effect sizes being stronger for prepregnancy BMI and weaker for birth weight in the full cohort. Our finding that prepregnancy BMI was positively associated with offspring adiposity in midlife is in accordance with the findings of other investigators who studied offspring BMI during the second, third, and fourth decades of life (13, 14). The quantile regression analyses highlighted the observation that this association strengthens across the distribution of BMIs in midlife. We did not observe a U-shaped association between GWG and BMI in daughters, unlike Michels et al. (32) in their study. While the adjusted relationship between GWG and BMI in daughters was U-shaped, once we adjusted for prepregnancy BMI, the association was linear. Given the high correlation between siblings, we could not directly assess the association between prepregnancy BMI and sibling differences in BMI, but the persisting relationship between GWG in siblings with similar maternal prepregnancy BMIs suggests that GWG is independently associated with BMI in midlife.

Accumulating data from animal and human studies have led to intriguing hypotheses related to potential mechanisms linking altered fetal development to metabolic diseases and weight increases, particularly in women (35–37), including insulin resistance, leptin insensitivity, and epigenetic changes (38, 39). Insulin resistance is a causal factor for maternal hyperglycemia, inducing fetal hyperinsulinemia, which has persistent effects on insulin sensitivity in childhood (40, 41). Leptin is an anorexigenic hormone secreted by adipose tissue and the placenta, but its main function is in the hypothalamus, decreasing appetite and food intake (42). Heinsbroek and van Dijk (43) showed in rats that brain melanocortin receptor blockade during pregnancy induced GWG and increased the body weight of offspring postnatally; the melanocortin receptor blockade can alter leptin and anorexigenic effects in rats, leading to postnatal obesity (44). In addition to rat models, a mouse model has supported the hypothesis that a high-fat diet in obese female mice can alter both adiposity and DNA hypomethylation of inflammation-associated genes in offspring (45). These animal studies support our findings that GWG and maternal obesity can lead to a higher offspring weight.

The main strength of this study was the prospective assessment of pregnancy characteristics and offspring size among siblings, which made it possible to evaluate the association of GWG and childhood growth with offspring BMI while controlling for unmeasured stable maternal or family traits. The distribution of prepregnancy BMI and GWG in our study, however, reflects a much leaner population than the current population. The overall sample size was adequate, but by definition the sample was much smaller than those in the 2 main cohort studies (the CHDS and CPP) from which our population was drawn. Selection bias is a

Table 3. Relationship of Maternal and Child Growth Factors to Offspring Body Mass Index in Midlife in 3 Regression Models (Quantile, Linear, and Logistic Regression) in the Early Determinants of Mammographic Density Study ($n = 929$), 1959–2008

Variable	Change in Daughter's BMI[a] in Midlife (Age 40 Years)							
	Quantile Regression (β (SE))					Linear Regression (β (SE))	Logistic Regression for BMI <25 vs. BMI ≥25	
	10th Percentile	25th Percentile	50th Percentile	75th Percentile	90th Percentile		OR	95% CI
Maternal factors								
Prepregnancy BMI	0.21 (0.07)[b]	0.36 (0.06)[b]	0.45 (0.06)[b]	0.51 (0.09)[b]	0.40 (0.16)[b]	0.41 (0.05)[b]	1.15[b]	1.10, 1.20
Maternal weight gain, kg	0.09 (0.05)	0.15 (0.05)[b]	0.24 (0.05)[b]	0.29 (0.07)[b]	0.22 (0.17)	0.20 (0.05)[b]	1.08[b]	1.04, 1.12
Maternal smoking (ever/never)	0.16 (0.31)	−0.01 (0.38)	−0.02 (0.47)	0.67 (0.72)	1.61 (0.79)[b]	0.50 (0.43)	1.08	0.79, 1.47
Infant characteristics[c]								
Birth weight, kg	1.77 (0.55)[b]	1.02 (0.71)[b]	1.49 (0.75)[b]	1.23 (1.14)	1.05 (1.84)	1.39 (0.65)[b]	1.63[b]	1.02, 2.61
Birth length, cm	−0.11 (0.13)	−0.11 (0.12)	−0.21 (0.11)	−0.27 (0.17)	−0.12 (0.35)	−0.20 (0.12)	0.95	0.88, 1.04
Gestational age, weeks	0.07 (0.14)	0.01 (0.09)	−0.03 (0.09)	0.06 (0.18)	0.11 (0.28)	−0.03 (0.11)	1.01[b]	0.94, 1.10
Childhood growth								
Weight percentile change[c]								
Ages birth–4 months	0.03 (0.01)[b]	0.03 (0.01)[b]	0.04 (0.01)[b]	0.06 (0.02)[b]	0.07 (0.03)[b]	0.04 (0.01)[b]	1.01[b]	1.00, 1.02
Ages 4 months–1 year	0.03 (0.01)[b]	0.03 (0.01)[b]	0.06 (0.01)[b]	0.09 (0.02)[b]	0.09 (0.04)[b]	0.06 (0.01)[b]	1.02[b]	1.01, 1.03
Ages 1 year–4 years	0.04 (0.01)[b]	0.05 (0.01)[b]	0.06 (0.01)[b]	0.08 (0.02)[b]	0.12 (0.03)[b]	0.07 (0.01)[b]	1.02[b]	1.01, 1.03
Height percentile change[c]								
Ages birth–4 months	−0.01 (0.01)	−0.01 (0.01)	−0.02 (0.02)	−0.04 (0.01)[b]	−0.04 (0.03)	−0.02 (0.01)	1.00	0.99, 1.01
Ages 4 months–1 year	0.00 (0.01)	−0.01 (0.01)	−0.02 (0.02)	−0.04 (0.02)[b]	−0.03 (0.04)	−0.02 (0.01)	1.00	0.99, 1.01
Ages 1 year–4 years	−0.02 (0.01)[b]	−0.02 (0.01)	−0.02 (0.02)[b]	−0.05 (0.02)[b]	−0.05 (0.04)	−0.04 (0.01)[b]	0.99	0.99, 1.00
Pattern of weight change relative to stable weight[d,e]								
Slow (catch-down)	−0.33 (0.57)	−0.45 (0.48)	−1.77 (0.60)[b]	−1.51 (0.96)	−4.00 (1.49)[b]	−1.65 (0.59)[b]	0.73	0.49, 1.11
Rapid (catch-up)	1.73 (0.46)[b]	2.20 (0.50)[b]	2.14 (0.76)[b]	2.96 (1.06)[b]	1.12 (1.99)	2.36 (0.61)[b]	1.87[b]	1.20, 2.92

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio; SE, standard error.

[a] Weight (kg)/height $(m)^2$.

[b] $P < 0.05$.

[c] The model adjusted for all maternal, birth, and weight/height percentile change variables listed in the table in addition to geographic site, race, and mother's education.

[d] The model adjusted for all maternal, birth, and height variables listed in the table in addition to geographic site, race, and mother's education.

[e] Pattern of weight change: slow = decreasing 2 major percentiles from birth to age 4 years; stable = staying within 2 major percentiles from birth to age 4 years; rapid = increasing 2 major percentiles from birth to age 4 years.

Table 4. Relationship of Maternal Factors to Adult Body Mass Index Differences Between Sibling Pairs in the Early Determinants of Mammographic Density Study (Sibling Analysis Using Quantile Regression), 1959–2008

Model and Variable	Difference[a] Between Sibling BMIs[b] in Midlife (Age 40 Years)					
	Quantile Regression (β (SE))					Linear Regression (β (SE))
	10th Percentile	25th Percentile	50th Percentile	75th Percentile	90th Percentile	
Model A[c]						
Gestational weight gain, kg	0.06 (0.05)	0.04 (0.07)	0.08 (0.06)	0.27 (0.30)	0.65 (0.27)[d]	0.21 (0.09)[d]
Model B[e]						
Gestational weight gain, kg	0.07 (0.04)[d]	0.04 (0.08)	0.09 (0.07)	0.30 (0.25)	0.64 (0.26)[d]	0.22 (0.10)[d]
Birth weight, kg	0.42 (0.45)	−0.15 (0.50)	0.80 (0.76)	3.21 (1.46)[d]	3.17 (2.59)	1.09 (0.90)
Gestational age, weeks	−0.06 (0.04)	−0.01 (0.10)	−0.12 (0.14)	0.08 (0.16)	0.08 (0.58)	−0.11 (0.16)
Birth length, cm	−0.07 (0.05)	−0.10 (0.09)	−0.15 (0.08)	−0.29 (0.21)	−0.06 (0.44)	−0.12 (0.13)
Model C[f]						
Gestational weight gain, kg	0.09 (0.05)	0.08 (0.05)	0.06 (0.10)	0.12 (0.15)	0.50 (0.30)	0.20 (0.10)[d]
Birth weight, kg	0.21 (0.92)	0.56 (0.77)	1.81 (0.79)[d]	4.04 (1.92)[d]	9.41 (1.67)[d]	3.17 (1.09)[d]
Gestational age, weeks	−0.06 (0.09)	0.03 (0.13)	−0.07 (0.13)	0.12 (0.27)	−0.06 (0.44)	−0.13 (0.16)
Birth length, cm	−0.05 (0.09)	−0.16 (0.10)	−0.33 (0.12)[d]	−0.42 (0.26)	−0.62 (0.50)	−0.35 (0.16)[d]
Weight percentile change						
Ages birth–4 months	−0.01 (0.01)	0.02 (0.01)	0.04 (0.01)[d]	0.08 (0.02)[d]	0.10 (0.03)[d]	0.05 (0.02)[d]
Ages 4 months–1 year	0.00 (0.02)	0.04 (0.01)[d]	0.06 (0.02)[d]	0.07 (0.02)[d]	0.07 (0.04)	0.06 (0.02)[d]
Ages 1 year–4 years	−0.01 (0.01)	0.02 (0.01)	0.03 (0.02)	0.06 (0.03)[d]	0.09 (0.05)	0.04 (0.02)[d]
Height percentile change						
Ages birth–4 months	0.00 (0.01)	0.00 (0.01)	−0.01 (0.01)	−0.03 (0.03)	−0.03 (0.03)	−0.02 (0.02)
Ages 4 months–1 year	0.00 (0.01)	−0.02 (0.01)	−0.04 (0.02)[d]	−0.04 (0.02)	−0.03 (0.04)	−0.04 (0.02)[d]
Ages 1 year–4 years	0.00 (0.01)	0.01 (0.01)	−0.03 (0.02)	−0.04 (0.03)	−0.03 (0.04)	−0.03 (0.02)

Abbreviations: BMI, body mass index; SE, standard error.

[a] Differences were derived by subtracting the value for the sibling who was lighter in adulthood from the value for the sibling who was heavier in adulthood.

[b] Weight (kg)/height $(m)^2$.

[c] Model A was the model with no adjustment ($n = 246$).

[d] $P < 0.05$.

[e] Model B adjusted for both pregnancy and the infant characteristics listed in the table ($n = 241$).

[f] Model C adjusted for all of the variables listed and childhood height variables ($n = 223$).

possibility; however, the characteristics of mothers in the EDMD cohort were comparable to US national data on women in the 1960s (46, 47). Nevertheless, the findings may not be generalizable to other populations. Although we relied on self-reported BMI in midlife, there was similar interobserver agreement between self-reported and clinical measures of obesity in the Early Determinants of Adult Health Study subset of participants (agreement = 90.5%; $\kappa = 0.81$ (SE, 0.07)). Interrater reliability was similar among women of different birth weights and prepregnancy BMIs, suggesting that there were no systematic differences in self-reporting of BMI. Interrater reliability was even stronger within siblings, supporting the conclusion that the overall inferences were not driven by self-reported body size.

The overall consistency in our findings across statistical models and between cohort and sibling analyses suggests that maternal GWG and childhood growth are independently associated with body size in women at midlife. Because maternal prepregnancy BMI, GWG, and childhood obesity rates are increasing, these findings suggest that maintaining a healthy BMI across the life course is important for reducing the risk of obesity in both mothers and the next generation.

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Author affiliations: Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, New York (Wietske A. Ester, Lauren C. Houghton, L. H. Lumey, Hans W. Hoek, Ezra S. Susser, Mary Beth Terry); Parnassia Psychiatric Institute, the Hague, the Netherlands (Wietske A. Ester, Hans W. Hoek); Herbert Irving Comprehensive Cancer Center, Columbia Medical Center, New York, New York (L. H. Lumey, Mary Beth Terry); Department of Epidemiology, Fielding School of Public Health, University of California, Los Angeles, Los

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