Published in final edited form as:

Paediatr Perinat Epidemiol. 2009 May ; 23(3): 207–215. doi:10.1111/j.1365-3016.2009.01029.x.

Prepregnancy body mass index change between pregnancies and preterm birth in the following pregnancy

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Summary

Maternal prepregnancy body mass index (BMI) may affect the risk of preterm birth. However, it is unclear how changes in BMI between pregnancies modify the risk of preterm birth in the following pregnancy. We studied this effect in the Collaborative Perinatal Project, when obesity was uncommon and the prevalence of labor induction was low. This analysis included 1,892 nulliparous women whose first enrolled (index) pregnancy was a singleton live birth and the second enrolled (outcome) pregnancy was a consecutive singleton pregnancy (both pregnancy within 20–51 weeks of gestation). We used Cox regression model to calculate the hazard ratio (HR) of preterm birth at the outcome pregnancy as a function of reduced BMI (<25th percentile of change) and increased BMI (>75th percentile), compared to stable BMI (25th–75th percentile), adjusted for prepregnancy BMI at the index pregnancy and other covariates. BMI reduction was associated with a non-significant increased risk of preterm birth, adjusted HR 1.17 (95% confidence interval 0.90–1.53); BMI increase had effects close to null (adjusted HR 1.08 [0.83–1.41]). In the model with linear BMI change, each 1 kg/m² increase was associated with an HR of 0.96 (0.89–1.03). The estimates associated with a BMI reduction were higher in women whose index pregnancy ended preterm (HR 1.49 [0.90–2.44]) and in those with BMI <25 kg/m² at the index pregnancy (HR 1.30 [0.98–1.71]). This study involved mainly low-to-normal weight women with spontaneous deliveries, and might suffer from type II error due to small sample size. The effect of BMI change in overweight and obese women needs to be studied using contemporary data.

Preterm birth currently occurs in about 13% of U.S. live births, one of the highest rates in developed countries.¹ Preterm birth is one of the leading causes of infant death.¹ As yet, only a few modifiable risk factors or effective interventions have been identified to prevent preterm birth.^{2–4} Earlier reports suggest that underweight women have a higher risk of preterm birth,^{5–7} while obese women may have a lower risk.⁸ Recent findings, however, suggest higher risk of medically indicated preterm birth among obese women,^{9, 10} likely due to a higher incidence of pregnancy complications, such as preeclampsia or macrosomia. For spontaneous preterm birth, however, the highest risks are seen among underweight women.^{8, 9} Since body mass index (BMI) may either be a cause of preterm birth in itself or a correlate of other causes, it is of interest to assess whether a change in prepregnancy BMI modifies the risk of preterm birth

in the following pregnancy. An exploratory study by Merlino and colleagues reported that a prepregnancy BMI decrease of 5 kg/m² or more was associated with higher risk of recurrent preterm birth in women with previous preterm birth.¹¹ However, only 5 women with a previous preterm birth had such an extreme BMI change. Therefore, it is worth exploring whether less extreme changes in BMI can modify the risk of preterm birth. This effect, if it exists, may depend on the woman's BMI prior to the previous pregnancy and the type of preterm birth (spontaneous or indicated). BMI change pattern may differ by parity and age. We studied this association among nulliparous women with two consecutive singleton pregnancies enrolled in the Collaborative Perinatal Project (CPP). The CPP was conducted in 1959-1966 in the U.S., when obesity was less common than at present and induced preterm birth was uncommon.

Methods

The CPP was a prospective pregnancy cohort of 58,760 pregnancies in 48,197 women, with 8,347 women contributing two or more pregnancies during the study period. Women were enrolled in 12 U.S. academic medical centers during pregnancy (median gestational week 21, interquartile range 15-28 weeks) and were followed through delivery, while their children were followed up to 8 years of age.^{12, 13}

Following the steps illustrated in figure 1, we retained for this analysis 1,892 nulliparous women whose first enrolled pregnancy (index pregnancy) was a singleton live birth and the second enrolled pregnancy (outcome pregnancy) was a singleton pregnancy consecutive to the index pregnancy. Additional requirements included that gestational age within 20-51 weeks (to allow for some error in reporting long gestational duration in babies who were likely born at term), prepregnancy BMI within 15-45 kg/m², and prepregnancy BMI change (BMI at outcome pregnancy minus that at index pregnancy) within -5 to 5 kg/m² (as such large differences were likely to have resulted from errors in reporting height or weight).

Prepregnancy weight and height were self-reported and recorded during the initial prenatal examination after enrollment. We calculated pre-pregnancy BMI as weight in kilograms divided by the squared height in meters (kg/m²). We categorized prepregnancy BMI as underweight (< 18.5 kg/m²), normal weight (18.5-24.9 kg/m²), overweight (25-29.9 kg/m²), and obese (≥ 30 kg/m²).^{14, 15} We categorized prepregnancy BMI change into three groups by interquartile range: BMI decrease (<25th percentile, i.e., <-0.32 kg/m²), stable BMI (25th to 75th percentile, -0.32 to 1.48 kg/m²), BMI increase (>75th percentile, >1.48 kg/m²).

Gestational length was estimated from the last menstrual period, and preterm birth was defined as a gestational age of less than 37 completed weeks. We treated the data as a prospective analysis of 1,892 women with a singleton live birth in the index pregnancy to study preterm birth rate in the consecutive outcome pregnancy. Since some outcome pregnancies ended in abortions and stillbirths (fetal deaths before and after 20 weeks of gestation, respectively), we used a Cox proportional hazard model with staggered entry (based on gestational age at recruitment) to calculate the hazard ratio of preterm birth while taking into consideration these competing risks.¹⁶ Censoring occurred at 37 completed weeks of gestation (259 days), as no women were at risk of preterm birth thereafter.

We first estimated the risk of preterm birth in the outcome pregnancy as a function of prepregnancy BMI in that pregnancy. Next, we performed the main analysis to estimate the effect of prepregnancy BMI in the index pregnancy and the effect of changes in BMI in one regression model. To test for a trend in the effect of prepregnancy BMI change, we entered a linear term of BMI change in the regression model, instead of categories. We additionally used penalized splines for BMI change in the Cox model to explore possible non-linear effect.¹⁷ Finally, we stratified the main analysis by whether the index pregnancy had ended in preterm

or term birth, since women with a previous preterm birth have about a threefold risk of recurrence in the following pregnancy compared to women whose previous birth ended at term.¹⁸⁻²⁰ We tested the interaction separately between BMI change and prepregnancy BMI at the index pregnancy (<25 or ≥ 25 kg/m²), age at index pregnancy (<20 or ≥ 20 years), race (White or African American), smoking at index pregnancy (yes or no), interpregnancy interval (time between birth of the index child and last menstrual period of the outcome pregnancy, <12 months or ≥ 12 months), by entering both the main effect and the interaction terms in the regression models.

As secondary analyses, we explored whether more refined samples resulted in different estimates associated with BMI change. Preterm birth was defined based on last menstrual period, and there were some implausibly high birth weights for gestational age,^{21, 22} which could have biased the estimation of preterm birth rate. We therefore excluded 74 live born babies (preterm and term) whose sex- and gestational-age-specific birthweight in the outcome pregnancy was greater than the 99th percentile of a standardized fetal growth reference (with particularly accurate assessment of gestational age)²³. Women with very short interpregnancy intervals (<4 months) may have more weight retention from prior pregnancy, and have higher risk of preterm birth.²⁴⁻²⁶ We thus excluded 416 women with interpregnancy interval <4 months in a separate analysis. In this study, spontaneous labor was predominant (about 90%), but we nonetheless performed an analysis examining change in pre-pregnancy BMI restricted to the 1,670 women with known spontaneous labor in the outcome pregnancy. We additionally restricted the analysis to 1,842 women whose index baby did not die in infancy, to reduce the potential effect of a dying infant on both maternal BMI status and duration of the interpregnancy interval.

We included in the model the following covariates for the outcome pregnancy, chosen *a priori* as potential determinants of both BMI status and preterm delivery (categorized as in Table 1): maternal age, race, maternal smoking during pregnancy, socioeconomic index (a composite index for education, occupation, and family income with low values indicating low socioeconomic index),²⁷ marital status, and interpregnancy interval. In addition, we adjusted for study center (Baltimore, Boston, Buffalo, Memphis, Minneapolis, New Orleans, New York Columbia, New York Metropolitan, Philadelphia, Portland, Providence, and Richmond). In a secondary analysis, we considered the potential interaction between prepregnancy BMI change and weekly pregnancy weight gain during the outcome pregnancy. However, additional adjustment for weekly pregnancy weight gain did not markedly change the estimates of BMI change, and will thus not be mentioned further. We used SAS 9.1 (SAS Institute Inc. Cary, NC) and R 2.4.0 (www.r-project.org) for statistical analysis and graphing.

Results

Among the 1,892 index pregnancies, 265 (14%) ended before the completion of the 37th week. Among the outcome pregnancies, 345 (18%) ended in a preterm birth, 1,476 in a term birth, and 71 ended in other outcomes (47 abortions, 12 stillbirths, and 12 live births with a gestational age outside the 20-51 weeks range). Women with preterm birth in the index pregnancy had a risk of preterm birth that was three times that of women whose index pregnancy ended at term (41% vs. 14%). The proportion of preterm births in the outcome pregnancy is shown in Table 1 as a function of various maternal characteristics specific to the pregnancy. The mean age of the 1,892 women in this study was 19.8 (standard deviation [SD] 3.7) years and 21.5 (SD 3.8) years for the index and outcome pregnancy, respectively. Being young, of non-White race, of low socioeconomic status, unmarried, and having had a short interpregnancy interval was associated with a higher risk of preterm birth.

The mean prepregnancy BMI at the index pregnancy was 21.5 kg/m² (SD 3.0 kg/m²). The mean prepregnancy BMI change was 0.57 kg/m² (SD 1.53 kg/m², median 0.47 kg/m², interquartile range -0.32 to 1.48 kg/m²). Change in BMI did not differ significantly as a function of whether the index pregnancy ended preterm or term (mean: 0.60 vs. 0.56 kg/m², median: 0.55 vs. 0.40 kg/m²). The mean, standard deviation, and median BMI change by maternal characteristics for the first enrolled pregnancy are shown in Table 2.

Table 3 reports the rates and adjusted hazard ratios (with 95% confidence intervals) of preterm birth in the outcome pregnancy as a function of prepregnancy BMI at the outcome pregnancy. Compared with normal weight women, women who were overweight or obese before the outcome pregnancy had a slightly decreased risk of preterm birth. In the model including prepregnancy BMI at index pregnancy and change in BMI between pregnancies, a reduction in prepregnancy BMI between pregnancies was associated with slightly increased risk of preterm birth in the outcome pregnancy, while a prepregnancy BMI increase yielded a hazard ratio close to one (Table 3). The unadjusted model, including BMI change and prepregnancy BMI at index pregnancy and no other covariates, produced estimates similar to those in Table 3 (data not shown). Including the actual BMI change as a linear term in a Cox model adjusted for prepregnancy BMI at index pregnancy and other covariates suggested that each 1 kg/m² increase in prepregnancy BMI was associated with a reduced risk of preterm birth (HR 0.96 [95% CI: 0.89-1.03]). Using penalized splines (with 3 degrees of freedom) for BMI change in the Cox model also indicated non-significant linear association when the BMI change was within -2 to 3 kg/m², while estimation was very imprecise outside this range due to much fewer subjects (Figure 2).

A reduction in BMI was associated with higher risk of preterm birth if the index pregnancy had also been a preterm birth (Table 4). Only the interaction between BMI change and prepregnancy BMI at the index pregnancy was significant ($p < 0.1$). However, the number of women with prepregnancy BMI ≥ 25 kg/m² was very small ($n = 189$). Among women with prepregnancy BMI < 25 kg/m² at the index pregnancy, the hazard ratio of BMI decrease was 1.30 (95% CI 0.98-1.71) (Table 4).

Excluding babies with implausible birth weight by sex and gestational age yielded similar estimates, while the result after excluding women with very short interpregnancy interval were close to null (Table 4). The estimate of each 1 kg/m² BMI change in linear term after either exclusion, however, was similar to the analysis including these women (0.96 [0.89-1.04]). Restricting the analysis to women with spontaneous labor at the outcome pregnancy or to women whose previous baby survived infancy did not result in markedly changed estimates (Table 4).

Discussion

In this analysis we saw that a decrease in self-reported prepregnancy BMI between pregnancies might be associated with a slightly increased risk of preterm birth, especially among women who had a prior preterm birth or had a prepregnancy BMI < 25 kg/m² at the index pregnancy. The study findings are likely to apply to spontaneous preterm birth, which was predominant in the 1960s when the cohort was enrolled.¹²

The effect of prepregnancy BMI change on preterm birth in the following pregnancy has not previously been explored in detail. Merlino et al. reported effects of BMI change over 5 kg/m² or BMI category change (i.e., from normal weight in the index pregnancy to underweight in the outcome pregnancy);¹¹ however, a change in BMI of over 5 kg/m² between pregnancies (i.e., 13.6 kg for a woman with a height of 1.65 m) would be uncommon in the general population.²⁸ BMI category change was not as rare but still requires a large sample size to be

properly studied. Furthermore, increases in a given number of BMI units may or may not result in a change in BMI category (i.e., 21 to 23 kg/m² vs. 24 to 26 kg/m²). Therefore, we did not attempt to reproduce Merlino and colleagues' findings in the main analysis. In an exploratory analysis that included 45 women with BMI decrease or increase over 5 units, the hazard ratio of preterm birth was virtually the same in women with BMI decrease or increase compared to women with stable BMI (data not shown). In addition, Merlino and colleagues did not adjust for prepregnancy BMI at the index pregnancy (which may affect both BMI change and the risk of preterm birth), or for other covariates.¹¹ Recently, studies on BMI change that examined preeclampsia, gestational hypertension, gestational diabetes, stillbirth, large-for-gestational-age birth, and caesarean section in the following pregnancy,²⁸⁻³⁰ reported that BMI increase was a risk factor for these outcomes. Another study reported that BMI increase may reduce the risk of small-for-gestational-age birth,³¹ as expected, but preterm birth was not examined.

Previous studies have suggested that being underweight is a risk factor for spontaneous preterm birth, while being overweight or obese may confer a reduced risk.^{8, 9} Analyses utilizing the full CPP datasets corroborated this finding.³² It is thus plausible that moderate decrease in prepregnancy BMI may slightly increase the risk of spontaneous preterm birth in the following pregnancy. A decrease in prepregnancy BMI may actually signal inadequate intake of proteins, fat, vitamins, and minerals,³³ which may contribute to higher risk of spontaneous preterm birth.⁸ Non-nutritional mechanisms, such as infection and inflammation related to underweight and preterm birth have been suggested, but not proven.^{34, 35} According to this analysis, a reduction in BMI in women who had given birth to a preterm baby in the previous pregnancy was suggestive of higher recurrence risk, but this needs to be corroborated in future studies. Because the association between prepregnancy BMI and preterm birth is likely to differ between induced and spontaneous preterm births (i.e., being underweight is likely related to spontaneous preterm birth, while obesity is related to induced preterm birth resulting from pregnancy complications), these two outcomes should be examined separately.

This study has several limitations. First, in the era when the CPP was conducted, obesity was uncommon (about 9% in the CPP,³⁶ compared to about 30% nowadays³⁷). Induction of labor and cesarean section were also uncommon in the CPP (about 8% and 5%, respectively), compared to the present time (22%³⁸ and 31%,¹² respectively). The CPP data may thus not be suitable for studying indicated preterm birth, but the association between prepregnancy BMI and spontaneous preterm birth appears unchanged since then.^{8, 9, 32} The average BMI change between pregnancies may have been subject to temporal variation as nutritional status, age at first childbirth, pregnancy weight gain, and interpregnancy interval have been changing. Nevertheless, the interquartile range of prepregnancy BMI change did not differ much between this study sample (−0.3 to 1.5 kg/m²) and a large contemporary dataset from Sweden (−0.3 to 1.7 kg/m²).²⁸

Additionally, this analysis was based on a relatively small sample size, and selection and misclassification bias cannot be ruled out. However, the inverse association between prepregnancy BMI and preterm birth risk was seen both in the full CPP dataset and in this study sample. Generally self-reported prepregnancy weight and height were reliable,^{39, 40} but inaccuracy in individual reporting was possible. In this study, however, both weight and height were reported prior to the occurrence of the outcome. Gestational age was estimated on the basis of the day of last menstrual period, leading to potential for errors in the estimated rates of preterm birth. Such errors would also have affected the calculation of the interpregnancy interval. This study sample had relatively high preterm birth rate, probably because of very young age and large proportion of African Americans. Exclusion of babies with birth weight over the 99th sex- and gestational-age-specific percentile reduced the possibility of misclassification, but the estimates did not change. Although a true gestational duration of 51 weeks is highly unlikely, we chose to retain women with up to this reported gestational duration,

since their babies were most likely born at term. However, restricting the sample to gestational age 20–44 weeks (41 exclusions) did not change the results (data not shown). The sample size limited our ability to study BMI change at both ends of its distribution. In fact, type II error might exist for this sample; our power to detect differences in risk estimates was limited. As we restricted the sample to nulliparous women at index pregnancy, we could not directly extrapolate the results to parous and older women. Despite our attempts to include all relevant confounders, residual confounding is still possible. Diet, physical activity, stress, and maternal diseases may all affect BMI change. It is possible that the change in BMI may have been due to some lifestyle or medical conditions that also affect the risk of preterm birth, in which case change in BMI would not be causally linked with preterm delivery. The study had also a number of strengths, including the high quality of the CPP data. Furthermore, we were able to adjust for prepregnancy BMI at the previous pregnancy and a number of other important covariates.

In conclusion, a decrease in BMI between pregnancies may slightly increase the risk of preterm birth (mainly spontaneous) among predominantly low to normal weight women. Analysis of contemporary data needs to be conducted to investigate the role of BMI change in overweight or obese women.

Acknowledgments

The authors thank Dr. Walter J. Rogan and Anne Marie Jukic at National Institute of Environmental Health Sciences for their helpful comments on an earlier version.

The study was supported by Creighton University School of Medicine Health Future Foundation. This research was supported in part by the Intramural Research Program of the NIH, National Institutes of Environmental Health Sciences (Z01 ES044003), and Eunice Kennedy Shriver National Institute of Child Health and Human Development.

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Figure 1.
Flow chart of sample selection for the analysis

Figure 2.

Hazard ratio of preterm birth in the outcome pregnancy as a function of prepregnancy BMI change in a Cox regression model with smoothing method. The solid line represents the hazard ratio and the dotted lines show 95% pointwise confidence intervals. The vertical bars on the x-axis show the density distribution of the prepregnancy BMI change. Adjusted for center, maternal age at pregnancy, race, maternal smoking during pregnancy, socioeconomic index, marital status, interpregnancy interval, and prepregnancy BMI at index pregnancy.

Table 1

Maternal characteristics and preterm birth in the outcome (second) pregnancies

Characteristics	n	% preterm
Maternal age at enrollment		
< 20 years	644	25.3
20-24 years	905	16.1
25-29 years	267	9.7
≥ 30 years	76	13.2
Maternal race		
White	1039	10.4
African American	796	28.0
Others	57	24.6
Maternal smoking during pregnancy		
No smoking	1015	18.2
0-9 cigarettes/day	380	22.6
10-19 cigarettes/day	208	16.4
≥ 20 cigarettes/day	278	14.4
Maternal socioeconomic index		
0.0-3.9	554	23.3
4.0-5.9	556	20.5
6.0-9.5	726	12.5
Marital status at pregnancy		
Married	1619	16.6
Unmarried	273	27.8
Interpregnancy interval		
<6 months	693	20.1
6-11 months	544	16.9
12-23 months	478	18.2
≥ 24 months	173	15.6

Table 2

Mean, standard deviation, and median of prepregnancy BMI change between pregnancies by maternal characteristics for the index (first) pregnancy

Maternal characteristics at the index pregnancy	n	Prepregnancy BMI change (kg/m ²)		
		Mean	SD	Median
Maternal age at enrollment				
< 20 years	1024	0.52	1.60	0.42
20-24 years	670	0.62	1.44	0.48
25-29 years	156	0.58	1.50	0.33
≥ 30 years	42	0.84	1.38	0.79
Maternal race				
White	1039	0.55	1.48	0.37
African American	796	0.60	1.60	0.53
Others	57	0.42	1.57	0.53
Maternal smoking during pregnancy				
Non-smokers	1038	0.67	1.58	0.53
0-9 cigarettes/day	419	0.35	1.41	0.31
10-19 cigarettes/day	233	0.43	1.46	0.31
≥ 20 cigarettes/day	196	0.63	1.53	0.43
Maternal socioeconomic index				
0.0-3.9	663	0.53	1.63	0.50
4.0-5.9	497	0.71	1.62	0.55
6.0-9.5	667	0.50	1.35	0.34
Marital status				
Married	1391	0.60	1.51	0.46
Unmarried	501	0.47	1.58	0.47
Prepregnancy BMI				
< 18.5 kg/m ²	210	0.73	1.07	0.58
18.5-24.9 kg/m ²	1493	0.57	1.48	0.39
25-29.9 kg/m ²	153	0.31	2.14	0.05
≥ 30 kg/m ²	36	0.77	2.40	1.22
Interpregnancy interval				
< 6 months	693	0.54	1.46	0.44
6-11 months	544	0.47	1.54	0.34
12-23 months	478	0.66	1.56	0.58
≥ 24 months	173	0.75	1.70	0.65

Table 3

Adjusted hazard ratios (95% confidence intervals) of preterm birth as a function of prepregnancy BMI and BMI change between pregnancies^{a,b}

	Outcome (second) pregnancy		
	n	% preterm birth	HR and 95% CI
Prepregnancy BMI in the outcome pregnancy			
< 18.5 kg/m ²	177	20.9	1.03 [0.72, 1.47]
18.5-24.9 kg/m ²	1448	18.2	reference
25-29.9 kg/m ²	218	17.0	0.89 [0.63, 1.26]
≥ 30 kg/m ²	49	14.3	0.70 [0.33, 1.49]
Prepregnancy BMI in the index pregnancy			
< 18.5 kg/m ²	210	22.9	1.19 [0.87, 1.65]
18.5-24.9 kg/m ²	1493	17.8	reference
25-29.9 kg/m ²	153	17.0	0.92 [0.61, 1.40]
≥ 30 kg/m ²	36	16.7	0.79 [0.34, 1.79]
Prepregnancy BMI change			
< -0.32 kg/m ²	473	19.7	1.17 [0.90, 1.53]
-0.32 to 1.48 kg/m ²	945	17.4	reference
> 1.48 kg/m ²	474	18.6	1.08 [0.83, 1.41]

^a Adjusted for center, maternal age at pregnancy, race, maternal smoking during pregnancy, socioeconomic index, marital status, and interpregnancy interval

^b The results in this table were from two separate models: one included prepregnancy BMI in the outcome pregnancy, the other included prepregnancy BMI in the index pregnancy and BMI change between pregnancies

Table 4

Hazard ratios [95% confidence interval] of preterm birth in the outcome pregnancy as a function of prepregnancy BMI change between pregnancies, stratified by maternal pregnancy characteristics^a

	Prepregnancy BMI change (kg/m ²)					
	< -0.32		-0.32 to 1.48		> 1.48	
	%	HR [95% CI]	%	HR	%	HR [95% CI]
Preterm birth at index pregnancy						
Preterm	51.6	1.49 [0.90, 2.44]	38.9	reference	35.7	0.77 [0.45, 1.29]
Term	14.7	1.07 [0.77, 1.48]	13.9	reference	15.6	1.21 [0.88, 1.66]
Prepregnancy BMI at index						
pregnancy	21.0	1.30 [0.98, 1.71]	17.0	reference	18.8	1.08 [0.82, 1.44]
<25 kg/m ²	11.6	0.36 [0.12, 1.04]	22.6	reference	17.2	0.89 [0.33, 2.39]
≥25 kg/m ²	16.7	1.29 [0.96, 1.73]	14.4	reference	15.4	1.12 [0.83, 1.51]
Babies with sex- and gestational-age-specific birthweight ≤ 99 th percentile						
Interpregnancy interval ≥ 4 months	18.7	1.02 [0.75, 1.38]	18.0	reference	18.4	0.95 [0.70, 1.28]
Restricted to pregnancies that ended as spontaneous labor in the outcome pregnancy	20.8	1.17 [0.89, 1.55]	18.0	reference	19.1	1.07 [0.81, 1.42]
Baby of index pregnancy did not die during follow-up	19.2	1.14 [0.87, 1.50]	16.8	reference	18.1	1.04 [0.79, 1.37]

^a Adjusted for center, maternal age at pregnancy, race, maternal smoking during pregnancy, socioeconomic index, marital status, interpregnancy interval, and prepregnancy BMI at index pregnancy (except for the stratification variable)