Adult Weight Change, Weight Cycling, and Prepregnancy Obesity in Relation to Risk of Preeclampsia

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Background: Preeclampsia has been shown to be associated with obesity, with other risk factors for cardiovascular disease, and with subsequent cardiovascular disease itself. However, the possible association with weight gain and weight cycling has not been evaluated.

Methods: In this prospective study of a cohort of 1644 pregnant women, we assessed adult weight change, intentional weight cycling, and prepregnancy obesity in relation to preeclampsia risk. Net weight change from age 18 years to the period 3 months before conception was determined for each participant. Weight cycling was defined as intentional weight loss and unintentional regain of at least 15 pounds during periods not related to pregnancy or lactation. We used multivariate regression procedures to calculate risk ratios (RRs) and 95% confidence intervals (CIs).

Results: Relative to women with stable weight (gained or lost <2.5 kg) women who gained 5.0–9.9 kg experienced a 2.6-fold increased risk of preeclampsia (95% CI = 1.0–6.7). The corresponding risk ratio (RR) for women who gained ≥10 kg was 5.1 (2.2–12.2). Intentional weight cycling, after controlling for weight at age 18 years, adult weight change, and other risk factors, was not associated with increased risk of preeclampsia (RR = 1.1; CI = 0.6–1.8). RRs increased monotonically with increasing prepregnancy body mass index greater than 19.8 kg/m^2. After adjusting for confounders, the RR for prepregnancy overweight women and obese women were 1.7 (0.6–4.9) and 3.4 (1.5–7.6) respectively.

Conclusions: These results suggest that adult weight gain and prepregnancy overweight and obesity status are associated with an increased risk of preeclampsia.

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Preeclampsia is one of the most common medical complications of pregnancy.[1] In the United States, the condition has been reported to be the second-leading cause of maternal mortality and is an important cause of preterm delivery, fetal growth retardation, and perinatal mortality.[1] Risk factors and pathophysiological characteristics of preeclampsia overlap with those of chronic cardiovascular disorders. For instance, women with preeclampsia, as compared with their normotensive counterparts, are more likely to be obese,[2–4] insulin resistant,[5] and dyslipidemic[5,6] and to have elevated plasma homocysteine.[7,8] Notably, women with preeclampsia, as compared with their counterparts who had normotensive pregnancies, appear to experience an increased risk of chronic hypertension[9] and cardiovascular disease later in life.[10] In addition, preeclampsia risk is positively associated with maternal prepregnancy obesity.[11–13]

It has been shown that adult weight gain and intentional weight cycling (ie, the intentional loss and unintentional regain of weight) are positively associated with systolic and diastolic blood pressure, insulin resistance, dyslipidemia, and type 2 diabetes mellitus.[14–21] However, the relation between weight gain and weight cycling during early adult life and risk of preeclampsia has not been studied. We therefore examined the association of adult weight gain and intentional weight cycling with risk of preeclampsia. We also re-examined the relationship between prepregnancy body mass index (BMI) and risk of preeclampsia.

METHODS

The Omega Study

The population for the present analysis was drawn from the participants of the ongoing Omega Study, a prospective cohort study of maternal dietary and other risk factors of preeclampsia and gestational diabetes mellitus. Women participating in the study attended prenatal care clinics affiliated with Swedish Medical Center (Seattle) and Tacoma General Hospital (Tacoma) between December 1996 and September 2002. Women eligible for inclusion were those who initiated prenatal care before 20 weeks' gestation, were at least 18 years of age, could speak and read English, planned to carry the pregnancy to term, and planned to deliver at either of the 2 study hospitals. In the first 18 months of the Omega Study, only nulliparous women were approached and enrolled; eli-

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gibility criteria were later expanded to include multiparous women.

Enrolled participants were asked to take part in an hour-long interview in which trained research personnel used a structured questionnaire to elicit information regarding maternal sociodemographic and anthropometric characteristics, lifestyle habits, and medical and reproductive histories. Participants also completed a 121-item semiquantitative food frequency questionnaire and provided nonfasting blood and urine samples. Pregnancy outcome information was ascertained by reviewing participants' hospital labor and delivery medical records and clinic records after delivery. The procedures used in this study were approved by the Institutional Review Boards of Swedish Medical Center and Tacoma General Hospital. All participants provided written informed consent.

Analytic Population

During the study period, 2381 eligible women were approached, and 2000 (84%) agreed to participate. We excluded from this analysis 120 women who were lost to follow-up (delivery outcome unknown or medical record not found). Also excluded were women who experienced an abortion or fetal demise before 28 weeks of gestation (n = 49), those with pregestational diabetes (n = 21), those with chronic or essential hypertension (n = 101), and those for whom information concerning prepregnancy BMI and/or adult weight gain were missing (n = 65). A cohort of 1644 women remained for analysis.

Preeclampsia

The diagnosis of preeclampsia was made using the then current American College of Obstetricians and Gynecologists (ACOG) guidelines.[1] These guidelines defined preeclampsia as sustained pregnancy-induced hypertension with proteinuria. Hypertension was defined as sustained blood pressure readings of ≥140/90 mmHg (with readings taken ≥6 hours apart) or with a sustained increase of 15 mmHg diastolic pressure or 30 mmHg in systolic pressure above first trimester blood pressure values. ACOG defined proteinuria as urine protein concentrations of ≥30 mg/dL (or 1+ on a urine dipstick) on ≥2 random specimens collected ≥4 hours apart. From this cohort, we identified 71 confirmed preeclampsia cases.

Covariates

Using structured questionnaire, interviewers collected information on maternal sociodemographic, behavioral, and medical characteristics. Covariate information included maternal age, reproductive and medical histories, and medical histories of first-degree family members. We also collected information on maternal educational attainment, annual household income, occupation, prenatal vitamin supplementation use, and smoking and alcohol consumption before and during pregnancy. We asked women to report whether they engaged in regular physical activity in the year before pregnancy and during early pregnancy. We asked participants to provide their attained height, weight at 18 years of age, and weight 3 months before the index pregnancy. Participants also provided information on the number of times they intentionally lost and unintentionally regained at least 15 pounds (6.8 kg) during periods not related to pregnancy or lactation. Maternal age at the time of interview was expressed in years. Parity was reported as the number of previous pregnancies lasting beyond 20 weeks gestation. Maternal and infant medical records were reviewed to collect detailed information concerning antepartum, labor and delivery characteristics, as well as conditions of the newborn.

Weight Change, Weight Cycling, and Other Variables

We used BMI (weight [in kg] divided by height [m^2]) as a measure of obesity. BMI was highly correlated with intra-abdominal (visceral) fat assessed using computed tomography in reproductive-aged women participating in an ancillary study of the Coronary Artery Risk Development in Young Adults (CARDIA) project.[22] BMI was computed for each woman at 18 years of age and again for the period just before she became pregnant. For each time period, we categorized study participants into 4 BMI groups as follows: <19.8 (lean), 19.8–26 (high normal), 26.1–29 (overweight), and >29 kg/m^2 (obese). Our limited sample size prohibited finer BMI categorizations, although we did perform analyses that sought to explore preeclampsia risk in relation to BMI expressed as a continuous covariate.

We computed net adult weight change from age 18 years to the 3 months before the index pregnancy by subtracting the former from the latter weight. Women were then divided a priori into 5 groups: weight loss of 2.6 kg or more, loss or gain of 2.5 kg or less, gain of 2.6–4.9 kg, gain of 5.0–9.9 kg, and gain of 10 kg or more. Women in the second category (ie, those who lost or gained up to 2.5 kg during the period of observation) were used as the referent group. These cut-points were derived after reviewing published reports concerning adult weight change in relation to the occurrence of chronic disorders in perimenopausal and postmenopausal women and before we undertook the present analyses involving reproductive age women.[15–18] Study participants who reported that they intentionally lost and unintentionally regained 6.8 kg or more during periods not associated with pregnancy or lactation were classified as weight cyclers. Weight cyclers were further classified as to the number of times they lost and regained at least 15 pounds (6.8 kg) when not pregnant or lactating. The definition of weight cycling was chosen a priori during questionnaire design phase of the present study.

Statistical Analysis

We examined the frequency distributions of maternal sociodemographic characteristics and medical and reproductive histories according to categories of maternal adult weight gain. We estimated the association between weight characteristics and risk of preeclampsia using Stata software (version 7.0; Stata Corp, College Station, TX). We fitted generalized linear models using a log-link function to derive risk ratios (RRs) and 95% confidence intervals (CIs).[23,24] We also explored the possibility of a nonlinear relation between weight characteristics and preeclampsia risk using general-

ized additive modeling procedures[25] in S-PLUS (version 6.1; Insightful Corp 2002). In multivariate analyses, we evaluated linear trends in risk by modeling the exposure as a grouped linear variable with scores (1, 2, 3, 4) assigned to categories.[26] We considered the following covariates as possible confounders in this analysis: maternal age, race/ethnicity, marital status, smoking during pregnancy, first-degree family history of chronic hypertension, participation in leisure time physical activity before and during pregnancy, prenatal vitamin use, and annual household income.

To assess confounding, we entered variables into a generalized linear model one at a time and then compared the adjusted and unadjusted RRs. Final generalized linear models included covariates that altered unadjusted RRs by at least 10%, as well as those covariates of a priori interest (eg, maternal age and parity). Whenever appropriate, we used the most parsimonious variable specification that achieved the greatest control of confounding. For example, in our assessment of the association of intentional weight cycling with preeclampsia risk, to control potential confounding from prepregnancy BMI, we explored adjustment of prepregnancy BMI as a continuous variable, as a categorical variable ($<$19.8, 19.8–26, 26.1–29, $>$29 kg/m^2) and as a grouped linear variable in the regression model. The greatest amount of control for confounding was achieved when BMI was expressed as a continuous variable.

Women with evidence of pregnancy-induced hypertension but who did not have proteinuria (ie, nonproteinuric gestational hypertension) were classified as not having preeclampsia, according to the ACOG definition. We retained those women in our cohort study analyses after determining that excluding them led to no meaningful differences in reported relative risk estimates. Finally, we conducted post-hoc analyses to examine the relations of maternal adult weight change, intentional weight cycling, and prepregnancy BMI with preeclampsia risk as defined using the newer criteria advocated by the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy.[27] After excluding 35 proteinuric women with increases in blood pressure of $\geq$30 mmHg systolic or $\geq$15 mmHg diastolic above baseline but who did not meet a minimum threshold of $\geq$140 mmHg systolic or $\geq$90 mmHg diastolic after 20 weeks, 46 preeclampsia cases remained for these post-hoc analyses.

RESULTS

The characteristics of study participants according to categories of maternal adult weight change are summarized in Table 1. Overall, participants were primarily white, well-educated, married, and employed during pregnancy. More than 96% of participants reported taking multivitamins during pregnancy. Approximately 29% gained at least 10 kg in the interval from their 18th year of age to the 3-month period before the index pregnancy. Notably, 24% of the cohort maintained their adult weight within 2.5 kg. Women with an adult weight gain of at least 10 kg were more likely to be multiparous, older, and overweight, to have a history of intentional weight cycling, and to have a family history of hypertension, as compared with women who maintained their adult weight. Marital status, educational attainment, physical activity status, smoking status, and maternal race/ethnicity did not vary appreciably across categories of adult weight gain.

Women whose BMI at age 18 years classified them as overweight experienced a 2.1-fold increased risk of preeclampsia as compared with lean women (Table 2). Only 1.6% of the study cohort reported weight and height that indicated they were obese and just one of these women developed preeclampsia.

We noted a strong positive relationship between maternal prepregnancy BMI and risk of preeclampsia (P for linear trend in risk $<$0.001; Table 2). Women who were overweight, as compared with lean women experienced a 1.7-fold (CI = 0.6–4.9) increased risk of preeclampsia. Obese women experienced a 3.4-fold increased risk of preeclampsia as compared with lean women. When we modeled maternal prepregnancy BMI as a continuous variable, we found that every 1 kg/m^2 increase in prepregnancy BMI resulted in an 8% increased risk of preeclampsia (adjusted RR = 1.08; CI = 1.05–1.11).

Next, we quantified the risk of preeclampsia in relation to net adult weight change (Table 2). After adjusting for maternal age, ethnicity/race, parity, educational attainment and weight at age 18, we noted that, relative to women who maintained a stable weight, women who gained 5.0–9.9 kg experienced a 2.6-fold increased risk of preeclampsia (CI = 1.0–6.7). The corresponding RR for women who gained $\geq$10 kg was 5.1 (2.2–12.2). Only one preeclampsia case reported losing more than 2.5 kg during the period of observation. Modeling maternal net adult weight gain as a continuous covariate, every 1 kg increase in weight resulted in a 4% increased risk of preeclampsia (adjusted RR = 1.04; 1.02–1.05).

We also studied the risk of preeclampsia in relation to maternal history of intentional weight cycling (Table 2). Any history of intentional weight cycling was associated with a 1.5-fold increased risk of preeclampsia. After adjusting for maternal age, race, parity, BMI at age 18 years, and weight change since age 18 years, the association was attenuated (adjusted RR = 1.1; CI = 0.6–1.8). There was no evidence of a linear relation between the number of intentional weight cycles and increasing risk of preeclampsia (P for linear trend = 0.831). Parity and maternal age were not effect modifiers of reported associations.

Figure 1 shows the effect of a combination of maternal adult weight change and history of having experienced at least one weight cycling episode on the risk of preeclampsia. Compared with women who maintained their adult weight without weight cycling, women who gained $\geq$10 kg and who reported at least one weight cycling episode experienced a 4.5-fold (CI = 1.8–11.2) increased risk of preeclampsia. Women who gained $\geq$10 kg but did not report a weight cycling episode experienced a 2.6-fold (0.9–7.1) increased risk of preeclampsia as compared with the reference group.

TABLE 1. Selected Characteristics of the Study Cohort According to Categories of Adult Weight Change, Seattle and Tacoma, Washington, 1996–2002 (n = 1644)

Characteristics	Categories of Adult Weight Change (kg)				
	<−2.6 (n = 120) %	−2.5 to 2.5 (n = 389) %	2.5 to 5.0 (n = 257) %	5.0 to 9.9 (n = 401) %	≥10.0 (n = 477) %
Maternal age (years)					
<20	0.8	2.3	0.4	0.0	0.2
20–34	77.5	74.6	71.2	71.1	64.8
35–39	20.8	19.8	23.0	23.9	26.8
≥40	0.8	3.3	5.5	5.0	8.0
Maternal race/ethnicity					
White	82.5	84.6	88.7	85.8	83.3
African American	0.8	2.3	0.0	2.0	2.7
Asian	10.0	9.5	6.2	6.5	6.5
Other	6.7	3.6	5.1	5.8	7.4
Nulliparous	65.0	67.9	71.2	70.6	63.9
First-degree family history of hypertension	50.8	44.5	51.4	49.4	52.4
Physical activity in year before pregnancy	92.3	91.7	91.4	94.3	89.7
Physical activity during pregnancy	86.7	84.6	82.5	81.8	82.4
Employed during pregnancy	80.0	81.0	84.8	83.8	82.8
Married	93.3	87.4	89.1	92.2	90.4
≤12 yr of education	4.3	5.0	4.0	4.6	4.7
No prenatal vitamin use	2.5	2.8	1.6	1.8	3.8
Smoked during pregnancy	9.2	5.9	4.3	5.3	8.4
Annual household income (U.S.$)					
<30,000	5.8	6.4	2.3	3.5	4.0
30,000–69,999	24.2	18.0	22.2	24.7	29.8
≥70,000	65.8	72.2	72.4	69.3	64.6
Not reported	4.2	3.3	3.1	2.5	1.7
Prepregnancy BMI (kg/m^2)					
<19.8 (lean)	40.0	42.5	20.2	8.2	0.6
19.8–26.0 (high normal)	57.9	53.8	76.4	86.3	58.1
26.1–29.0 (overweight)	1.3	1.9	1.9	2.7	20.2
>29.0 (obese)	1.3	1.9	1.4	2.7	21.1
Ever intentional weight cycled					
No	77.4	73.6	80.8	68.6	46.0
Yes	22.6	26.4	19.2	31.4	54.0

When analyses were restricted to those preeclampsia cases meeting the newer suggested diagnostic criteria,[27] the relations of prepregnancy BMI, BMI at age 18 years, and adult weight change, with preeclampsia risk were similar in direction and even more pronounced in magnitude to those reported previously (data not shown). Even women with a high normal prepregnancy BMI experienced more than a doubling in preeclampsia risk as compared with lean women (RR = 3.2; CI = 0.7–13.4). Obese women experienced a 10.3-fold (2.3–46) increased risk of preeclampsia compared with the referent group.

DISCUSSION

Our findings concerning the positive association between maternal prepregnancy adiposity and preeclampsia risk are in general agreement with previous reports.[2–4,11,14,28] Eskenazi et al[4] reported that women who had BMI of <18.9 kg/m^2, as compared with women with BMI 18.9–25.8 kg/m^2, experienced an almost 60% reduction in risk of preeclampsia. These observations were corroborated by Richardson and Baird[28] who reported that the frequency of preeclampsia increased with each successive category of BMI among white and African American women. For each category (<20.0, 20.0–22.5, 22.6–24.9, and ≥25 kg/m^2) they reported that the frequency of preeclampsia among white women was 0.6%, 1.9%, 2.8%, and 9.4%, respectively, and among African-American women was 2.0%, 2.3%, 2.2%, and 7.6%. Taken together, these results[2–4,11,12,14,28] strongly implicate maternal prepregnancy obesity as a consistent and strong risk factor for preeclampsia.

Our observations extend the existing literature by suggesting an association between being overweight at age 18

TABLE 2. Association of Body Mass Index, Adult Weight Change and Intentional Weight Cycling With Preeclampsia

Measurement	No. of Cases	No. of Women	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
BMI (kg/m^2) age 18 years				
<19.8 (lean)	33	762	1.0	1.0*
19.8–26.0 (high normal)	34	825	0.9 (0.6–1.5)	0.9 (0.6–1.6)
26.1–29.0 (overweight)	3	31	2.2 (0.7–7.3)	2.1 (0.6–7.0)
>29.0 (obese)	1	26	0.9 (0.1–6.5)	0.6 (0.1–4.6)
P for trend			0.80	0.99
Prepregnancy				
<19.8 (lean)	11	296	1.0	1.0*
19.8–26.0 (high normal)	36	1078	0.9 (0.5–1.8)	1.0 (0.5–2.2)
26.1–29.0 (overweight)	6	241	1.5 (0.5–4.0)	1.7 (0.6–4.9)
>29.0 (obese)	18	161	3.0 (1.4–6.4)	3.4 (1.5–7.6)
P for trend			<0.001	<0.001
Weight change from age 18 years to prepregnancy (kg)				
≤−2.6	1	120	0.5 (0.7–4.9)	0.6† (0.7–4.7)
−2.5 to +2.5	6	389	1.0	1.0
2.6–4.9	9	257	2.3 (0.8–6.4)	2.1 (0.7–5.9)
5.0–9.9	18	401	2.9 (1.2–7.3)	2.6 (1.0–6.7)
≥10.0	37	477	5.1 (2.1–11.9)	5.1 (2.2–12.2)
P for trend			<0.001	<0.001
Intentional weight cycling				
No	40	1083	1.0	1.0‡
Yes	31	559	1.5 (0.9–2.4)	1.1 (0.6–1.8)
Missing	0	2		
No. cycles				
0	40	1083	1.0‡	1.0‡
1	11	272	1.1 (0.6–2.1)	1.0 (0.5–2.0)
2	9	143	1.7 (0.8–3.5)	1.3 (0.6–2.8)
3+	11	144	2.1 (1.1–4.0)	1.0 (0.4–2.3)
Missing	0	2		
P for trend			<0.020	0.831

*These sets of results adjusted for maternal age, ethnicity/race, parity, and educational attainment.
†These sets of results adjusted for maternal age, ethnicity/race, parity, educational attainment, and weight at age 18 years.
‡These sets of results adjusted for maternal age, ethnicity/race, parity, BMI at age 18, and weight change since age 18 years.

years and subsequent risk of preeclampsia. We also document relations with adult weight gain. After adjusting for confounders, intentional weight cycling was not an independent risk factor for preeclampsia. We know of no previously published reports that have examined the risk of preeclampsia in relation to maternal net weight change and intentional weight cycling during the reproductive years. Our results are consistent, however, with a relatively large body of literature that documents adverse health outcomes (including hypertension, dyslipidemia, insulin resistance, type 2 diabetes mellitus, and cardiovascular disease) associated with adult weight gain and intentional weight cycling[15–20] in nonpregnant women and men.

In this present study, the high follow-up rate minimized the likelihood of selection bias. Prospective collection of weight and weight gain information (before preeclampsia was diagnosed) also served to attenuate concerns about systematic errors in recall of the exposures of interest. Nevertheless, several limitations of the present study merit discussion. First, errors in reporting of anthropometric characteristics are likely to have occurred. Weights reported by participants in other studies, however, have been shown to be valid.[29,30] Troy et al[30] reported that women's self-reported recalled weight at 18 years was highly correlated ($r = 0.87$) with weight at ages 17–21 years abstracted from nursing school records. Because of the prospective nature of our study, any misclassification of weight characteristics is likely to be nondifferential with regard to pregnancy outcome, thus biasing the risk estimates to the null. Second, although we adjusted for several known and suspected confounders, we cannot exclude the possibility of residual confounding. Third, small numbers impeded some aspects of this analysis. Estimated effect measures were imprecise, as reflected by their relatively wide 95% CIs. The

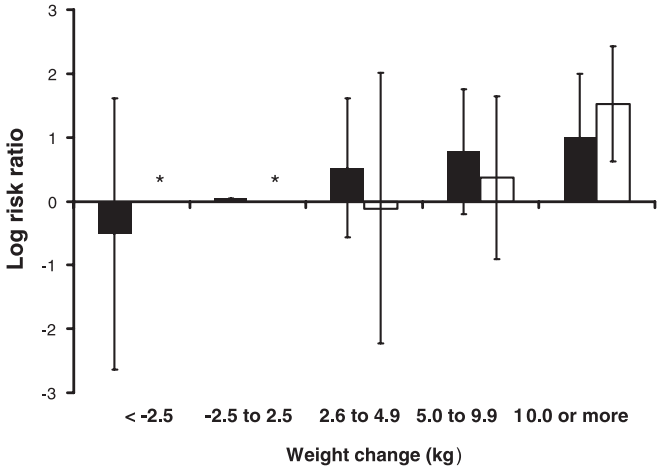

FIGURE 1. Log risk ratio of preeclampsia in relation to adult weight change and history of intentional weight cycling: exploration of potential effect modification. The referent group comprises women who gained or lost less than 2.5 kg with no weight cycling. White bars indicate no cycling, and black bars indicate any cycling. Asterisk indicates inestimable coefficient due to zero cases.

small sample size prevented us from examining varying degrees of preeclampsia severity according to maternal weight characteristics. Fourth, indices of maternal adiposity, weight change and weight cycling are strongly related to each other. Despite careful multivariable statistical modeling, we cannot exclude the possibility of residual confounding, and we acknowledge that we may not have been able to fully isolate the influence of each characteristic on preeclampsia risk. Larger studies that can accommodate statistically inefficient approaches, such as stratified analyses, may overcome concerns about possible residual confounding; such studies would help to further quantify the independent effects of adolescent and prepregnancy adiposity, adult weight changing and weight cycling on preeclampsia risk. Lastly, the cohort consisted primarily of white, well-educated women from the Pacific Northwest. Therefore, the generalizability of results may be limited. These inferences will be strengthened if our findings are corroborated in studies conducted in other populations across the United States and elsewhere.

The findings from our study are biologically plausible. Although preeclampsia is clinically characterized by maternal high blood pressure and proteinuria, women with the disorder also experience physiological disturbances, including dyslipidemia,[5] oxidative stress,[31] insulin resistance,[5] sympathetic nervous system over-reactivity,[32] increased vascular resistance,[33] and chronic inflammation.[34] We are not aware of published clinical or experimental data concerning biologic relations of indices of maternal adiposity, weight gain or weight cycling with insulin resistance and blood pressure control in pregnancy. However, adult weight gain, weight cycling, and obesity have profound effects on a multitude of physiological functions, and these effects may conceivably mediate the risk of preeclampsia via several biologic pathways. First, obese women have been shown to have increased blood volume and cardiac output.[35] Investigators have postulated that pregnancy-induced hemodynamic alterations coupled with increased oxygen consumption secondary to maternal obesity predispose women to increased cardiac output, endothelial injury, and preeclampsia.[5,14] Second, investigators have speculated that a positive association between obesity and hypertension may be explained within the axis of impaired glucose tolerance, insulin resistance, and hyperinsulinemia.[35,36] Third, other investigators have hypothesized that insulin resistance and hyperinsulinemia, which are prevalent among obese individuals, may contribute to increased tubular sodium reabsorption, increased sympathetic nerve activity and hypertension.[16] Fourth, investigators have speculated that dyslipidemia, likely to be more frequent among obese pregnant women,[14,28] may contribute to the pathophysiology of preeclampsia.

Knopp and colleagues[37] have shown that BMI is positively correlated with plasma triglycerides in pregnant women. Hyperlipidemia, associated with maternal obesity, may predispose subjects to increased oxidative stress that may lead to diffuse endothelial dysfunction and an imbalance of the synthesis of vasoactive compounds including thromboxane and prostacyclin. Excessive lipid peroxidation, endothelial cell dysfunction, and altered thromboxane and prostacyclin biosynthesis frequently are observed in women with preeclampsia, as compared with normotensive pregnant women.[5,38–40] Metabolic studies are needed to elucidate endocrine and other biologic mechanisms for the observed associations between maternal obesity, adult weight gain, weight cycling and preeclampsia risk. Furthermore, prospective studies that allow for the evaluation of preeclampsia risk in relation to maternal prepregnancy fat distribution may also add greater specificity to the associations observed in our study.

The associations between preeclampsia and maternal obesity observed here and elsewhere[2–4,12,14,28] are of similar or greater magnitude to associations reported previously between preeclampsia and other factors such as chronic hypertension, antiphospholipid syndrome, diabetes mellitus and nulliparity[1,3] Given the strength and consistency of the association between maternal obesity and preeclampsia risk, it is reasonable to speculate that the worldwide increase in obesity will likely be coupled with considerable increases in the occurrence of preeclampsia. Since the mid-1990s, considerable evidence has accumulated to implicate adult weight gain, even modest weight gain, and intentional weight cycling in the development of hypertension, type 2 diabetes mellitus, and other chronic disorders.[14–21] These studies have not focused on reproductive-aged women, and none evaluated the impact of adult weight patterns on reproductive health.

We found that women who gained ≥10 kg greater than their weight at age 18 years experienced a 5.1-fold increased risk of developing preeclampsia when compared with their counterparts who maintained their weight. Further, we found that the association between adult weight gain and preeclampsia risk appeared to be strongest among women with a history of weight cycling. If confirmed, our results may call attention to the need to consider reproductive health out-

comes when establishing guidelines for adult weight gain. Our results may also motivate the development and promotion of public health campaigns that target young adults who may be more attuned to making healthful behavioral changes that can positively impact their reproductive outcomes and long-term health.

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REFERENCES

1. American College of Obstetricians and Gynecologists. Hypertension in pregnancy. *ACOG Tech Bull*. 1996;219:1–8.
2. Mahomed K, Williams MA, Woelk GB, et al. Risk factors for pre-eclampsia among Zimbabwean women: Maternal arm circumference and other anthropometric measures of obesity. *Paediatr Perinatal Epidemiol*. 1998;12:253–262.
3. Kabiru W, Raynor BD. Obstetric outcomes associated with increase in BMI category during pregnancy. *Am J Obstet Gynecol*. 2004;191:928–932.
4. Eskenazi B, Fenster L, Sidney A. A multivariate analysis of risk factors for preeclampsia. *JAMA*. 1992;266:237–241.
5. Kaaja R, Tikkanen MJ, Vinnikka L, et al. Serum lipoproteins, insulin, and urinary prostanoid metabolites in normal and hypertensive pregnant women. *Obstet Gynecol*. 1995;85:353–356.
6. Enquobahrie DA, Williams MA, Butler CL, et al. Maternal plasma lipid concentrations in early pregnancy and the risk of preeclampsia. *Am J Hypertens*. 2004;17:574–581.
7. Sorensen TK, Malinow MR, Williams MA, et al. Elevated second trimester serum homocyst(e)ine levels and subsequent risk of pre-eclampsia. *Gynecol Obstet Invest*. 1999;48:98–103.
8. Sanchez SE, Zhang C, Malinow MR, et al. Plasma folate, vitamin B_{12} and homocyst(e)ine concentrations in preeclamptic and normotensive Peruvian women. *Am J Epidemiol*. 2001;153:474–480.
9. Nisell H, Lintu H, Lunell NO, et al. Blood pressure and renal function seven years after pregnancy complicated by hypertension. *Br J Obstet Gynaecol*. 1995;102:876–881.
10. Rosenberg L, Miller DR, Kaufman DW, et al. Myocardial infraction in women under 50 years of age. *JAMA*. 1983;250:2801–2806.
11. Bodnar LM, Ness RB, Markovic N, et al. The risk of preeclampsia rises with increasing prepregnancy body mass index. *Ann Epidemiol*. 2005; 15:475–482.
12. Connde-Aguedo A, Belizan JM. Risk factors for pre-eclampsia in a large cohort of Latin American and Caribbean women. *BJOG*. 2000;107:75–83.
13. O'Brien TE, Ray JG, Chan W. Maternal body mass index and the risk of preeclampsia: a systematic overview. *Epidemiol*. 2003;14:368–374.
14. Stone JL, Lockwood CJ, Berkowitz GS, et al. Risk factors for severe preeclampsia. *Obstet Gynecol*. 1994;83:357–361.
15. Willett WC, Manson JE, Stampfer MJ, et al. Weight, weight change, and coronary heart disease in women. Risk within the "normal" weight range. *JAMA*. 1995;273:461–465.
16. Haung Z, Willett WC, Manson JE, et al. Body weight, weight change, and risk of hypertension in women. *Ann Intern Med*. 1998;12:81–87.
17. Everson SA, Goldberg DE, Helmrich SP, et al. Weight gain and the risk of developing insulin resistance syndrome. *Diabetes Care*. 1998;21: 1637–1643.
18. Field AE, Byers T, Hunter DJ, et al. Weight cycling, weight gain, and risk of hypertension in women. *Am J Epidemiol*. 1999;150:573–579.
19. Guagnano MT, Ballone E, Pace-Palitti V, et al. Risk factors for hypertension in obese women. The role of weight cycling. *Eur J Clin Nutr*. 2000;54:356–360.
20. Olson MB, Kelsey SF, Bittner V, et al. Weight cycling and high-density lipoprotein cholesterol in women: evidence of an adverse effect. *J Am Coll Cardiol*. 2000;36:1565–1571.
21. Resnick HE, Valsania P, Halter JB, et al. Relation of weight gain and weight loss on subsequent diabetes risk in overweight adults. *J Epidemiol Community Health*. 2000;54:596–602.
22. Sidney S, Lewis CE, Hill JO, et al. Association of total and central adiposity measure with fasting insulin in a biracial population of young adults with normal glucose tolerance: the CARDIA study. *Obes Res*. 1999;7:265–272.
23. Barker RJ, Nelder JA. *The Generalized Linear Interactive Modeling System*, release 3. 77. Oxford Numerical Algorithms Group; 1985.
24. Hardin JW, Hilbe J. *Generalized Linear Models and Extensions.* College Station, TX: Stata Press; 2001.
25. Hastie TJ, Tibshirani RJ. *Generalized Additive Models.* London: Chapman-Hall; 1990.
26. Rothman KJ, Greenland S. *Modern Epidemiology*. 2nd ed. Philadelphia: Lippincott-Raven Publishers; 1998.
27. National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy.Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. *Am J Obstet Gynecol*. 2000;183:S1–S22.
28. Richardson BE, Baird DD. A study of milk and calcium supplement intake and subsequent preeclampsia in a cohort of pregnant women. *Am J Epidemiol*. 1995;141:667–673.
29. Willett WC, Stampfer MJ, Bain C, et al. Cigarette smoking, relative weight, and menopause. *Am J Epidemiol*. 1983;117:651–658.
30. Troy LM, Hunter DJ, Manson JE, et al. The validity of recalled weight among younger women. *Int J Obes Relat Metab Discord*. 1995;19:570–572.
31. Hubel CA, Roberts JM, Taylor RN, et al. Lipid peroxidation in pregnancy: new perspectives on preeclampsia. *Am J Obstet Gynecol*. 1989; 161:1025–1034.
32. Schobel HP, Fischer T, Heuszer K, et al. Preeclampsia-a state of sympathetic overactivity. *N Engl J Med*. 1996;335:1480–1485.
33. Roberts JM, Redman CW. Pre-eclampsia: more than pregnancy-induced hypertension. *Lancet*. 1993;341:1447–1451.
34. Williams MA, Farrand A, Mittendorf R, et al. Maternal second-trimester serum tumor necrosis factor-α soluble receptor p55 (sTNFp55) and subsequent risk of preeclampsia. *Am J Epidemiol*. 1999;149:323–329.
35. Paulson DJ, Tahiliani AG. Cardiovascular abnormalities associated in human and rodent obesity. *Life Sci*. 1992;51:1557–1569.
36. Haynes WG, Morgan DA, Walsh SA, et al. Cardiovascular consequences of obesity: role of leptin. *Clin Exp Pharmacol Physiol*. 1998; 25:65–69.
37. Knopp RH, Bergelin RO, Wahl PW, et al. Population-based lipoprotein lipid reference values for pregnant women compared to nonpregnant women classified by sex hormone status. *Am J Obstet Gynecol*. 1982; 143:626–637.
38. Walsh SW. Preeclampsia: an imbalance in placental prostacyclin and thromboxane production. *Am J Obstet Gynecol*. 1985;152:335–340.
39. Meagher EA, FtizGerald GA. Disordered eicosanoid formation in pregnancy-induced hypertension. *Circulation*. 1993;88:1324–1333.
40. FitzGerald DJ, Entman SS, Mulloy K, et al. Decreased prostacyclin biosynthesis preceding the clinical manifestation of pregnancy-induced hypertension. *Circulation*. 1987;75:956–963.

