ORIGINAL RESEARCH

CURRENT DEVELOPMENTS IN NUTRITION

Nutritional Epidemiology and Public Health

Associations of Pregnancy History with BMI and Weight Gain in 45–54-Year-Old Women

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ABSTRACT

Background: Midlife women have a higher risk of cardiometabolic disease than younger women, but the lifelong biological/lifestyle factors responsible for this increase are unclear.

Objectives: We investigated whether pregnancy history is a risk factor for midlife overweight/obesity and evaluated potential hormonal mechanisms.

Methods: The Baltimore Midlife Women's Health Study, a prospective cohort, recruited 772 women aged 45–54 y. Women reported pregnancy characteristics via questionnaires, trained staff measured weight/height to calculate midlife BMI, and serum hormones were assessed by ELISA. Logistic regression models assessed associations of pregnancy history with risk of midlife overweight/obesity and BMI gain since age 18. We additionally explored whether associations differed by menopausal status, and whether midlife hormones mediated relationships of pregnancy history and midlife BMI.

Results: These premenopausal or perimenopausal women were 66% Caucasian/White and 30% African American/Black, with a median of 2 live births (range: 0–11) and median age at first birth of 27 y (range: 12–46 y). Women with 0 and ≥2 live births had lower odds of overweight/obesity than those with 1 birth (OR = 0.47; 95% CI: 0.23, 0.96; $P = 0.04$, and OR = 0.58; 95% CI: 0.35, 0.95; $P = 0.03$, respectively). Women with ≥2 live births also had lower odds of BMI gain than those with 1 birth (OR = 0.66; 95% CI: 0.41, 1.06; $P = 0.08$). Furthermore, women who were older at their first birth had lower odds of overweight/obesity (OR = 0.96; 95% CI: 0.92, 1.00; $P = 0.03$) and BMI gain (OR = 0.97; 95% CI: 0.93, 1.00; $P = 0.06$). Number of pregnancies and age at last pregnancy were not associated with midlife overweight/obesity or BMI gain. Associations did not differ by menopausal status and were not explained by midlife hormones.

Conclusions: Earlier childbirth and having 1 child increased women's risk of midlife overweight/obesity and BMI gain since age 18. Additional studies should focus on women's childbearing years as a critical determinant of midlife metabolic health. *Curr Dev Nutr* 2019;4:nzz139.

Keywords: pregnancy, obesity, menopause, hormones, weight accumulation

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Abbreviations used: CVD, cardiovascular disease; LOD, level of detection; MWHS, Midlife Women's Health Study.

Introduction

In 2017, 72% of US adults were overweight or obese, and 40% were obese (1), which exceeded the global 2015–2016 prevalence (2). Specifically, 44.7% of 40–59-y-old US women were obese, which was higher than for younger women and men (3). This is concerning because midlife obesity in women is a major risk factor for many chronic diseases, including type 2 diabetes mellitus (4), stroke (5), depression (6), cardiovascular disease (CVD) (7), Alzheimer's disease (8), and hormonally driven cancers, including breast and endometrial cancers (9). Some of these deleterious health outcomes are likely directly caused by the menopausal transition (perimenopause), which occurs naturally when women are 49–52 y of age (on average) (10). Perimenopause is characterized by the depletion of ovarian follicles and alterations in reproductive hormone concentrations (11–13), leading to rapid fat mass accumulation at central sites, which is an important predictor of cardiometabolic diseases (14, 15). For example, in a diverse cohort of US pre- and perimenopausal women, increased androgen (16, 17) and decreased estradiol concentrations (16) were associated with higher risk of obesity and other CVD-

related risk factors. Given that obesity is an important predictor of various chronic diseases, it is likely that women who enter menopause being overweight or obese are at an even greater risk of menopause-driven cardiometabolic disruptions.

Another important consequence of being obese prior to and during menopause is that obese women appear to have more severe menopausal characteristics and symptoms. A large meta-analysis suggested that overweight/obese premenopausal women enter natural menopause at an older age than normal-weight women (18). Interestingly, whereas this delay in menopause can protect against certain diseases, including CVD (19), delayed menopause is associated with increased risk of breast cancer (20). Compared with normal-weight women, obese women undergoing the menopausal transition are also more likely to experience exacerbated menopausal symptoms, including urogenital and vasomotor symptoms (21, 22), which we previously showed could be related to midlife hormonal shifts in obese women (23). Overall, these results suggest that in addition to putting women at greater risk of cardiometabolic dysregulations, being overweight/obese can increase the severity of menopausal symptoms. Therefore, it is essential to understand factors associated with elevated obesity risk in middle-aged women.

Several studies in women of different menopausal stages suggest that pregnancy and childbirth can additionally modify a woman's risk of midlife obesity. In a representative sample of Korean postmenopausal women, younger age at first birth and higher parity (giving birth to more children) were associated with increased risk of general and abdominal obesity after menopause (24). Similarly, in a representative sample of retired US women, higher parity was also associated with higher BMI (25). Although other studies have evaluated associations of pregnancy history with midlife obesity in pre-, peri-, and postmenopausal women separately (25–30), it is unclear whether observed associations would differ by menopausal status. The menopausal transition is associated with hormonal and metabolic shifts, so our first aim was to assess relations between pregnancy history and midlife overweight/obesity and determine whether these associations differ between pre- and perimenopausal women. Because few studies have assessed whether pregnancy history influences lifelong weight accumulation, our second aim was to assess associations of pregnancy history with change in obesity status since age 18. Lastly, pregnancy is also characterized by numerous hormonal and metabolic shifts that can persist into midlife and influence midlife obesity risk (31). Therefore our third aim was to evaluate whether adulthood estradiol, testosterone, or progesterone mediate associations between pregnancy history and midlife BMI.

Methods

Participant recruitment and selection

This study consisted of a secondary data analysis of the Midlife Women's Health Study (MWHS), a prospective cohort in the Baltimore metropolitan area evaluating risk factors of hot flashes in 45–54-y-old women from 2006 until 2015. No part of the MWHS was a clinical trial, and study methodology is fully described elsewhere (32). Briefly, 45–54-y-old women were invited to participate in the study via mail, and interested women contacted the clinic to determine eligibility. Eligible women were 45–54 y old, had intact ovaries and uteri, and were pre- or perimenopausal. Premenopausal women were those who experienced their last menstrual period within the past 3 mo and reported ≥11 menstrual periods within the past year. Women were characterized as perimenopausal if they either *1*) experienced their last menstrual period within the past year, but not within the past 3 mo, or *2*) experienced their last menstrual period within the past 3 mo, but reported ≤10 menstrual periods within the past year. Women were excluded if they were pregnant, taking hormone replacement therapy/hormonal contraceptives, had a history of ovarian or uterine cancer, or were postmenopausal (had not experienced a menstrual period within the past year). Ultimately, 772 pre- and perimenopausal women enrolled into the study and provided written informed consent according to a procedure approved by the University of Illinois and Johns Hopkins University Institutional Review Boards.

Collection of demographic/lifestyle characteristics

Eligible MWHS participants came for a baseline visit at a Johns Hopkins clinical site to report important demographic/lifestyle characteristics, including those outlined in **Table 1**. Women's race/ethnicity was determined using the question: "What is your main ethnic/racial background? Mark only one; Answer = Caucasian/White, African American/Black, Hispanic/Latino, Asian, or Other." Women also reported the highest grade or year of schooling they completed, their current employment status, current marital status, and total household income during the year prior to study enrollment. To measure midlife physical activity, women answered the question: "In comparison with others my own age, I think my physical activity leisure time is…; Answer = much more, more, as much, less, or much less." The question "In the last 12 months have you had at least 12 drinks of any kind of alcoholic beverage? Answer = yes, no" evaluated a woman's alcohol consumption status, whereas smoking status was categorized as "never, former, or current smoker" using the questions "Have you ever smoked cigarettes?" and "Do you still smoke cigarettes?" Women also answered whether their mother smoked cigarettes while pregnant with them (Answer = yes, no, or don't know). Women reported the number of years they used oral contraceptives, and presence of fertility problems was assessed by asking "Did you ever seek medical consultation because of difficulty in getting pregnant? Answer = yes, no." Self-reported weight at age 18 and midlife height were used to calculate BMI at age 18.

Collection of pregnancy history

At baseline, women also answered questions about gravidity (number of pregnancies), parity (number of live births), and ages at first birth and last pregnancy. Gravidity and parity were reported as counts and categorized as 0 pregnancies/births, 1 pregnancy/birth, and ≥2 pregnancies/births. Ages at first birth and last pregnancy were reported in years and assessed as continuous variables.

Collection of anthropometrics

Weight and height were measured without shoes by trained clinic staff, and values were rounded to the nearest 0.5 pound and 0.5 inch, respectively. We calculated BMI (kg/m^2) using weight (kilograms) and height (meters) and categorized BMI as under-/normal weight (BMI <25) or overweight/obese (BMI ≥25) (33). We also categorized women by their BMI at ages 18 and 45–54 as follows: women who remained normal weight through age 45–54 (under-/normal weight at

TABLE 1 Demographic or lifestyle characteristics of women in the Midlife Women's Health Study ($n = 768$)

Demographic and lifestyle characteristic	*n* (%)[1]
Age, y	
45–49	501 (65.2)
50–54	267 (34.8)
Menopausal status[2]	
Premenopausal	496 (64.6)
Perimenopausal	272 (35.4)
Race/ethnicity[2]	
Caucasian/White	503 (65.5)
African American/Black	233 (30.3)
Other	30 (3.9)
Annual household income	
<$40,000	176 (22.9)
$40,000–99,999	250 (32.6)
≥$100,000	321 (41.8)
Education level	
Some college or less	275 (35.8)
College graduate or higher	490 (63.8)
Employment status	
Employed	608 (79.2)
Full-time student or homemaker	72 (9.4)
Unemployed/retired/medical leave/disability	86 (11.2)
Marital status	
Single	140 (18.2)
Married/living with partner	499 (65.0)
Widowed/divorced/separated	126 (16.4)
Physical activity compared with others	
Less than others	255 (33.2)
As much as others	240 (31.3)
More than others	264 (34.4)
Alcohol consumption during past year	
Yes	500 (65.1)
No	128 (16.7)
Participant smoking status	
Current smoker	78 (10.2)
Former smoker	269 (35.0)
Never smoked	420 (54.7)
Maternal smoking status during pregnancy[2]	
Yes	184 (24.0)
No	436 (56.8)
Don't know	137 (17.8)
Medical consultation for fertility problems[2]	
Yes	142 (18.5)
No	621 (80.9)
Oral contraceptive use[2]	
Never	113 (14.7)
<1 y	106 (13.8)
1–4 y	203 (26.4)
5–10 y	183 (23.8)
>10 y	159 (20.7)
BMI at age 18 y,[2] kg/m^2	
Underweight (<18.5)	132 (17.2)
Normal weight (18.5–24.9)	531 (69.1)
Overweight (25–29.9)	65 (8.5)
Obese (≥30)	32 (4.2)
BMI at age 45–54 y, kg/m^2	
Underweight (<18.5)	11 (1.4)
Normal weight (18.5–24.9)	291 (37.9)
Overweight (25–29.9)	208 (27.1)
Obese (≥30)	258 (33.6)
Change in BMI from age 18 to 45–54	
Remained under-/normal weight	294 (38.3)
Became overweight/obese	369 (48.1)
Became under-/normal weight	5 (0.7)
Remained overweight/obese	92 (12.0)

[1]May not add up to 100% due to missing data.
[2]Variables selected as potential confounders in logistic and linear regression models based on a directed acyclic graph.

TABLE 2 Pregnancy history of women in the Midlife Women's Health Study ($n = 768$)

Pregnancy characteristic	*n* (%) or median (range)
Gravidity (number of pregnancies)	
Never pregnant	87 (11.3)
1 pregnancy	91 (11.9)
≥2 pregnancies	590 (76.8)
Parity (number of live births)	
Never pregnant	87 (11.3)
No live births	78 (10.2)
1 live birth	139 (18.1)
≥2 live births	462 (60.2)
Missing	2 (0.3)
Age at first birth, y	27.0 (12.0–46.0)
Age at last pregnancy, y	33.0 (14.0–53.0)

ages 18 and 45–54), women who became overweight/obese by age 45–54 (under-/normal weight at age 18 but overweight/obese at age 45–54), women who became normal weight by age 45–54 (overweight/obese at age 18 but under-/normal weight at age 45–54), and those who remained overweight/obese through age 45–54 (overweight/obese at ages 18 and 45–54).

Assessment of midlife hormones

Hormone analyses are described in detail elsewhere (32). Briefly, fasting morning blood samples were collected at baseline and once per week for 4 consecutive weeks to assess serum estradiol, testosterone, and progesterone concentrations at all phases of the menstrual cycle (averaged across the 4 visits). Participants were compensated after each clinic visit for their time and travel to the clinic (32). Hormone concentrations were assessed using commercially available and previously validated ELISA (DRG, Springfield, New Jersey, USA) according to manufacturers' instructions. Mean values of duplicates were used in analyses. Average intra- and interassay coefficients of variation were <5% (32, 34). Limits of detection (LOD) for each hormone were as follows: estradiol = 9.71 pg/mL; testosterone = 0.08 ng/mL; progesterone = 0.05 ng/mL (35). Values less than the LOD were assigned the LOD for that hormone.

Statistical analysis

Three women were excluded from the analysis because of missing information about pregnancy history, baseline weight/height, and/or progesterone concentrations. Another woman was excluded for having extreme testosterone concentrations across all visits. Therefore, 768 pre- and perimenopausal women were available to assess associations of pregnancy history with midlife BMI. Binary logistic regression models assessed whether pregnancy history increased or decreased the probability of being overweight/obese compared with being under-/normal weight. To assess whether relations were linear across BMI, we also assessed the associations between pregnancy history and continuous midlife BMI using linear regression. In linear regression models, midlife BMI was natural log-transformed to meet normality assumptions.

To evaluate whether pregnancy history was associated with a "shift" in BMI status from age 18 to 45–54 (as described above), we aimed to assess whether pregnancy history was associated with changes in BMI across a woman's reproductive window (from under-/normal weight to

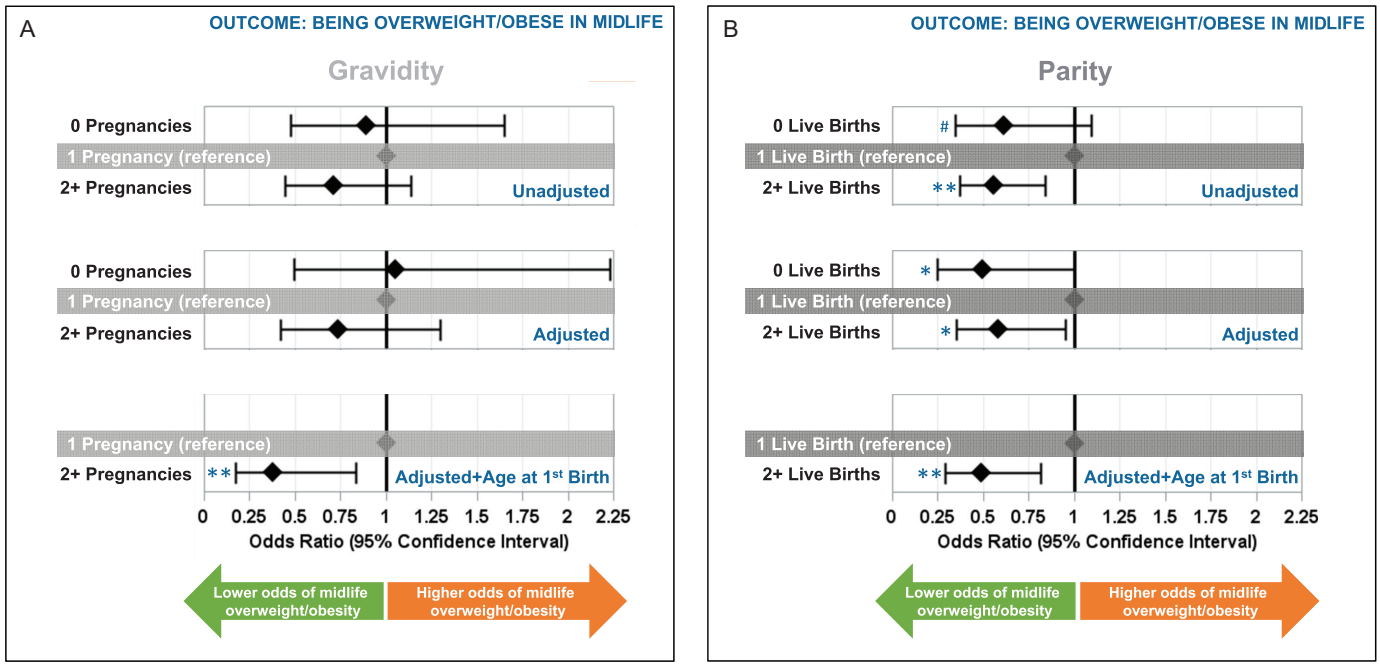

FIGURE 1 Associations of gravidity (number of pregnancies) and parity (number of live births) with midlife overweight/obesity. Binary logistic regression models evaluated associations of (A) gravidity and (B) parity with the probability of being overweight/obese compared with under-/normal weight in midlife. Results are expressed as ORs (filled diamonds) and 95% CIs (solid lines) for the unadjusted, adjusted, and additionally adjusted models. Analyses control for race, maternal smoking status, fertility problems, oral contraceptive use, BMI at age 18, and menopausal status, and additionally control for age at first birth. Significant associations are those that do not cross the null (OR = 1.0) at $^{\#}P < 0.10$, $^{*}P < 0.05$, and $^{**}P < 0.01$.

overweight/obese or from overweight/obese to under-/normal weight). Only 5 women who were overweight/obese at age 18 became under/normal weight at age 45–54, so we ultimately only evaluated associations between pregnancy history and the risk of becoming overweight/obese at 45–54 y of age. We did not compare women who were overweight/obese at age 18 and remained overweight/obese at age 45–54 with other groups because these women were obese prior to being pregnant, which would not allow us to ask whether pregnancy history was the cause of their overweight/obesity. Furthermore, 8 women did not report their weight at age 18, thus 663 women were available for assessing these associations in final binary logistic regression models. In sensitivity analyses, we examined associations between pregnancy history and BMI gain since age 18 but excluded women whose first birth occurred before age 18 in order to evaluate whether pregnancy history was the potential cause of weight gain/loss since age 18, specifically.

Data are presented before and after we controlled for potential confounders selected using previous literature that informed a directed acyclic graph (36), which was similar to the one published by Pirkle et al. (37) in 2014. Final covariate-adjusted models included race, maternal smoking status, fertility problems, oral contraceptive use, menopausal status, and BMI at age 18 (except where we assessed BMI gain as our outcome). Associations of gravidity and parity with midlife BMI or BMI gain were additionally adjusted for age at first birth (only in women who had ever given birth), because age at first birth could impact the number of pregnancies and births a woman could have. Similarly, associations of ages at first birth and last pregnancy with midlife BMI or BMI gain since age 18 were additionally adjusted for parity (for age at first birth) and gravidity (for age at last pregnancy).

To understand whether hormones partially explained (mediated) the proposed relations between pregnancy history and midlife BMI, we used a system of structural equations controlling for the same confounders mentioned above. Specifically, mediation analyses assessed the total effect (to evaluate the overall relationship between pregnancy history and midlife overweight/obesity), the natural direct effect (to assess how much of the total relationship is explained by the direct relationship between pregnancy history → midlife overweight/obesity), and natural indirect effect (to test how much of the total relationship is mediated through hormones: pregnancy history → hormone → midlife overweight/obesity) (38). All hormone data were natural log-transformed to meet normality assumptions.

Because we hypothesized a priori that associations of pregnancy history with midlife BMI or BMI gain since age 18 could differ between pre- and perimenopausal women, we also assessed these associations separately by menopausal status. All associations were considered significant at $P < 0.05$ using SAS 9.4 (version 14.3, SAS Institute), including PROC CAUSALMED to evaluate mediation.

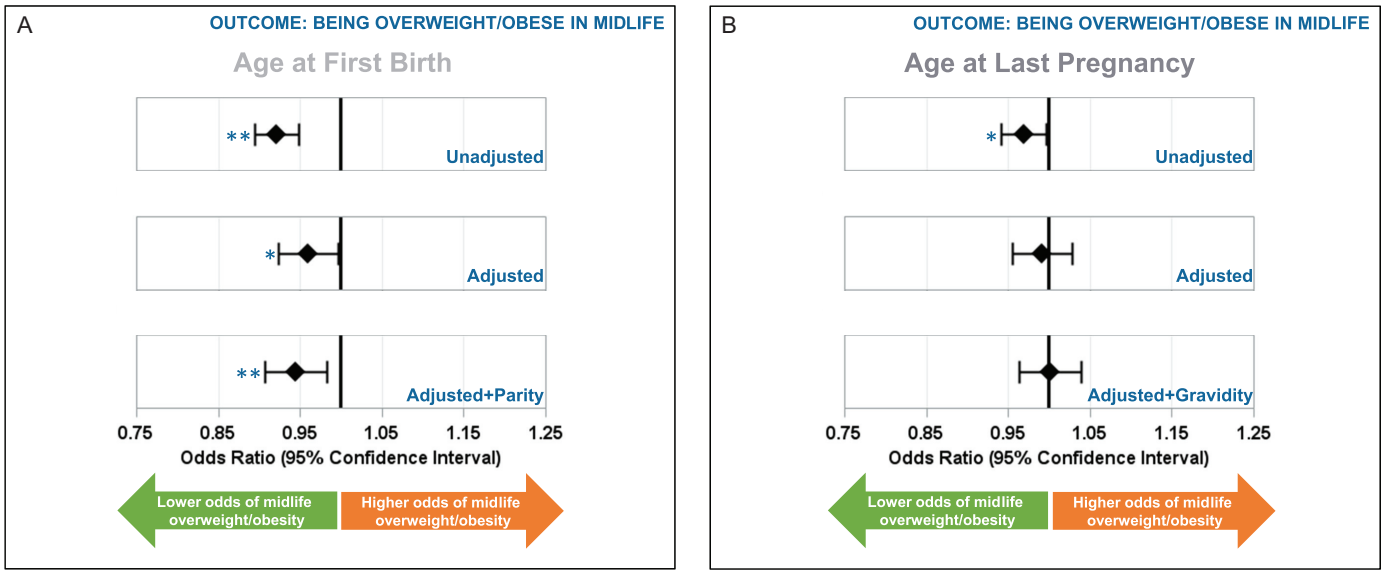

FIGURE 2 Associations of age at first birth and last pregnancy with midlife overweight/obesity. Binary logistic regression models evaluated associations of age at (A) first birth and (B) last pregnancy with the probability of being overweight/obese compared with under-/normal weight in midlife. Results are expressed as ORs (filled diamonds) and 95% CIs (solid lines) for the unadjusted, adjusted, and additionally adjusted models. Analyses control for race, maternal smoking status, fertility problems, oral contraceptive use, BMI at age 18, and menopausal status, and additionally control for parity (for age at first birth) or gravidity (for age at last pregnancy). Significant associations are those that do not cross the null (OR = 1.0) at $^{*}P < 0.05$ and $^{**}P < 0.01$.

Results

Characteristics/pregnancy history of MWHS participants

At the baseline visit, the majority of women were 45–49 y old (65.2%), premenopausal (64.6%), Caucasian/White (65.5%), college graduates (63.8%), employed (79.2%), married or living with a partner (65.0%), and had annual household incomes ≥$40,000 (74.4%) (Table 1). Physical activity "compared to others" was evenly distributed between "less than others" (33.2%), "as much as others" (31.3%), and "more than others" (34.4%). Most women (65.1%) reported consuming alcohol during the year before the study, whereas 54.7% reported never smoking, and 56.8% reported that their mother did not smoke while pregnant with them. Approximately 81% of women had never sought medical consultation for fertility problems, and 70.9% used oral contraceptives for ≥1 y (Table 1).

Most women had ≥2 pregnancies (76.8%) or live births (60.2%). The median (range) age at first birth was 27 (12–46) y, whereas the median (range) age at last pregnancy was 33 (14–53) y (**Table 2**). Although 69.1% of women reported having a normal weight at age 18, the majority (60.7%) were overweight/obese at 45–54 y. Around half of women did not change BMI categories since age 18, whereas 48.1% of women gained weight from age 18 to 45–54. Median (range) midlife hormone concentrations were as follows: estradiol: 56.70 (9.71–434.52) pg/mL; testosterone: 0.29 (0.08–5.40) ng/mL; and progesterone: 1.60 (0.05–32.93) ng/mL.

Associations of pregnancy history with midlife overweight/obesity

We first assessed whether pregnancy history was associated with BMI status at 45–54 y of age, where BMI was assessed in categories (logistic regression analysis) or linearly (linear regression analysis). We found that gravidity was not associated with midlife overweight/obesity in unadjusted or covariate-adjusted models (**Figure 1**A). After additionally adjusting for age at first birth, women with ≥2 pregnancies had 62% lower odds of overweight/obesity than women with 1 pregnancy (OR = 0.38; 95% CI: 0.17, 0.83; $P = 0.02$). The linear relation between gravidity and midlife BMI was attenuated compared with results from logistic models, where women with ≥2 pregnancies had a nonsignificant 4.9% lower BMI compared with those with 1 pregnancy after adjusting for age at last pregnancy ($\beta = -0.05$; 95% CI: −0.11, 0.007; $P = 0.09$; **Supplemental Table 1**).

Compared with women who had 1 live birth, women who never gave birth and those who gave birth ≥2 times had lower odds of being overweight/obese by age 45–54 y (Figure 1B). In unadjusted models, women who gave birth ≥2 times had 44% lower odds of overweight/obesity than women who only gave birth once (OR = 0.56; 95% CI: 0.37, 0.84; $P = 0.005$), and women who had never given birth had 40% lower odds of overweight/obesity than women with 1 live birth, but this was marginally nonsignificant (OR = 0.60; 95% CI: 0.34, 1.07; $P = 0.09$). After adjusting for potential confounders, women with 0 or ≥2 live births had 53% (OR = 0.47; 95% CI: 0.23, 0.96; $P = 0.04$) and 42% (OR = 0.58; 95% CI: 0.35, 0.95; $P = 0.03$), respectively, lower odds of overweight/obesity than women who only gave birth once. Even after additionally adjusting for age at first birth, women with ≥2 live births had 51% (OR = 0.49; 95% CI: 0.29, 0.82; $P = 0.007$) lower odds of overweight/obesity than women with 1 birth. Linear regression models evaluating these associations differed somewhat from logistic regression analyses (Supplemental Table 1). In the unadjusted linear model, women with ≥2 live births had 7.1% lower midlife BMI compared with women with 1 birth ($\beta = -0.07$; 95% CI: −0.12, −0.03;

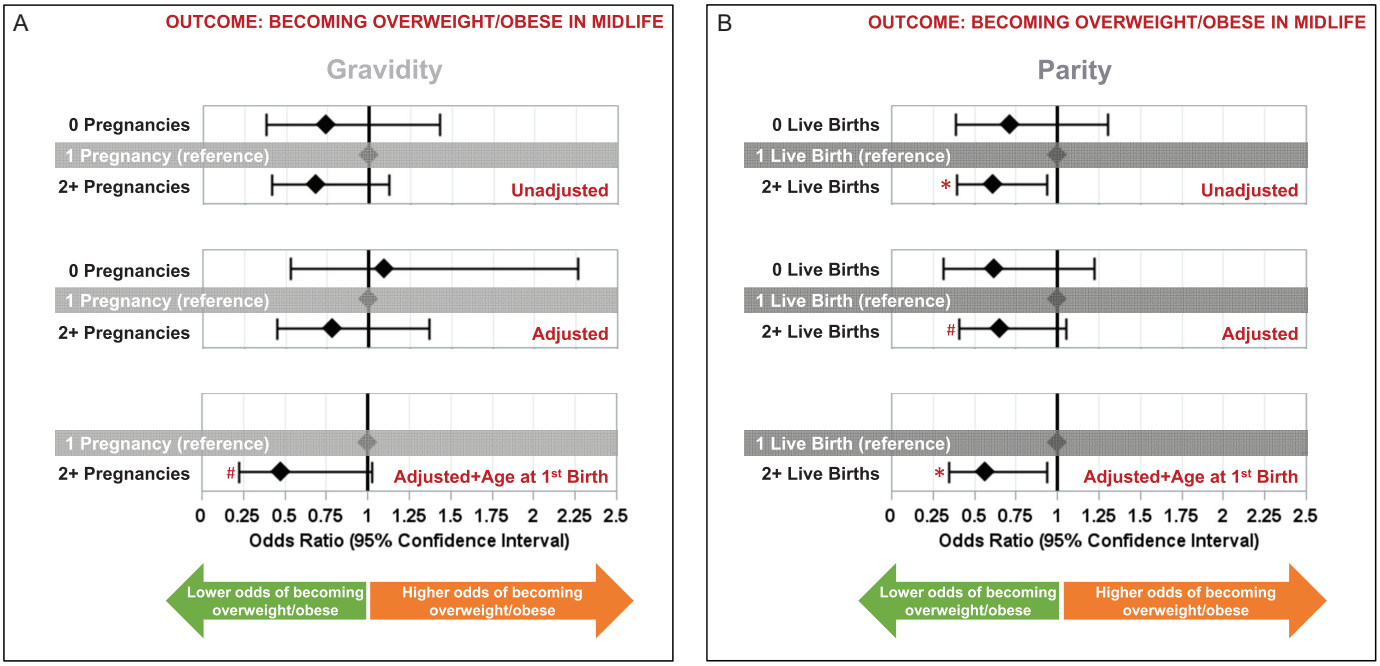

FIGURE 3 Associations of gravidity (number of pregnancies) and parity (number of live births) with becoming overweight/obese in midlife. Binary logistic regression models evaluated associations of (A) gravidity and (B) parity with the probability of becoming overweight/obese compared with remaining under-/normal weight from age 18 to midlife. Results are expressed as ORs (filled diamonds) and 95% CIs (solid lines) for the unadjusted, adjusted, and additionally adjusted models. Models controlled for race, maternal smoking status, fertility problems, oral contraceptive use, BMI at age 18, and menopausal status, and additionally controlled for age at first birth. Significant associations are those that do not cross the null (OR = 1.0) at $^{\#}P < 0.10$ and $^{*}P < 0.05$.

$P = 0.002$), but this was attenuated after adjusting for potential confounders and age at first birth. In linear regression models, midlife BMI did not differ between women who never gave birth and those who gave birth once.

The age at which women gave birth to their first child was associated with midlife overweight/obesity in all logistic regression models (**Figure 2**A). In unadjusted models, each 1-y increase in age at first birth was associated with 8% lower odds of midlife overweight/obesity (OR = 0.92; 95% CI: 0.90, 0.95; $P < 0.0001$). After adjusting for potential confounders and additionally adjusting for parity, each 1-y increase in age at first birth was associated with 4% (OR = 0.96; 95% CI: 0.92, 1.00; $P = 0.03$) and 6% (OR = 0.94; 95% CI: 0.91, 0.98; $P = 0.005$), respectively, lower odds of midlife overweight/obesity. In unadjusted linear regression models (Supplemental Table 1), each 1-y increase in age at first birth was associated with a 0.9% decrease in midlife BMI ($\beta = -0.009$; 95% CI: −0.01, −0.005; $P < 0.0001$), which was attenuated after adjusting for confounders.

Age at last pregnancy was associated with midlife overweight/obesity only in the unadjusted logistic regression model, such that every 1-y increase in age at last pregnancy was associated with 3% lower odds of midlife overweight/obesity (OR = 0.97; 95% CI: 0.94, 1.00; $P = 0.03$; Figure 2B). Similarly, only in the unadjusted linear regression model was age at last pregnancy associated with midlife BMI, where every 1-y increase in age at last pregnancy was associated with 0.4% lower midlife BMI ($\beta = -0.004$; 95% CI: −0.007, −0.001; $P = 0.01$; Supplemental Table 1). Associations between pregnancy history and midlife overweight/obesity were not different by menopausal status (**Supplemental Table 2**).

Associations of pregnancy history with BMI gain since age 18

Because we observed associations between pregnancy history and BMI status at age 45–54, we also wanted to ask whether pregnancy history was associated with BMI change (or more specifically, BMI gain) from age 18 to age 45–54. Our data suggest that parity, but not gravidity, was associated with BMI gain since age 18 (**Figure 3**). In the unadjusted model, compared with women who gave birth once, those with ≥2 births had 39% lower odds of becoming overweight/obese (OR = 0.61; 95% CI: 0.40, 0.93; $P = 0.02$; Figure 3B). This association was marginally nonsignificant after adjusting for confounders (OR = 0.66; 95% CI: 0.41, 1.06; $P = 0.08$). However, after additionally adjusting for age at first birth, women who gave birth ≥2 times had 43% lower odds of becoming overweight/obese in midlife compared with women who only gave birth once (OR = 0.57; 95% CI: 0.34, 0.94; $P = 0.03$). BMI gain since age 18 in women who never gave birth was not significantly different from women who gave birth only once.

Age at first birth was also associated with BMI gain since age 18 (**Figure 4**A). In unadjusted models, each 1-y increase in age at first birth was associated with 8% lower odds of becoming overweight/obese in midlife (OR = 0.92; 95% CI: 0.89, 0.95; $P < 0.0001$). After adjusting for confounders and additionally adjusting for parity, each 1-y increase in age at first birth was associated with 3% (OR = 0.97; 95%

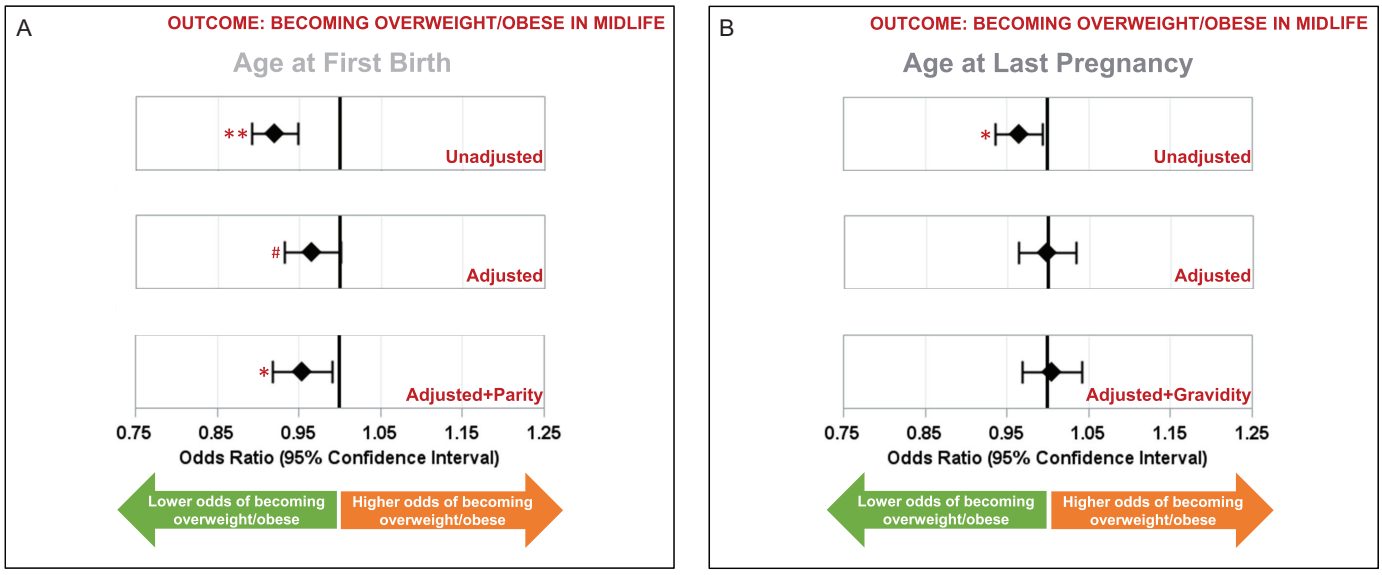

FIGURE 4 Associations of age at first birth and last pregnancy with becoming overweight/obese in midlife. Binary logistic regression models evaluated associations of age at (A) first birth and (B) last pregnancy with the probability of becoming overweight/obese compared with remaining under-/normal weight from age 18 to midlife. Results are expressed as ORs (filled diamonds) and 95% CIs (solid lines) for the unadjusted, adjusted, and additionally adjusted models. Models controlled for race, maternal smoking status, fertility problems, oral contraceptive use, BMI at age 18, and menopausal status, and additionally controlled for parity (for age at first birth) or gravidity (for age at last pregnancy). Significant associations are those that do not cross the null (OR = 1.0) at $^{\#}P < 0.10$, $^{*}P < 0.05$, and $^{**}P < 0.01$.

CI: 0.93, 1.00; $P = 0.06$) and 5% (OR = 0.95; 95% CI: 0.92, 0.99; $P = 0.01$), respectively, lower odds of becoming overweight/obese in midlife. Age at last pregnancy was only associated with BMI gain in the unadjusted model, where every 1-y increase in age at last pregnancy was associated with 4% lower odds of becoming overweight/obese in midlife (OR = 0.96; 95% CI: 0.94, 0.99; $P = 0.02$; Figure 4B). Associations between age at last pregnancy and BMI gain since age 18 were attenuated after adjusting for confounders and additionally adjusting for gravidity. Associations between pregnancy history and BMI gain since age 18 were not different by menopausal status (**Supplemental Table 3**). All associations remained consistent in sensitivity analyses excluding women who gave birth before age 18 (**Supplemental Table 4**).

Associations of pregnancy history and midlife BMI mediated by midlife reproductive hormones

We previously reported associations of midlife hormones with midlife BMI (23). Presently, we observed consistent associations of parity and age at first birth with both midlife overweight/obesity and BMI gain since age 18. Therefore, we assessed whether midlife estradiol, testosterone, or progesterone concentrations mediated these associations (**Figure 5**). Although we observed that parity was significantly associated with midlife overweight/obesity (natural direct effect), there was no mediation of the relationship between parity and midlife overweight/obesity by estradiol, testosterone, or progesterone (natural indirect effect, Figure 5A). Similarly, age at first birth was also significantly associated with midlife overweight/obesity (natural direct effect), but there was no mediation of the relationship between age at first birth and midlife overweight/obesity by estradiol, testosterone, or progesterone (natural indirect effect, Figure 5B). Hormones also did not mediate these associations after concurrently adjusting for parity or age at first birth, and relationships in the mediation analyses were also not modified by menopausal status (data not shown).

Discussion

Results from this study suggest that parity and age at first birth are important predictors of overweight/obesity in pre- and perimenopausal women. Specifically, women who gave birth only once and those who were younger at their first birth had higher odds of being overweight/obese in midlife, even after controlling for important confounders. Additionally, parity and age at first birth were independently associated with weight gain from age 18 to age 45–54. These associations were consistent between pre- and perimenopausal women, and associations of parity and age at first birth with midlife BMI were not explained by midlife hormones.

Parity, but not gravidity, was associated with midlife overweight/obesity and BMI gain since age 18

Adaptations in maternal carbohydrate and lipid metabolism, especially in mid-to-late pregnancy, lead to gestation-related fat accumulation to central regions (39, 40). This could partially explain why we observed that parity, but not gravidity, was strongly associated with midlife obesity and adult weight accumulation. Carrying a child to full term is associated with maternal metabolic changes and weight gain that persist after pregnancy. Furthermore, having children is accompanied by unique biological and lifestyle shifts, which put parous women at higher risk of

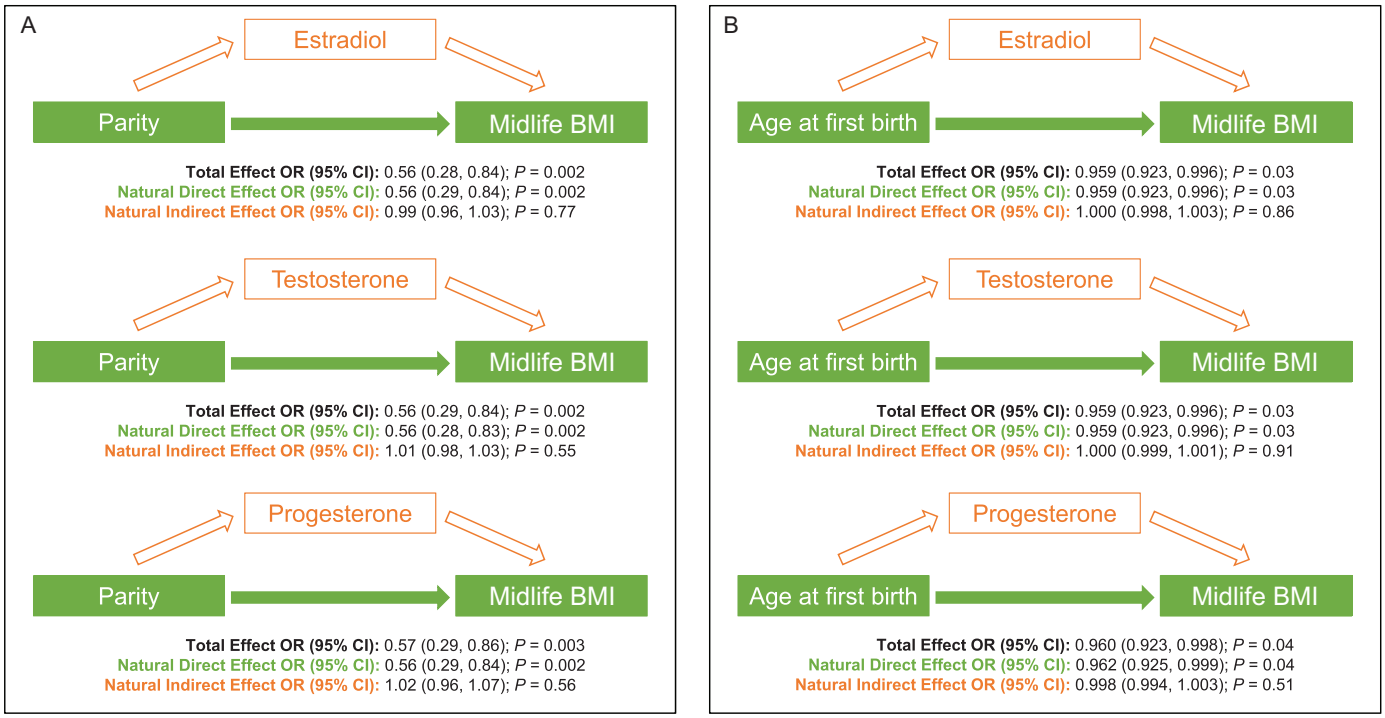

FIGURE 5 Associations of parity (number of live births) and age at first birth with midlife BMI—mediation by midlife hormones. A system of structural equations assessed the mediating effect of estradiol, testosterone, and progesterone on associations of parity and age at first birth with midlife BMI. Models were adjusted for race, maternal smoking status, fertility problems, oral contraceptive use, BMI at age 18, and menopausal status. Results are expressed as ORs (95% CIs) for the total effect, natural direct effect (green), and natural indirect effect (orange). Green filled arrows represent significant ($P < 0.05$) associations, whereas orange unfilled arrows represent nonsignificant ($P > 0.05$) associations.

obesity compared with nulliparous women (specifically those who become pregnant but do not give birth to a child).

Interestingly, our observation that having 1 child (being primiparous) puts women at greatest risk of midlife overweight/obesity is consistent with studies showing that parous women gain the most weight during their first pregnancy/birth compared with subsequent ones (41, 42). This suggests that there is a higher likelihood of drastic and persistent body composition and metabolic changes after having 1 child. Although the exact causes of this "primiparous paradox" are not clear, studies suggest that multiparous women (compared with those who only have 1 child) are less likely to experience anxiety and depression after pregnancy (43), and are more motivated to make dietary changes and lose weight after subsequent pregnancies (44), which could put primiparous women at higher risk of obesity. Similar to our observations, a large prospective cohort of US Caucasian/White and African American/Black premenopausal women found that women with 1 live birth (but not ≥2 live births), had higher weight gain and waist-to-hip ratio compared with women with no live births over a 5-y follow-up (45). Similar findings were observed at the 10-y follow-up of the same cohort, where substantial weight gain occurred in women who had only 1 birth, whereas higher-order births were not associated with excess weight gain (46). These findings are analogous to ours, showing that women who give birth only once have higher odds of midlife overweight/obesity than women who never give birth or those who give birth ≥2 times.

Our results are somewhat inconsistent with several other studies in racially/ethnically diverse populations of only pre- (47, 48), post- (24, 49, 50), or a combination of pre-, peri-, and postmenopausal women (25–30), showing that having more live births is linearly associated with higher BMI or with weight gain since age 18 (27). Given that most women in our study were Caucasian/White or African American/Black and none were postmenopausal, these discrepant findings could be due to racial/ethnic and/or menopausal status differences, which will need to be further investigated. Overall, as discussed above, our findings are supported by previous research, and appear to suggest that women who give birth only once are more likely to experience weight gain during their reproductive years, but substantially more data are needed to understand the social and lifestyle factors that influence this observation.

Age at first birth, not age at last pregnancy, was associated with midlife overweight/obesity and BMI gain since age 18

Pregnancy itself is associated with numerous metabolic changes to support fetal growth, including insulin resistance and fat accumulation (40, 51), and these metabolic changes can persist after pregnancy (52). Additionally, pregnancy and obstetric complications could impact physical activity and mobility well after delivery (53). These deleterious effects would emerge earlier in women who have children at a younger age, which could have major implications for lifelong health. Our find-

ing that women who have their first child at a younger age are at elevated risk for midlife overweight/obesity is consistent with previous studies in pre-, peri-, and postmenopausal women (24, 47, 54, 55). One study proposed that giving birth at a younger age provides women with more time to have children, leading to weight accumulation between pregnancies (54). The same study also found that among postmenopausal Chinese women, having more reproductive years was associated with higher midlife BMI and waist circumference (54). In our study, younger age at first birth was associated with higher risk of BMI gain from age 18 to 45–54, and this was independent of parity. Because younger age at first birth has been associated with higher central adiposity (24, 54) and poorer physical performance during midlife (53), earlier childbirth could be an independent risk factor for midlife overweight/obesity.

Beyond biological factors, earlier childbirth is associated with numerous lifestyle shifts. For example, women who give birth in their teens or 20s might have to stall their education to care for their child (56). Younger mothers might also have lower incomes, leading to poorer diet quality compared with older mothers (57). Although we did not record age at last birth, our findings were consistent with other studies showing no associations between age at last pregnancy and midlife obesity or weight accumulation (24, 58), suggesting that age at first birth is a stronger predictor of lifetime obesity risk than the age at which a woman stops having children.

Hormones did not mediate associations of parity and age at first birth with midlife overweight/obesity

We previously reported that as midlife BMI increases, midlife estradiol and progesterone concentrations decrease, whereas testosterone concentrations increase (23). In the current study, we hypothesized that pregnancy-related changes in hormones might persist into midlife and partially explain observed associations of parity and age at first birth with midlife overweight/obesity. However, we did not observe such a mediation. The relationship between reproductive hormones and obesity, especially during the menopausal transition, is complex. Studies in pre-, peri-, and postmenopausal women have shown that adipose tissue deposition can be influenced by reproductive hormones (17), but that the reverse can also be true (23, 59). Therefore, additional studies are needed to better understand the mechanisms connecting midlife obesity and shifts in reproductive hormones.

Strengths and limitations

This study has several strengths and limitations. Although this cohort is not a true representative sample of US women, we were able to contribute to the growing literature supporting pregnancy history as a predictor of midlife obesity in US pre- and perimenopausal women. However, because this study was designed to evaluate predictors of hot flashes in midlife women, future studies should additionally obtain information about prepregnancy weight, gestational weight gain, and lifestyle before and during pregnancies. Although there is potential for bias from pregnancy history self-recall, there is good-to-excellent agreement between pregnancy history recall compared with medical records (60, 61). Additionally, each woman's midlife height and weight were measured and recorded by trained clinical staff, which reduced the potential for bias and variability in our outcome. There is also potential for bias with self-reported weight at age 18; one validation study suggests that individuals have a tendency to underreport past body weight; however, the same study suggests that self-recall of past body weight is accurate at the population level (62). Although women in the study were predominantly Caucasian/White and African American/Black (and not any other races/ethnicities), this relatively homogeneous population provided us with the power to assess potential hormonal mechanisms driving associations of pregnancy history with midlife obesity. Lastly, blood samples were not drawn on specific days or phases of the menstrual cycle. Because women were experiencing irregular menses, the lack of standardized blood collection could have introduced variability in hormone measurements. Despite this limitation, 4 blood samples over 4 consecutive weeks were collected and averaged to provide better estimates of each woman's reproductive hormone status.

Conclusions

Findings from this study suggest that having 1 child or being younger at first childbirth are important and persistent predictors of a woman's health before and during menopause. We observed that associations between pregnancy history and midlife BMI are potentially unrelated to midlife hormone concentrations, suggesting that other unmeasured modifiable/intervenable factors are involved in pregnancy-related midlife obesity. Therefore, to reduce the prevalence and incidence of midlife obesity and its associated morbidities in women, primiparous women and those who are younger at their first childbirth, specifically, might benefit from interventions that teach healthy lifestyle habits during their reproductive years.

Acknowledgments

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