ARTICLE IN PRESS

Reproductive Toxicology xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Reproductive Toxicology

journal homepage: www.elsevier.com/locate/reprotox

Body size at birth, early-life growth and the timing of the menopausal transition and natural menopause

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ARTICLE INFO

Keywords:
Birth weight
Menopause
Early life
Prenatal exposure
Growth

ABSTRACT

Background: Whether birth weight and early-life growth are associated with age at menopause has not been resolved.
Methods: We conducted a prospective study in two U.S. birth cohorts to investigate the relation of weight at birth and weight and growth trajectory through age 4 years to menstrual status among 1001 women ages 39–49 years. We used logistic regression models with GEE.
Results: Women who weighed more at birth and at one year were less likely to have experienced the menopausal transition or natural menopause by age 39–49 years (odds ratio(OR) = 0.50, 95% confidence interval (CI) = 0.32, 0.77 and OR = 0.82, 95%CI = 0.68, 0.99 per kilogram increase at birth and age one, respectively).
Conclusions: Women who had a lighter weight at birth and women who were lighter than their peers through infancy experienced the menopausal transition or natural menopause at an earlier age.

1. Introduction

Age at menopause has significant implications for women's health. Earlier age at natural menopause is associated with increased risks of some chronic conditions, including cardiovascular disease [1,2], type 2 diabetes [3] and osteoporosis [4], but decreased risks of subtypes of breast [5,6] and ovarian cancer [7]. Earlier age at menopause is also associated with an increase in all-cause mortality [8]. Identifying risk factors associated with earlier age at menopause is important for understanding and potentially modifying the long-term health effects of ovarian aging.

The developmental origins hypothesis proposes that adaptations made by the fetus in response to the intrauterine environment affect the structure and function of the developing organs, with consequences that persist into adulthood and influence chronic disease risk [9]. The ovarian follicle supply is established by 5 months gestation [10,11]. Menopause occurs when the number of ovarian follicles falls below a critical threshold [10,12–14]. Under life history theory, a poor intrauterine and early life environment could accelerate ovarian aging in anticipation of a reduced lifespan [15] through a reduction in the number of follicles formed during gestation and/or an increase in the rate of follicle atresia.

Under the hypothesis that the timing of reproductive events including menopause may be influenced by the intrauterine environment [16–18], it was proposed that low birth weight, an indicator of suboptimal intrauterine conditions including undernutrition and impaired fetal growth [19], would be associated with an earlier age at natural menopause [20]. Several studies have examined the association between birth weight and the timing of menopause, however, with inconsistent results [21–29]; a recent review found that the association

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https://doi.org/10.1016/j.reprotox.2019.02.013
Received 14 September 2018; Received in revised form 6 February 2019; Accepted 28 February 2019
0890-6238/

between birth weight and age at menopause was largely null [30]. Interpretations of these studies are limited, however, by the quality of the data, namely the use of birth weight recalled in adulthood [22,25,27,29] and/or recalled age at menopause in samples assessed outside the age range when menopause usually occurs [21,25]. In a follow-up of women ages 44–45 years with prospective birth weight data from the 1958 British Birth Cohort, the association between birth weight and age at menopause was U-shaped, with both low and high birth weight babies at increased risk of earlier menopause [26]. In the 1946 British Birth Cohort, birth weight was unrelated to age at menopause in follow-ups conducted at 53 and 57 years, but lower weight at two years of age was associated with earlier age at menopause [23,24]. Together, these studies suggest that both intrauterine and infant growth may influence menopausal timing.

We draw on data from an adult follow-up study of two birth cohorts to examine whether prospective measures of weight and length at birth and rate of weight and height gain during infancy and early childhood is related to menstrual status at ages 39–49 years, adjusting for other early-life factors including *in utero* smoke exposure. Our primary outcome is the occurrence of the menopausal transition, including women who have reached natural menopause (since by definition these women have experienced the transition).

2. Methods

2.1. Study participants

We used prospectively collected data from the Early Determinants of Mammographic Density (EDMD) study to examine the relations between birth size, early-life growth and menopausal timing. Details of this cohort have been previously published [31–33]. In brief, EDMD is an adult follow-up of 1134 women ages 39–49 years whose mothers enrolled in two birth cohorts, the New England Collaborative Perinatal Project (CPP) and the California Child Health and Development Study (CHDS), during their pregnancies from 1959-1967 [34,35]. We used prospective data from mothers collected during pregnancy and anthropometric data on their daughters collected through age 4 years. We obtained data on menstrual status from participants at adult follow-up using a computer-assisted telephone interview [32]. The study was approved by the institutional review boards at Columbia University Medical Center, Kaiser Permanente, Brigham and Women's Hospital, and Brown University.

2.2. Baseline maternal and childhood data collection

The data collected from the maternal interview at clinic visits during pregnancy included the mother's smoking status during pregnancy, the mother's education and family income. Gestational age was calculated as the date of delivery minus the date of the last menstrual period (LMP). Shortly after birth, trained personnel weighed each infant to the nearest gram (g) and measured for length to the nearest centimeter (cm) from crown to heel. In the CPP, trained clinical staff measured childhood height and weight at each follow-up visit, including at 4 months, 12 months, and 4 years of age [34]. In the CHDS, childhood height and weight data was abstracted from medical records of pediatric visits through at least age 5 [36].

2.3. Adult data collection

The data collected from the interview with the adult daughter included the participant's age at interview, weight and height in the 20s, 30s and at interview, smoking status, and menstrual status. We used self-reported weight and height in the 20s and at interview to calculate body mass index (BMI). Participants reported if, during the 12 months preceding the interview, there was a time when they went for 60 days or longer without menstruating (but were not pregnant or nursing), the number of menstrual periods in the last 12 months and the first day of their LMP. We asked participants whether their periods stopped because of gynecologic surgery, including a hysterectomy or oophorectomy, medication, radiation, chemotherapy, or other reasons besides natural menopause. We recorded age at surgery for participants who reported bilateral oophorectomy or hysterectomy. In addition, participants reported if they had ever used or were currently using hormone therapy (HT) and the age at which they started using it. Since the exact dates for surgery and HT use were not available, we used the integer age reported and added 0.5 years to that when calculating intervals between two dates. We did not model the age at menopause or the menopausal transition directly as the outcome since the age at LMP may not accurately reflect the age at onset of the menopausal transition. We instead dichotomized the outcome based on the menstrual status at the time of adult interview when participants were 39–49 years of age.

2.4. Classification of menstrual status

Participants were classified as menstruating, having experienced the menopausal transition or having experienced natural menopause based on the information provided at interview. We excluded women who had experienced surgical menopause (N = 91) and women with unknown menstrual status (n = 42) from the analyses. The latter group included women who began using HT before reaching natural menopause (LMP + 12 months) and were either currently using HT or had stopped using HT but had not experienced an unmedicated period after stopping HT.

i) **Menstruating:** Participants who were menstruating and had not experienced 60 consecutive days of amenorrhea during the 12 months preceding the interview were classified as menstruating. Pregnant participants were included in this category.
ii) **Menopausal transition:** Participants were classified as having experienced the onset of the menopausal transition if they reported that in the last 12 months i) they had at least one period and ii) had experienced at least one 60 day episode of amenorrhea unrelated to pregnancy or lactation. This definition for the late menopausal transition has been recommended for use in research by the Stages of Reproductive Ageing Workshop (STRAW) in 2001 [37]. The definition was re-evaluated in four large cohorts by researchers in the ReSTAGE Collaboration who again recommended it as a marker for the late menopausal transition [38].
iii) **Natural menopause:** We classified participants whose LMP had occurred more than 12 months before the interview and who did not attribute their amenorrhea to surgery, radiation, chemotherapy or exogenous hormones or other medications as having experienced natural menopause. We also classified participants whose LMP occurred at least 12 months before starting HT as having experienced natural menopause.
iv) **Combined Category:** Participants who experienced natural menopause have, by definition, experienced 60 days or more of amenorrhea during the 12 months preceding the interview. Thus, we defined an outcome category that included participants in the menopausal transition and participants who had experienced natural menopause (hereafter the "combined category").

2.5. Statistical analysis

We examined the associations between birth weight, birth length, weight and length at 4 months and 1 year, and BMI at 4 years and in the 20s and menstrual status. We used measures of weight and length in infancy rather than BMI because BMI is not recommended for clinical use before age 2 years [39]. We also considered ponderal index at birth in a separate model as an alternate measure of adiposity and symmetry at birth. We used individual cubic splines to interpolate height and weight measurements at 4 months, 12 months and 4 years, since not all

Table 1
Characteristics of participants by menstrual status at adult interview (n = 1001).

	Menstruating		Menopausal transition		Natural menopause	
	n = 773		n = 190		n = 38	
Early Life (N, column %)						
EDMD Study Site[a]						
California CHDS	396	51.2	87	45.8	7	18.4
New England CPP	377	48.8	103	54.2	31	81.6
Maternal education at registration[a]						
Less than high school	177	23.1	49	26.1	21	55.3
High school graduate	316	41.1	80	42.5	13	34.2
Some college, college graduate or higher	275	35.8	59	31.4	4	10.5
Family income at registration[a]						
< US$5000	234	30.3	70	36.8	18	47.4
US$5000 to < US$7000	239	30.9	55	29.0	10	26.3
≥ US$7000	237	30.7	51	26.8	4	10.5
Unknown	63	8.1	14	7.4	6	15.8
Prenatal smoke exposure[a]						
Yes	298	39.7	74	40.2	24	63.2
No	452	60.3	110	59.8	14	36.8
Gestational age in weeks (mean, SD)	40.2	1.9	39.9	2.2	40.5	2.1
Early Life Body Size (mean, SD)						
Birth weight (kg)[a]	3.5	0.5	3.4	0.5	3.3	0.6
Birth length (cm)	51.4	3.0	51.0	2.7	50.8	2.5
Ponderal index (kg/m^3)	26.0	6.8	25.3	3.6	24.9	3.4
Weight at 4 months (kg)[a]	6.5	0.8	6.3	0.8	6.1	1.2
Weight at 1 year (kg)[a]	9.7	1.2	9.5	1.3	9.4	1.4
Weight at 4 years (kg)	16.8	2.3	16.5	2.6	16.8	2.5
Height at 4 months (cm)	62.5	2.7	61.9	3.3	62.1	4.3
Height at 1 year (cm)	73.9	3.1	73.4	3.4	73.9	3.4
Height at 4 years (cm)	100.7	4.7	99.8	4.7	100.5	4.3
Early Life Growth Patterns (N, column %)						
Weight pattern from 0–4 months						
Rapid[b]	289	37.4	77	40.7	10	26.3
Stable[c]	207	26.8	44	23.3	12	31.6
Slow[d]	276	35.8	68	36.0	16	42.1
Weight pattern from 4–12 months[a]						
Rapid[b]	210	27.6	40	21.2	18	48.7
Stable[c]	328	43.0	98	51.9	16	43.2
Slow[d]	224	29.4	51	27.0	3	8.1
Weight pattern from 1–4 years						
Rapid[b]	211	28.6	56	30.9	14	37.8
Stable[c]	274	37.2	69	38.1	14	37.8
Slow[d]	252	34.2	56	30.9	9	24.3
Height pattern from 0–4 months						
Rapid[b]	243	31.6	62	33.0	15	39.5
Stable[c]	230	29.9	48	25.5	9	23.7
Slow[d]	297	38.6	78	41.5	14	36.9
Height pattern from 4–12 months						
Rapid[b]	254	33.4	66	35.1	15	40.5
Stable[c]	252	33.2	59	31.4	11	29.7
Slow[d]	254	33.4	63	33.5	11	29.7
Height pattern from 1–4 years						
Rapid[b]	236	32.1	53	29.4	10	27.0
Stable[c]	243	33.1	62	34.4	11	29.7
Slow[d]	256	34.8	65	36.1	16	43.2
Adult (mean, SD)						
Age at interview [a]	43.8	1.8	44.7	1.9	44.8	1.7
BMI at interview (kg/m^2) [a]	26.7	5.9	28.1	7.6	27.4	5.9
BMI in the 20s (kg/m^2)	22.2	4.0	22.8	4.7	22.4	4.7
Race (N, column %)						
Non-Hispanic White	605	78.4	151	79.9	31	81.6
Non-Hispanic Black	87	11.3	20	10.6	6	15.8
Hispanic	47	6.1	11	5.8	1	2.6
Non-Hispanic API/other	33	4.3	7	3.7	0	0

API: Asian Pacific Islander; BMI: Body Mass Index; CHDS: Child Health and Development Studies; CPP: Collaborative Perinatal Project.
Note: < 5% of observations are missing for all variables and are not shown, with the exception of family income.
[a] $p < .05$, comparison of means by menstrual status for continuous variables and continuous of frequencies by menstrual status for categorical variables.
[b] Rapid growth is defined as an increase of ≥1 major CDC reference percentiles (5th, 10th, 25th, 50th, 75th, 95th).
[c] Stable growth is defined as staying within 1 major CDC reference percentile.
[d] Slow growth is defined as a decrease of ≥1 major CDC reference percentiles (5th, 10th, 25th, 50th, 75th, 95th).

clinic visits occurred at these exact time points [40]. We also examined postnatal weight and height gain in three time periods (0–4 months, 4–12 months, and 1–4 years). Since the growth rate of weight and height changes with age, we defined the height and weight gains respectively by their within-cohort percentile rank changes in each of the time periods. Alternatively, we categorized the percentile rank changes

Table 2
Odds ratios (ORs) and 95% confidence intervals relating birth size and early life growth characteristics to menstrual status at adult interview: natural menopause, the menopausal transition, and the combined category compared with menstruating women, EDMD Study.

	Menopausal Transition				Natural Menopause				Combined			
	Age and site-adjusted		Multivariable-adjusted		Age and site-adjusted		Multivariable-adjusted		Age and site-adjusted		Multivariable-adjusted	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Birth weight (per 1 kg increase)[a]	**0.49**	**0.32, 0.75**	**0.52**	**0.33, 0.83**	**0.36**	**0.13, 0.99**	0.37	0.13, 1.08	**0.47**	**0.31, 0.71**	**0.50**	**0.32, 0.77**
Birth length (per 1 cm increase)[a]	1.06	0.97, 1.15	1.05	0.95, 1.15	1.15	0.96, 1.38	1.13	0.92, 1.39	1.07	0.98, 1.16	1.05	0.96, 1.15
Ponderal index (per 1 kg/m^3 increase)[b]	0.96	0.90, 1.02	0.97	0.91, 1.03	0.89	0.78, 1.02	0.90	0.79, 1.03	0.95	0.90, 1.01	0.96	0.90, 1.02
Absolute size												
Weight at 4 months (per 1 kg increase)[c]	0.81	0.62, 1.06	0.81	0.61, 1.07	0.62	0.27, 1.45	0.75	0.31, 1.80	0.79	0.60, 1.03	0.80	0.61, 1.06
Weight at 1 year (per 1 kg increase)[d]	**0.82**	**0.67, 1.00**	0.83	0.68, 1.02	0.69	0.42, 1.11	0.76	0.47, 1.22	**0.80**	**0.66, 0.97**	**0.82**	**0.68, 0.99**
BMI at 4 years (per 1 kg/m^2 increase)[e]	1.04	0.91, 1.19	1.00	0.87, 1.16	1.11	0.89, 1.37	1.14	0.92, 1.42	1.05	0.93, 1.19	1.02	0.89, 1.16
BMI in the 20s (per 1 kg/m^2 increase)[f]	**1.05**	**1.01, 1.09**	**1.05**	**1.01, 1.09**	1.03	0.95, 1.12	1.02	0.94, 1.12	**1.05**	**1.01, 1.09**	**1.05**	**1.01, 1.09**
Relative change												
Percentile Rank Change in Weight 0–4 months (per 10 unit increase)[g]	0.95	0.88, 1.02	0.95	0.88, 1.02	**0.82**	**0.69, 0.98**	0.86	0.71, 1.03	**0.93**	**0.87, 1.00**	**0.93**	**0.87, 1.00**
Percentile Rank Change in Length 0–4 months (per 10 unit increase)[g]	0.99	0.92, 1.07	1.00	0.93, 1.08	1.09	0.94, 1.26	1.08	0.92, 1.27	1.01	0.94, 1.08	1.02	0.95, 1.09
Percentile Rank Change in Weight 4–12 months (per 10 unit increase)[h]	0.93	0.84, 1.04	0.95	0.85, 1.06	0.95	0.76, 1.20	0.95	0.74, 1.21	0.94	0.85, 1.04	0.95	0.86, 1.06
Percentile Rank Change in Length 4–12 months (per 10 unit increase)[h]	1.04	0.95, 1.14	1.02	0.94, 1.12	1.19	0.98, 1.45	1.12	0.90, 1.40	1.06	0.98, 1.15	1.05	0.96, 1.14
Percentile Rank Change in Weight 1–4 years (per 10 unit increase)[i]	0.98	0.89, 1.08	0.96	0.87, 1.06	1.03	0.86, 1.24	1.05	0.88, 1.26	0.98	0.90, 1.08	0.97	0.88, 1.06
Percentile Rank Change in Length 1–4 years (per 10 unit increase)[i]	0.98	0.89, 1.09	1.00	0.90, 1.11	1.12	0.93, 1.36	1.11	0.92, 1.34	1.01	0.92, 1.11	1.02	0.92, 1.12

BMI: body mass index; CI: confidence interval; EDMD: Early Determinants of Mammographic Density; kg: kilograms.

Note: All exposures are continuous. The inverse of the ORs represent the association between smaller size (1-unit decrease) or slower growth (10-percentile decrease in percentile rank change in weight or height) and the menstrual status outcome. Estimates that are statistically significant at $p < .05$ are in bold.

[a] Multivariable model includes birth weight, birth length, age at interview, site, prenatal smoke exposure, maternal education at birth, family income at birth and gestational age.

[b] Multivariable model includes age at interview, site, prenatal smoke exposure, maternal education at birth, family income at birth and gestational age.

[c] Multivariable model includes everything in previous model described in [a] plus weight and length at 4 months.

[d] Multivariable model includes everything in previous model described in [a] plus weight and length at 1 year.

[e] Multivariable model includes everything in previous model described in [d] plus BMI at 4 years.

[f] Multivariable model includes everything in previous model described in [e] plus BMI at 20s.

[g] Multivariable model includes everything in previous model described in [a] plus percentile rank change in weight and length from 0 to 4 months.

[h] Multivariable model includes everything in previous model described in [g] plus percentile rank change in weight and length from 4 to 12 months.

[i] Multivariable model includes everything in previous model described in [h] plus percentile rank change in weight and length from 1 to 4 years.

in weight and height within each time period into rapid, stable and slow growth patterns. We defined the rapid growth pattern as a within-cohort percentile rank increase of at least one major CDC reference percentile (5th, 10th, 25th, 50th, 75th, and 95th) in height or weight, respectively. For example, an increase from the 10th percentile to over the 25th percentile is considered as `rapid' weight gain. We defined the slow growth pattern as a within-cohort percentile rank decrease of at least one major CDC reference percentile. We used the stable growth pattern, defined as a within-cohort percentile rank that remained within one major reference percentile, as the referent group in these analyses.

We examined the associations between birth size and infancy and early childhood growth with menstrual status using logistic regression with generalized estimating equations to account for correlations in menstrual status between the 499 sisters in the sample [41]. For each model, we examined associations with the menstrual status outcome defined in three ways: i) whether the participant was in the menopausal transition at the time of interview; ii) whether the participant had experienced natural menopause at the time of interview; and (iii) whether the participant had experienced the combined category of the menopausal transition and natural menopause at the time of interview. In each analysis, the reference group was menstruating women, and age is included as a covariate. Associations between size and growth measures and these three outcomes were in the same direction. We therefore use the combined category as the primary outcome.

All models were adjusted for study site and age at adult interview as a continuous variable, which allows the odds ratios (OR) for the early-life exposures to be interpreted as an association with the timing of the menstrual status outcome. An OR of greater than 1 indicates that the exposure is associated with earlier age at the menopausal transition or natural menopause, and an OR of less than 1 indicates an association with later age. We assessed the association of age at interview with the combined menstrual status outcome using graphical methods and by examining linear, quadratic and cubic age terms in the models. This assessment revealed that age at interview was correctly fitted as a linear variable.

We used a progressive modeling strategy and controlled for size or growth measures in the same or earlier time periods only. For example, we did not adjust for postnatal size or growth variables when investigating the association between birth weight and birth length and menstrual status. However, when we examined the associations between size or growth from 1 to 4 years, we adjusted for birth weight, birth length and measures from 0 to 4 months and 4 to 12 months. In the models that included weight at 1 year, we did not adjust for weight at 4 months since these measures were highly correlated (r = 0.80). We first adjusted for age at interview and study site only. We additionally adjusted for *in utero* smoke exposure, gestational age in weeks, maternal education during pregnancy, and family income at birth in multivariable models. Associations were unchanged when gestational age was not included in multivariable models. Although current smokers had an earlier age at the menopausal transition and natural menopause in this cohort [33], associations were essentially unchanged with adjustment for adult smoking status (data not shown) and thus this variable was not included in the final models. This was an expected result since adult smoking is unlikely to be on the causal pathway between birth size and early-life growth and age at menopause.

We tested whether associations varied with study site by adding cross-product terms to the models. We also used cross-product terms to test whether associations between postnatal changes in weight and height varied with birth weight. We conducted sensitivity analyses for infant growth models stratified by low birth weight status, defined as a birth weight less than the 10th within-cohort percentile. Participants with missing data on either the size or growth measures or covariates were excluded from relevant models. We conducted sensitivity analyses excluding participants with any missing data from all analyses, yielding similar results (data not shown).

3. Results

The final analytic sample included 1001 women with a median age of 44.1 years (range = 39.3–49.2 years). Seventy-seven percent were menstruating, 19% were in the menopausal transition and 4% had experienced natural menopause (Table 1). Given the age range of the cohort, women who were in the menopausal transition or had experienced natural menopause experienced these events at a relatively early age, which may have significant health implications.

3.1. Absolute body size (weight or BMI)

Higher birth weight was associated with lower odds of having experienced the menopausal transition or natural menopause (the combined category) at interview after adjusting for age, birth length, study site, gestational age, *in utero* smoke exposure, maternal education, and family income at birth (OR = 0.50 per 1 kg increase in birth weight, 95% confidence interval (CI) = 0.32–0.77) (Table 2). Women with a lower birth weight (i.e. 2.5 kg compared to 3.5 kg) therefore had a two-fold increased risk of having experienced the menopausal transition or natural menopause by age 39–49 years. Birth length was not associated with menstrual status and the association with ponderal index at birth was inverse but not statistically significant. The inverse association between weight and the combined menopausal transition and menopause category was observed through the first year of life, but did not extend to age 4 years. Higher BMI in the 20s was associated with higher odds of having experienced the menopausal transition or natural menopause (adjusted OR = 1.05, 95% CI 1.01–1.09). Associations were similar when the menopausal transition and natural menopause were examined separately.

3.2. Weight gain

Adjusting for size at birth, faster weight gain from 0 to 4 months was associated with decreased odds of having experienced the menopausal transition or natural menopause at interview (adjusted OR = 0.93 per 10-percentile increase, 95% CI 0.87–1.00) (Table 2). The association between weight gain from 4 to 12 months and the combined menopausal transition and menopause category was also inverse, but was not statistically significant. Rate of weight gain from 1 to 4 years was not associated with menstrual status. Rates of height gain from 0 to 4 months, 4 to 12 months and 1 to 4 years were also not associated with menstrual status. The results were generally consistent when height and weight gain were categorized into rapid, stable and slow growth patterns (Supplemental Table 1).

The associations between the postnatal growth measures and menstrual status did not vary with study site or birth weight, defined continuously. When we considered low birth weight as a dichotomous variable (< 10th percentile corresponding to 2806.7 g compared with ≥10th percentile), there was an interaction of borderline statistical significance between low birth weight and weight gain from 0 to 4 months (p for interaction = 0.05). Faster weight gain from 0 to 4 months was associated with decreased odds of having experienced the combined menopausal transition and menopause outcome among both lower birth weight infants (OR = 0.70 per 10-percentile increase, 95% CI 0.47–1.02) and infants with a birth weight ≥10th percentile (OR = 0.93, 95% CI 0.86–1.00), but the magnitude of association was smaller in the higher birth weight group.

4. Discussion

We found that women who have a lighter weight at birth and women who are lighter than their peers through infancy experience the menopausal transition or natural menopause at an earlier age. Since birth weight adjusted for gestational age can be interpreted as a measure of velocity, our results for low birth weight suggest that slow fetal

growth is associated with earlier age at the menopausal transition or natural menopause. Women with slow weight gain during infancy were also more likely to experience the menopausal transition or natural menopause at an earlier age across the range of birth weight. These associations were similar in magnitude with and without adjustment for *in utero* smoke exposure, which was associated with earlier age at natural menopause but not the age at the menopausal transition in this cohort [33], suggesting that *in utero* smoke exposure and birth weight may influence age at menopause through different mechanisms.

Our results are in line with previous reports of an association between lower birth weight and earlier age at menopause. [26,27] In the 1958 British Birth Cohort, ages 44–45 years at follow-up, low (< 2.5 kg) and high (≥ 4 kg) birth weight were both associated with earlier age at menopause compared with those with a birth weight of 3–3.49 kg [26]. Higher birth weight was associated with later age at menopause in our sample. When we examined natural menopause and the menopausal transition separately, decreasing birth weight was associated with earlier age at each outcome. The inclusion of women in the menopausal transition in the reference group along with menstruating women could explain why some previous studies were null [23,24] or observed an association of smaller magnitude between low birth weight and earlier age at menopause than we observed [26,27]. The use of recalled birth weight data, which is reported with error in adulthood [42,43], and recalled age at menopause outside of the age range when menopause usually occurs, which studies have shown is less reliable with increasing time since menopause [44–46], may have also biased the results of previous studies towards the null [21,22,25,27,29].

We observed that lower weight through 1 year of age was associated with earlier age at menopause or menopausal transition. This finding is consistent with that from the 1946 British birth cohort in which low weight at age 2 years was associated with an earlier age at menopause (HR = 0.75, 95% CI 0.54–1.02 for highest quartile of weight at 2 years compared with lowest quartile) [23]. A previous small study also detected an association between lower weight at age 1 and earlier menopause [21], although age at menopause was based on the woman's recall of when her periods had stopped and may not have been accurate since the women were 60–71 years of age at assessment. Our study extends these observations by assessing rates of weight and height gain in infancy, in addition to absolute measures of weight, and suggests that slow infant weight gain is associated with earlier age at menopause, independent of birth size.

Birth weight is often used as a proxy measure of the intrauterine environment, and a low birth weight may indicate fetal undernutrition and impaired growth [19]. One study examining the association between intrauterine growth restriction (IUGR) and estimated volume percent of ovarian follicles among four growth-restricted neonates and four gestation-matched controls with normal birth weights reported a significantly lower volume percentage of primordial follicles among the growth-restricted neonates, suggesting that growth-restricted infants may have a smaller ovarian reserve at birth [47]. However, no difference in volume percentage was observed in a second study by the investigators that included seven growth-restricted neonates and 21 controls [48]. It is possible that the same intrauterine conditions that influence birth weight may also affect ovarian development or the number and quality of ovarian follicles formed. Another possibility is that the hormone systems that control the function of the ovary may be adversely affected by suboptimal uterine conditions. Evidence from animal studies suggest that prenatal stress and maternal nutrient restriction are associated with changes in the endocrine system of offspring, including the hypothalamic-pituitary-adrenal (HPA) axis (for reviews, see [49,50]). Early-life stress could affect reproductive aging in humans, regulated by the hypothalamic-pituitary-ovarian axis, through interactions with the HPA axis [51,52].

Our data show an association between early-life weight gain and timing of natural menopause and the menopause transition. Postnatal exposures might accelerate the rate of follicle atresia, leading to earlier age at menopause [10,13]. There is evidence from animal studies that maternal malnutrition in the form of protein restriction during lactation may influence folliculogenesis and the expression of several enzymes and hormones that control the reproductive process in rats [53,54]. In humans, one report shows earlier age at menopause in women exposed to severe caloric restriction in childhood during the Dutch hunger winter compared with unexposed women [55]. Interpretation of this observation is hindered because the sample comprised only post-menopausal women and age at menopause was based on recall [44–46]. In any event, it seems unlikely that observations related to famine extrapolate to our sample, which is unlikely to have been malnourished in early life. Thus, we propose replication of the findings related to famine before seeking biologic explanations.

A key strength of our study is that measures of body size at birth and in early life were assessed prospectively by trained personnel, minimizing measurement error. We also had prospective data on maternal education at birth and *in utero* smoke exposure which allowed us to examine whether these factors confounded the associations between birth weight and menstrual status. Due to the relatively young age of participants at adult follow-up, a limitation of this study is that the number of participants who reached natural menopause was small (n = 38), which affected the precision of effect estimates in models examining natural menopause only. Menstrual status was assessed via self-report, which may be reported with error. However, the young age of the participants allowed us to examine the menopausal transition using interviews at ages proximal to the transition, minimizing recall errors. The associations between birth weight and weight gain in infancy were similar for natural menopause and the menopausal transition. The interpretation of the findings in regards to the menopausal transition, however, is hindered by uncertainty about whether the size or quality of the follicle pool influence age at onset of the menopausal transition.

5. Conclusions

Our study suggests that women with a low weight at birth and in infancy are more likely to be in the menopausal transition or have experienced natural menopause by age 39–49 years. These associations are not explained by other early-life exposures such as *in utero* smoke exposure and lower maternal education at birth. These findings support the developmental origins hypothesis that the early-life environment may adversely affect follicular development and the rate of follicle loss, accelerating ovarian aging. Since birthweight is inversely associated with the risk of cardiovascular and metabolic diseases [9] and positively associated with breast cancer risk [56,57], our findings suggest that the intrauterine and early life environment which influences growth may contribute to associations between earlier age at menopause and chronic disease risk.

Funding

This work was supported by the National Cancer Institute [grant numbers R01CA104842-03 and K07CA90685] and the National Institute of Child Health and Development [grant number P01AG023028-01].

Conflict of interest

The authors have no conflicts of interest to disclose.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.reprotox.2019.02.013.

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