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ORIGINAL PAPER

Energy balance, early life body size, and plasma prolactin levels in postmenopausal women

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Abstract
Objective We examined the relationships of prolactin with birth weight; childhood, adolescent and adult body size measures; adult physical activity and inactivity; and alcohol consumption among 1,423 postmenopausal women from the Nurses' Health Study.
Methods Information on exposures was collected on biennial questionnaires beginning in 1976. Blood was collected from 32,826 participants in 1990; prolactin was measured in a subset of women who were controls for a nested breast cancer case–control study. Generalized linear models were adjusted for assay batch, medication use at blood draw, and other potential predictors of prolactin.
Results No associations were observed for adult factors (p-trend $\geq$ 0.17), body mass index at age 18, birth weight, or height (p-trend $\geq$ 0.27). There was an inverse association between body size at ages 5 (p-trend = 0.03) and 10 (p-trend = 0.05) and prolactin, with levels 9% lower among women with the heaviest versus leanest average childhood body size. This association was more pronounced among women with a birth weight <7 pounds (p-trend = 0.004; p-interaction between birth weight and childhood body size = 0.01).
Conclusions Our results suggest that few adult lifestyle risk factors are associated with prolactin levels in postmenopausal women; however, childhood body size may be a predictor of levels later in life.

Keywords Energy balance · Early life body size · Prolactin

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Introduction

Prolactin is a polypeptide hormone involved in the proliferation and differentiation of normal mammary epithelium [1, 2]. Animal and in vitro data support an important role of prolactin in breast carcinogenesis and epidemiologic data suggest a positive association between prolactin levels and breast cancer risk [3, 4]. However, few lifestyle factors have been associated with lower prolactin levels in postmenopausal women, reducing our ability to make prevention recommendations, and our understanding whether prolactin may be a mechanism through which such factors alter breast cancer risk.

While several potential breast cancer risk factors, including adult adiposity, physical activity, and alcohol consumption, have been examined in relation to postmenopausal prolactin levels, the results are conflicting. Although weight [5] or height alone [6, 7] was not associated with prolactin concentrations in postmenopausal women, BMI has been positively related to levels in some [8–10], but not all [7] studies. Further, most [11–18] studies except one [19] among young athletic individuals reported increased levels after acute exercise or resistance training; however, the effect of chronic exercise especially among older women is unclear [20]. Acute alcohol intake increases prolactin concentrations in postmenopausal women using a transdermal

estradiol patch [21], but no association was observed between long-term alcohol consumption and plasma prolactin levels in a cross-sectional study [7]. In addition, some evidence supports a possible link between birth weight and altered sex hormone and gonadotropin profiles in childhood and adolescence [22–26]. However, to our knowledge, no studies have examined the relations between postmenopausal prolactin concentrations and early life exposures or with other measures of adult energy balance such as waist circumference.

Conflicting results may be due to the relatively small sample sizes in previous studies. The current analysis expands upon an earlier study [7] and examines the associations of birth weight, body sizes at ages 5 and 10, BMI at age 18, current BMI, waist-to-hip ratio, waist circumference, alcohol consumption, and physical activity, with plasma prolactin levels among 1,423 postmenopausal women in the Nurses' Health Study (NHS).

Materials and methods

Study population

The NHS is an ongoing cohort study that was initiated in 1976, when 121,700 United States female registered nurses aged 30 and 55 years completed and returned a mailed, self-administered questionnaire. Information on various exposure variables and disease outcomes has been updated every two years by questionnaire since inception.

In 1989–1990, blood samples were collected from 32,826 NHS participants between 43 and 69 years of age at blood collection. Details regarding the NHS blood collection methods have been published previously [7]. Briefly, each woman arranged to have her blood drawn and shipped to our laboratory via overnight courier with an ice-pack. Whole blood samples were centrifuged and separated into plasma, red blood cell, and white blood cell components. The stability of prolactin in whole blood for 24–48 h has been shown previously [27]. All samples have been stored in continuously alarmed and monitored liquid nitrogen freezers since collection. At blood collection, women completed a short questionnaire asking about current weight, postmenopausal hormone use, and the use of antidepressant medication.

The current analysis included women who were controls from a nested case–control study of plasma prolactin levels and breast cancer risk ($n = 2{,}204$) [28]. We also included baseline samples from a hormone reproducibility study over three years ($n = 80$) [29], and women with low fat, high alcohol, or high caffeine intake ($n = 80$). The analysis was then restricted to postmenopausal women with measured prolactin values ($n = 1{,}434$). Women were defined as postmenopausal if they: (1) reported having a natural menopause (e.g., no menses for at least 12 months prior to blood collection), (2) had a bilateral oophorectomy, or (3) had a hysterectomy with at least one ovary remaining and were at least 56 (if a nonsmoker) or 54 (if a current smoker) years old, ages at which 90% of women in the overall NHS cohort reported natural menopause. The study was approved by the Committee on the Use of Human Subjects in Research at the Brigham and Women's Hospital.

Laboratory assays

Prolactin was measured using a microparticle enzyme immunoassay. About 45% of the samples were assayed in three initial batches at the University of Massachusetts Medical Center (Boston, MA) using the IMx System (Abbott Laboratory, Abbott Park, IL) between 1993 and 1997. The remaining samples (55%) were assayed in three batches at the Reproductive Endocrinology Unit Laboratory at the Massachusetts General Hospital, using the AxSYM Immunoassay system (Abbott Diagnostics, Chicago, IL) between 2001 and 2003. A subset of 60 samples was assayed at both laboratories; the correlation between the two was 0.91. The limit of detection (for both laboratories) was 0.6 ng/ml. Replicate plasma samples were included in each batch to assess laboratory precision. The intra-assay coefficient of variation ranged from 5.4 to 9.3%. In the final (sixth) batch assayed in 2003 we included 15 control plasma samples from each of the previous five batches, hereafter referred to as drift samples, to assess laboratory drift.

Exposures and covariates assessment

Information on exposures and covariates was obtained from the questionnaire completed at blood collection and the biennial study questionnaires. BMI at blood draw and at age 18 were calculated as weight in kg divided by height (at study entry) in meters squared. Waist and hip circumferences were collected in 1986 and birth weight in 1992. In the NHS, the correlation between the nurse's self-reported birth weight and that reported by her mother (considered the gold standard) was 0.77 [30]. Further the nurse's report of being born full-term (>37 weeks) versus pre-term (≤37 weeks) had 97% concordance with the mother's report. In 1988, women were asked to choose one of nine pictorial diagrams (somatotypes) that best depicted their body outline at ages 5 and 10 (Fig. 1). The method of using a nine-level figure drawing to describe body size was originally developed by Stunkard and colleagues [31]. Among older women (aged 71–76), the correlations between measured BMI and recalled somatotype were 0.57 at age 5, 0.70 at age 10, and 0.64 at age 20; the correlations were similar after controlling for current BMI [32].

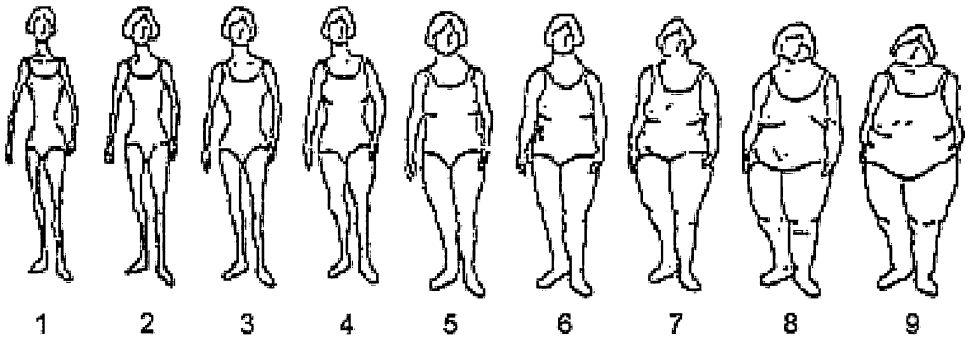

Fig. 1 Pictorial diagram used for estimating body shape at ages 5 and 10 years old

Alcohol consumption was assessed every two to four years and measured by self-administered semi-quantitative food frequency questionnaire (FFQ). We asked about consumption of beer, red wine, white wine, and liquor, and then calculated total alcohol consumption. In this analysis, we used average consumption between 1986 and 1990 to dampen variation due to measurement error and true changes in consumption. Physical activity data were collected in 1986 and 1988 when women recorded the number of hours per week spent doing various physical activities, such as walking, jogging, running, biking, swimming, and tennis. A metabolic equivalent score (MET) was assigned to each activity, and the MET-hours/week of total physical activity was calculated based on the amount of time a woman reported spending on a particular activity per week times the MET score. We used average MET-hours/week between 1986 and 1988 for total activity, walking, and moderate-to-vigorous activity. Activity cutpoints were in multiples of three MET-hours/week, as this is equivalent to one hour of walking. A previous validation study of this activity questionnaire observed a correlation between total MET-hours/week from the questionnaire and four seven-day activity diaries of 0.62 [33]. In addition, we asked women to report the total number of hours per week they spent standing at work or home and sitting at work, watching TV, or other sitting at home. These were summed to provide the total number of hours/week standing and sitting and total inactivity.

For covariate information, age at menarche, parity, and age at first birth were assessed in 1976, and the latter two variables were updated biennially until 1984. In 1986, women were asked to report the total number of months spent breastfeeding. Age at menopause and diagnosis of benign breast disease were assessed biennially. Family history of breast cancer was queried in 1976, 1982, and 1988. Details about the blood collection date, time, and fasting status, and use of postmenopausal hormones and antidepressant medications at the time of blood collection were reported on the blood questionnaire.

Statistical analyses

We identified statistical outliers using the generalized extreme studentized deviate many-outlier approach [34] and excluded these observations from analyses ($n = 10$, $\leq$0.52 or $\geq$49.4 ng/ml). We also excluded one woman with a missing height value as this was a key variable for several exposures. The final sample size included 1,423 postmenopausal women.

Generalized linear models were used to estimate mean prolactin levels across categories of predictive factors, regressing natural log-transformed prolactin values on exposures and adjusting for potential confounders. Results were then exponentiated to obtain geometric means and are reported on the original scale. Tests for trend were conducted by modeling exposure measures as continuous variables and calculating the Wald statistic. For all exposures we performed secondary analyses restricting to parous women given prolactin levels are lower in parous compared to nulliparous women [35]. In the analyses of birth weight and childhood body sizes we excluded 74 women who were born pre-term or as part of a multiple birth. This potentially reduced the variability introduced by including premature or multiple births, as these events could effect hormone levels in later life through different mechanisms than birthweight alone. We further tested interactions between birth weight and average body size of ages 5 and 10, and did stratified analyses of early life body sizes among women with a birth weight <7 pounds and 7+ pounds.

Mean plasma prolactin concentrations from quality control samples run in multiple batches differed by batch, indicating that there was some laboratory drift over time. Therefore, we included an indicator for laboratory batch in all analyses. We secondarily conducted analyses using corrected prolactin values calculated from drift samples included in the final batch (see ref. [28] for details). All analyses were adjusted for factors that are known or hypothesized to influence prolactin levels including: age at blood draw ($\leq$55, >55–60, >60–65, >65 yrs), month of

blood draw (≤09/1989, 10/1989–12/1989, 01/1990–04/1990, ≥05/1990), time of day of blood draw (1–7 am, 8–10 am, 11 am–1 pm, 2 pm-midnight), fasting status (>8 h vs. ≤8 h), duration of PMH use (never, past, current <5 yrs, current ≥5 yrs), and use of steroids, thyroid drugs, and antidepressant medications (all defined as taking vs. not taking, missing). We further adjusted for age at menarche (≤11, 12, 13, ≥14 yrs), age at menopause (≤44, 45–49, 50–54, ≥55 yrs), oopherectomy status (both ovaries removed vs. not), parity (continuous), breast feeding (continuous), history of BBD (yes vs. no), and family history of breast cancer (yes vs. no). In the analyses for walking and moderate-to-vigorous activity, we mutually adjusted for each variable. We also adjusted for BMI in the analyses of waist circumference and waist hip ratio. All *p*-values were two-sided and considered statistically significant if ≤0.05. All analyses were conducted using SAS version 9 (SAS Institute, Cary, NC).

Results

The mean prolactin value of the study participants was 10.2 (SD = 5.5) ng/ml and the average age at blood draw was 61.0 years (Table 1). Mean BMI at age 18 and blood collection were 21.4 and 25.5 kg/m^2, respectively. Average total alcohol consumption reported in 1986 and 1990 was 6.2 g/day, and average total physical activity between 1986 and 1988 was 16.2 MET-hours/week. Only 179 (12.6%) women reported family history of breast cancer, and 442 (31.1%) had previously reported a diagnosis of BBD.

Body size at age 5 was significantly inversely associated with plasma prolactin levels (*p*-trend = 0.03 for multivariate adjusted model) (Table 2). Women who reported pictorial diagrams four to eight (representing the heaviest girls) had the lowest levels [mean = 8.5 ng/ml, 95% CI (8.0, 9.0)] in adulthood, while women who reported diagram two (representing a leaner body shape) had the highest levels [mean = 9.4, 95% CI (9.0, 9.9)]. Prolactin values for women with diagrams one and three were 9.1 ng/ml [95% CI (8.8, 9.5)] and 8.8 ng/ml [95% CI (8.4, 9.3)], respectively. Similar inverse associations also were observed for body size at age 10 and average body size of ages 5 and 10, although these associations were of borderline significance in the multivariate adjusted model (*p*-trend = 0.05 for both). However, the results of average body size of ages 5 and 10 became more significant after adjustment for birth weight (*p*-trend = 0.01). Postmenopausal prolactin levels were not associated with birth weight (*p*-trend = 0.27), BMI at age 18 (*p*-trend = 0.84), or height (*p*-trend = 0.79). Results for height were essentially unchanged when adjusting for weight (data not shown).

Table 1 Characteristics of postmenopausal women at blood draw in the Nurses' Health Study

Characteristics	Mean (SD) (n = 1,423)
Prolactin, ng/ml	10.2 (5.5)
Age, yrs	61.0 (5.0)
BMI, kg/m^2	25.5 (4.6)
Weight, lbs	151.3 (28.6)
Waist circumference, in.[a]	31.7 (4.2)
Waist-to-hip ratio[b]	0.8 (0.1)
Height, in.	64.6 (2.4)
BMI at age 18, kg/m^2	21.4 (2.9)
Total physical activity, MET-hours/week[c]	16.2 (19.7)
Total alcohol consumption, g/day[d]	6.2 (10.3)
Age at menarche, yrs	12.6 (1.4)
Age at menopause, yrs	49.6 (4.3)
Parity[e]	3.5 (1.6)
	n (%)
Birth weight, ≥7 lbs[f]	654 (65.9)
Average body size of ages 5 and 10, diagram ≥3.5[g]	297 (22.9)
Family history of breast cancer, yes	179 (12.6)
History of benign breast disease, yes	442 (31.1)
PMH use	
Never	646 (45.4)
Past use	325 (22.8)
Current use <5 years	185 (13.0)
Current use ≥5 years	267 (18.8)
Both ovaries removed by 1990	289 (20.3)
Breast fed infants ≥ 12 months[h]	241 (18.4)

[a] 370 women had missing data. Total n = 1,053

[b] 374 women had missing data. Total n = 1,049

[c] Average of physical activity reported in 1986 and 1988

[d] Average of consumption reported in 1986 and 1990

[e] Among parous women (n = 1,324)

[f] Excluded 74 women who were born pre-term or as part of a multiple birth. 356 women had missing data. Total n = 993

[g] Determined on a scale from 1 to 9, with 1 being the leanest and 9 being the heaviest. Also excluded 74 women who were born pre-term or as part of a multiple birth. 51 women had missing data. Total n = 1,298

[h] Among women who were parous and had breast fed infants. 113 women had missing data. Total n = 1,310

Overall no significant associations were observed for current BMI (*p*-trend = 0.64), total physical activity (*p*-trend = 0.64), walking (*p*-trend = 0.28), moderate-to-vigorous activity (*p*-trend = 0.88), total inactivity (*p*-trend = 0.63), or total alcohol consumption (*p*-trend = 0.29) with postmenopausal prolactin levels (Table 3). Similarly, we did not find significant associations between plasma prolactin concentrations and weight at blood draw (*p*-trend = 0.71), waist circumference (*p*-trend = 0.79),

Table 2 Multivariate adjusted geometric mean prolactin levels (ng/ml) for factors in early or adolescent life

Variable	*n* (%) (*n* = 1,349–1,423)	Geometric mean (95% CI)[a]
Birth weight, lbs		
<7	339 (34.1)	9.1 (8.7, 9.6)
≥7–<8½	487 (49.0)	8.8 (8.4, 9.1)
≥8½	167 (16.8)	8.7 (8.2, 9.3)
p trend		0.27
Body size at age 5		
Diagram #1	523 (40.2)	9.1 (8.8, 9.5)
Diagram #2	281 (21.6)	9.4 (9.0, 9.9)
Diagram #3	261 (20.1)	8.8 (8.4, 9.3)
Diagram #4–8	236 (18.1)	8.5 (8.0, 9.0)
p trend		0.03
Body size at age 10		
Diagram #1	417 (31.8)	9.2 (8.8, 9.6)
Diagram #2	329 (25.1)	9.1 (8.7, 9.5)
Diagram #3	257 (19.6)	9.2 (8.7, 9.7)
Diagram #4–8	307 (23.4)	8.5 (8.1, 8.9)
p trend		0.05
Average body size of ages 5 and 10		
Diagram #1	394 (30.4)	9.3 (8.9, 9.7)
Diagram #1.5–2	336 (25.9)	9.2 (8.7, 9.6)
Diagram #2.5–3	271 (20.9)	9.1 (8.6, 9.6)
Diagram #3.5–7.5	297 (22.9)	8.5 (8.1, 9.0)
p trend		0.05
BMI at age 18, kg/m^2		
<20	431 (31.7)	9.3 (8.9, 9.6)
20–<21.25	301 (22.2)	8.9 (8.4, 9.3)
21.25–<22.5	256 (18.8)	9.2 (8.7, 9.7)
≥22.5	371 (27.3)	9.0 (8.6, 9.4)
p trend		0.84
Height, in.		
58–62	298 (20.9)	9.1 (8.6, 9.5)
63–64	421 (29.6)	9.1 (8.7, 9.5)
65–66	405 (28.5)	8.9 (8.5, 9.3)
≥67	299 (21.0)	9.2 (8.7, 9.7)
p trend		0.79

[a] Adjusted for batch, age at blood draw (≤55, >55–60, >60–65, >65 yrs), month of blood draw (≤09/1989, 10/1989–12/1989, 01/1990–04/1990,≥05/1990), time of day of blood draw (1–7 am, 8–10 am, 11 am–1 pm, 2 pm-midnight), fasting status (>8 h vs. ≤8 h), duration of PMH use (never, past, current <5 yrs, current ≥5 yrs), use of steroids, thyroid drugs, and antidepressant medications (all defined as taking vs. not taking, missing), age at menarche (≤11, 12, 13, ≥14 yrs), age at menopause (≤44, 45–49, 50–54, ≥55 yrs), oopherectomy status (both ovaries removed vs. not), parity (continuous), breast feeding (continuous), history of BBD (yes vs. no), and family history of breast cancer (yes vs. no)

waist-to-hip ratio (*p*-trend = 0.39), or intake of each individual type of alcoholic beverage (*p*-trend ≥ 0.18) (data not shown). Similar results were observed for weight when adjusting for height (data not shown). Further, no associations were observed for hours per week of standing (*p*-trend = 0.17) or sitting (*p*-trend = 0.40).

The results did not change when we restricted the analyses to parous women (data not shown). Furthermore, when we used corrected prolactin values calculated from the drift samples, the same trend across exposure variables was observed although the geometric mean values of prolactin were, as expected, slightly different (data not shown).

To test for interaction, we dichotomized birth weight as 7+ lbs vs. <7 lbs and average body size between ages 5 and 10 as diagram 3.5+ vs. <3.5. A significant interaction was found between these two variables (*p*-interaction = 0.01). Among women with birth weight less than 7 lbs, mean prolactin values were 26% lower for women with a heavier average childhood body size [7.7, 95% CI (6.9, 8.7)] than for women with a leaner childhood body size [9.7, 95% CI (8.9, 10.4)], with a significant *p*-trend of 0.004 (Table 4). However, among women with birth weight 7+ lbs, no appreciable difference of mean prolactin levels was observed by childhood body size (*p*-trend = 0.28).

Discussion

In this study, we observed that childhood adiposity was significantly associated with circulating prolactin levels among postmenopausal women. However, other early life and adolescent exposures, as well as adult measures of body size, physical activity, or inactivity, were not important predictors of postmenopausal prolactin levels. Finally, no associations were observed for alcohol consumption, including intake of total alcohol and each individual type of alcohol (beer, red wine, white wine, or liquor). Overall, no lifestyle factors were clearly associated with postmenopausal prolactin levels except possibly early life body size in this large study.

The relation between in-utero and early life exposures and breast cancer has recently received much research interest. Birth weight, a marker of the intrauterine environment, appears to be positively associated with breast cancer risk [30, 36–40]. In the NHS, women in the lowest birth weight category (<5.5 lbs) had a 45% lower risk [RR = 0.55, 95% CI (0.33–0.93)] of breast cancer than those in the highest category (≥8.8 lbs) [30]. Conversely, childhood body size has been inversely linked to breast cancer risk [36], in both pre- [41, 42] and postmenopausal women [41]. Further, height has been consistently associated with increased risk of breast cancer overall [38–40]. Hypothesized biologic mechanisms for these relationships include that early life exposures may set growth and steroid hormone levels throughout life [22–25, 43].

Table 3 Multivariate adjusted geometric mean prolactin levels (ng/ml) by measures of adult body size, physical activity, and alcohol consumption

Variable	*n* (%) (*n* = 1,423)	Geometric mean (95% CI)[a]
BMI, kg/m^2		
<22.5	403 (28.3)	9.2 (8.9, 9.7)
22.5–<25	343 (24.1)	9.0 (8.6, 9.4)
25–<27.5	302 (21.2)	9.1 (8.6, 9.5)
27.5–<30	163 (11.5)	9.0 (8.4, 9.7)
≥30	212 (14.9)	8.9 (8.3, 9.4)
p trend		0.64
Total physical activity, MET-hours/week[b]		
<3	238 (16.8)	9.1 (8.6, 9.6)
3–<9	404 (28.5)	9.2 (8.8, 9.6)
9–<18	305 (21.5)	8.9 (8.5, 9.4)
18–<27	216 (15.2)	9.1 (8.6, 9.6)
≥27	255 (18.0)	9.0 (8.5, 9.5)
p trend		0.64
Walking, MET-hours/week[b]		
<3	494 (35.1)	9.2 (8.9, 9.6)
3–<9	471 (33.5)	9.1 (8.7, 9.5)
9–<18	262 (18.6)	8.7 (8.2, 9.2)
≥18	180 (12.8)	9.0 (8.4, 9.6)
p trend		0.28
Moderate-to-vigorous activity, MET-hours/week[b]		
<3	737 (52.0)	8.9 (8.6, 9.2)
3–<9	305 (21.5)	9.1 (8.6, 9.5)
9–<18	196 (13.8)	9.5 (8.9, 10.1)
≥18	180 (12.7)	9.3 (8.7, 9.9)
p trend		0.88
Inactivity, hours/week		
<20	306 (22.2)	9.0 (8.5, 9.4)
20–<40	180 (13.1)	9.2 (8.6, 9.8)
40–<60	204 (14.8)	8.9 (8.3, 9.4)
60–<80	260 (18.9)	9.3 (8.8, 9.8)
≥80	427 (31.0)	9.1 (8.7, 9.5)
p trend		0.63
Total alcohol consumption, g/day[c]		
0	427 (30.5)	9.1 (8.7, 9.5)
>0–5	522 (37.3)	9.0 (8.7, 9.4)
>5–10	168 (12.0)	9.4 (8.8, 10.1)
>10–15	108 (7.7)	8.7 (8.0, 9.5)
>15	174 (12.4)	8.8 (8.2, 9.4)
p trend		0.29

[a] Adjusted for batch, age at blood draw (≤55, >55–60, >60–65, >65 yrs), month of blood draw (≤09/1989, 10/1989–12/1989, 01/1990–04/1990,≥05/1990), time of day of blood draw (1–7 am, 8–10 am, 11 am–1 pm, 2 pm-midnight), fasting status (>8 h vs.≤8 h), duration of PMH use (never, past, current <5 yrs, current ≥5 yrs), use of steroids, thyroid drugs, and antidepressant medications (all defined as taking vs. not taking, missing), age at menarche (≤11, 12, 13, ≥14 yrs), age at menopause (≤44, 45–49, 50–54, ≥55 yrs), oopherectomy status (both ovaries removed vs. not), parity (continuous), breast feeding (continuous), history of BBD (yes vs. no), and family history of breast cancer (yes vs. no)

[b] Average of 1986 and 1988. For walking and moderate-to-vigorous activity, mutually adjusted for each variable

[c] Average of 1986 and 1990

To our knowledge, no previous studies have examined the relationships between early childhood exposures and postmenopausal prolactin levels. We found significant inverse associations between somatotypes at ages 5 and 10 and the average body size of ages 5 and 10 with postmenopausal plasma prolactin levels, such that those who were most overweight during childhood had the lowest prolactin levels after menopause. This is compatible with the relations of both childhood adiposity and prolactin with breast cancer risk, and suggests that the effect of these anthropometric factors on breast cancer may be partly mediated through prolactin. It is possible that body size in early years could set endocrine profiles in adulthood [22–25, 43]. In contrast, a previous study in the Nurses' Health Study II did not observe

Table 4 Multivariate adjusted geometric mean prolactin levels (ng/ml) for childhood body size variables by birth weight (less than 7 lbs versus 7 lbs or above)

Variable	<7 lbs[a]		≥7 lbs[a]	
	n (%) (*n* = 339)	Geometric mean (95% CI)	*n* (%) (*n* = 654)	Geometric mean (95% CI)
Body size at age 5				
Diagram #1	160 (48.8)	9.7 (9.0, 10.3)	224 (35.4)	8.9 (8.4, 9.5)
Diagram #2	74 (22.6)	9.2 (8.3, 10.2)	133 (21.0)	9.0 (8.3, 9.7)
Diagram #3	51 (15.6)	8.4 (7.4, 9.5)	137 (21.6)	8.9 (8.2, 9.5)
Diagram #4–8	43 (13.1)	8.0 (7.0, 9.2)	139 (22.0)	8.4 (7.8, 9.0)
p trend		0.005		0.23
Body size at age 10				
Diagram #1	134 (40.4)	9.7 (9.0, 10.4)	170 (26.8)	9.2 (8.6, 9.8)
Diagram #2	80 (24.1)	9.0 (8.1, 9.9)	159 (25.1)	8.7 (8.1, 9.4)
Diagram #3	60 (18.1)	9.4 (8.4, 10.5)	136 (21.5)	8.9 (8.2, 9.6)
Diagram #4–8	58 (17.5)	7.7 (6.9, 8.6)	169 (26.7)	8.5 (7.9, 9.1)
p trend		0.003		0.32
Average body size of ages 5 and 10				
Diagram #1	127 (38.8)	9.7 (8.9, 10.4)	159 (25.2)	9.3 (8.7, 10.0)
Diagram #1.5–2	84 (25.7)	9.2 (8.4, 10.2)	161 (25.5)	8.7 (8.1, 9.3)
Diagram #2.5–3	60 (18.4)	9.3 (8.3, 10.4)	145 (22.9)	8.7 (8.1, 9.4)
Diagram #3.5–7.5	56 (17.1)	7.7 (6.9, 8.7)	167 (26.4)	8.6 (8.0, 9.2)
p trend		0.004		0.28

[a] Adjusted for batch, age at blood draw (≤55, >55–60, >60–65, >65 yrs), month of blood draw (≤09/1989, 10/1989–12/1989, 01/1990–04/1990, ≥05/1990), time of day of blood draw (1–7 am, 8–10 am, 11 am–1 pm, 2 pm-midnight), fasting status (>8 h vs.≤8 h), duration of PMH use (never, past, current <5 yrs, current ≥5 yrs), use of steroids, thyroid drugs, and antidepressant medications (all defined as taking vs. not taking, missing), age at menarche (≤11, 12, 13, ≥14 yrs), age at menopause (≤44, 45–49, 50–54, ≥55 yrs), oopherectomy status (both ovaries removed vs. not), parity (continuous), breast feeding (continuous), history of BBD (yes vs. no), and family history of breast cancer (yes vs. no)

an association between early life body sizes and prolactin levels among premenopausal women [44], although higher childhood body size was associated with lower adult IGF-I levels in this population [43]. It is unclear why the results differ, although the study of premenopausal women was substantially smaller ($n = 518$), which limited power for the primary analysis and precluded stratification by birthweight, a potentially important modifier. However, given the number of comparisons in this study, the observed association between early life body size and prolactin could be due to chance. Interestingly, we did not find a significant association for BMI at age 18, suggesting a specific childhood affect. More studies need to be conducted to confirm our current findings and elucidate the biological mechanisms potentially underlying these associations.

We observed that women of higher birth weight had non-significant lower prolactin values than women of low birth weight. Interestingly though, the childhood body size/prolactin relation varied by birth weight, with a strong inverse association between childhood body size and prolactin levels observed only among women with a lower birth weight. It is possible that both childhood body size and birth weight are involved in setting prolactin levels. Low birth weight may be a sign of stress and women with low birth weight and large childhood body size might have gone through large catch-up growth. To support such growth, various growth factors and possibly prolactin may be increased in childhood [45]. This increased prolactin may desensitize the pituitary gland due to negative feedback and eventually this adaptive response may lead to lower prolactin concentrations later in life. Animal models have reported reduced prolactin levels as a consequence of repeated exposure to a particular stressor [46], and a study of chronic exercise has shown that women who increased fitness levels lowered their prolactin concentrations [20], further supporting this hypothesis. However, these potential biological mechanisms are only speculative, and clearly more research should examine and clarify these relationships. Consistent with two previous studies (50 and 217 women, respectively) [6, 7], we did not observe an association between height and prolactin with a much larger sample size. This is consistent with a lack of association between height and adult IGF-1 levels, another growth factor, possibly

because height is more strongly associated with levels earlier in life [43].

We did not find significant associations for any adult adiposity measures, which is somewhat inconsistent with the previous literature. BMI has been positively associated with prolactin concentrations in postmenopausal women in some [8–10], but not all studies [7]. The studies that did observe an association examined prolactin levels at night, which may possibly explain the discrepant findings given the circadian variation in prolactin levels [47]. Physical activity [11–17] and resistance training [18] acutely increases prolactin concentrations. However, we did not observe any evidence that long-term activity levels are associated with higher prolactin concentrations. This is consistent with the results from a 12-month randomized clinical trial of exercise on serum prolactin concentrations in postmenopausal women, which observed no overall change in prolactin with exercise [20]. Further, we did not observe any significant associations between postmenopausal prolactin levels and physical inactivity (total inactivity, standing, or sitting). Reassuringly, chronic exercise does not appear to translate to a long-term increase in prolactin levels.

Although alcohol intake also may acutely increase prolactin levels [21], overall alcohol consumption does not appear to be related to levels. More specifically, previous data suggested that beer increased prolactin levels [48, 49]. However, we did not observe associations for beer or other types of alcoholic beverages. With more than 1,000 additional women, the findings in current study confirmed the null associations in a previous study of 217 postmenopausal women in the NHS [7]. Given the large sample size of our study, alcohol and other energy balance measures like BMI and physical activity are unlikely to influence postmenopausal breast cancer risk via prolactin, but these exposures may be involved in other hormonal pathways, such as estrogens [50–57].

The major strength of this study is its large sample size, such that we had sufficient power to detect even small associations and to assess effect modifications. However, the study does have several limitations. The nature of the study precludes the ability to determine causal relationships and further establish biological mechanisms as we only had one adulthood measure of prolactin. It also is difficult to reconcile the discrepancies of the findings between pre- and postmenopausal prolactin levels and body size during early life, which requires further investigation. The nature of prolactin, with multiple isoforms that have varying biological activity [1], poses another limitation, as it is possible that a specific isoform is associated with the factors studied. The assay we used identifies most prolactin forms, but cannot distinguish between them [58]. A third limitation is that a single blood sample may provide a somewhat imprecise measure of long-term average hormone levels given the relatively low within-person stability (intra-class correlation = 0.49) [29], and thus could attenuate our results. Laboratory drift between batches may have introduced some random error, but the correlation between batches was high and we controlled for batch in all analyses. Furthermore, the same results were observed when using prolactin values recalibrated to correct for laboratory drift. Finally, the circadian variation in prolactin [47] and increase after noon meal [59] is another potential limitation, but we controlled for time and fasting status in all analyses.

In conclusion, our results suggest that childhood body size may be associated with postmenopausal prolactin levels, but these results need to be replicated in future studies and underlying biological mechanisms evaluated. No associations were observed with birth weight, adolescent body measures, adult adiposity, alcohol consumption, or physical activity. Given the modest, but consistent association between prolactin levels and breast cancer and that there are very few known correlates of prolactin levels, more research is needed in this area to identify other predictors of prolactin concentrations, particularly those factors which are potentially modifiable.

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