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Age at menarche, androgen concentrations, and midlife obesity: Findings from the Midlife Women's Health Study

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Abstract

Objective—Studies have shown that earlier age at menarche is associated with a higher risk of midlife obesity; however, the mechanism underlying this association is not known. The purpose of this study was to examine whether the association between age at menarche and midlife obesity is due to variation in circulating androgen concentrations.

Methods—Baseline data were analyzed from 748 women aged 45 to 54 years enrolled in the Midlife Women's Health Study, a prospective cohort study conducted in the Baltimore, Maryland region. Information on age at menarche was collected through a self-administered questionnaire. Body mass index (BMI) was calculated using height and weight measured at a clinic visit. Obesity was defined as a BMI between 30 and 34.9 kg/m²; super obesity was defined as a BMI greater than 35 kg/m². Hormone concentrations [testosterone, estradiol, sex hormone-binding globulin (SHBG)] were measured in blood samples using enzyme-linked immunosorbent assays. The free androgen index (FAI) was calculated using the formula: (testosterone × 3.467)/SHBG × 100.

Results—After adjustment for covariates, for each year increase in age at menarche, the odds of obesity and super obesity decreased by 31% (odds ratio (OR) 0.69; 95% confidence limits (CL) 0.59, 0.81) and 34% (OR 0.66; 95% CL 0.52, 0.83), respectively. Addition of the FAI into the models did not attenuate the observed estimates.

Conclusions—The results of this study indicate that age at menarche is associated with midlife obesity independent of free testosterone concentrations measured in adulthood.

Keywords

androgens; menarche; menopause; obesity

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Introduction

Obesity is a major public health concern among midlife women in the United States. Approximately one third of midlife women are obese, and 66% are overweight or obese.¹ Obesity is a known risk factor for a number of adverse health outcomes, including cardiovascular disease and cancer; it is also associated with higher mortality.^{2–4} Thus, understanding the risk factors for the development of obesity, with the goal of intervening to prevent weight gain, is crucial for maintaining good health over a woman's lifetime.

Puberty is an important reproductive milestone in a woman's life that is initiated by a number of neuroendocrine changes and is characterized by increased production of adrenal androgens and reactivation of the hypothalamic-pituitary-gonadal axis.^{5, 6} Menarche, or the initiation of the menstrual cycle, is a marker of the onset of puberty in girls that is often used in epidemiologic studies to examine the association between pubertal timing and health outcomes later in life. Several published studies have shown that earlier age at menarche is associated with a higher risk of midlife obesity^{7–14}; however, the mechanism underlying this association is unclear. One hypothesis is that higher androgen concentrations resulting from earlier age at menarche promote the development of obesity later in life.¹³ This hypothesis was postulated based on data showing that adult women who are obese have higher androgen concentrations than their normal weight counterparts.¹⁵

The present study was undertaken to test this hypothesis, as, currently, there is limited understanding regarding the role of androgens in mediating the association between age at menarche and obesity in adult women. To our knowledge, only one previously published study has examined this issue, although the published study used a more specific endpoint (an unhealthy obesity phenotype, defined as body mass index (BMI) ≥ 30 kg/m² and at least two metabolic syndrome components) than a generalized adiposity endpoint, most often measured using only BMI. In that study, Bleil et al.¹³ showed that, among a sample of 704 pre-menopausal women aged 25 to 45 years at baseline participating in the Ovarian Aging Study, earlier age at menarche was significantly associated with the risk of an unhealthy obesity phenotype in adulthood, and that this increase in risk was due, in part, to androgen concentrations. The present study adds to this literature by examining the associations between age at menarche, androgen concentrations, and a generalized adiposity endpoint (BMI) among an older group of midlife women aged 45 to 54 years undergoing the menopausal transition. It has been well-documented that during the menopausal transition, the hormone milieu changes^{16,17}; although total androgen concentrations remain relatively steady (with only small declines), levels of sex hormone-binding globulin (SHBG) decrease, thereby leading to increases in circulating concentrations of free androgens, including testosterone. As a secondary aim of this study, the role of estradiol concentrations, which drop dramatically during the menopausal transition, was also explored.

Methods

Study sample

Baseline data were analyzed from the Midlife Women's Health Study, a prospective cohort study of women aged 45 to 54 years at enrollment that started in 2006 in Baltimore,

Maryland and the surrounding counties. Details of recruitment of participants into the study are described in detail elsewhere.¹⁸ Briefly, women in the target age range were recruited by mail and asked to call the clinic to determine eligibility. Women were eligible if they had intact ovaries and uteri and were pre- or perimenopausal. Women were excluded if they were pregnant, had a history of cancer, were currently taking exogenous hormone therapy or herbal/plant substances, or were postmenopausal. Menopausal status was defined as follows: premenopausal women were those women who experienced their last menstrual period within the past 3 months and reported 11 or more periods within the past year; perimenopausal women were those who experienced 1) their last menstrual period within the past year, but not within the past 3 months, or 2) their last menstrual period within the past 3 months and experienced 10 or fewer periods within the past year; postmenopausal women were those women who had not experienced a menstrual period within the past year. All participants gave written informed consent according to procedures approved by the University of Illinois and Johns Hopkins University Institutional Review Boards.

Eligible participants were scheduled for a baseline clinic visit, which included measurements of height and weight, completion of a detailed 26-page baseline survey, and collection of a blood sample. Participants were also asked to come to the clinic once a week for the three weeks following the baseline visit to donate additional blood samples. Neither the baseline visit nor the subsequent visits were scheduled for a specific day or time period during the menstrual cycle, as many of the women in the study were perimenopausal and did not have regular menstrual cycles. A total of 772 women were enrolled in the study, completed the baseline visit, and donated at least one blood sample. Women were then followed annually for up to seven years.

Study measures

Height and weight were measured at the clinic visit and used to calculate BMI, which was categorized as less than 25 kg/m² (normal weight), 25–29.9 kg/m² (overweight), 30–34.9 kg/m² (obese), and ≥ 35 kg/m² (super obese). On the baseline questionnaire, women were queried about their age at first menstrual period (menarche) and also provided information on a number of demographic, health habit, and reproductive characteristics. Smoking status was categorized as current, former, and never using the questions: “Have you ever smoked cigarettes?” and “Do you still smoke cigarettes?” Current alcohol use at each visit was assessed using the question “In the last 12 months, have you had at least 12 drinks of any kind of alcohol beverage?”

Serum samples extracted from the collected blood samples were used to measure estradiol, testosterone, and sex hormone-binding globulin (SHBG) in each sample using commercially available, previously validated enzyme-linked immunosorbent assay (ELISA) kits (DRG, Springfield, New Jersey, USA).^{19–21} Each sample was measured in duplicate within the same assay and the value averaged. The average intra-assay and inter-assay coefficients of variation for all assays were less than 5%. The minimum detection limits were as follows: estradiol, 7 pg/mL; testosterone, 0.04 ng/mL; and SHBG, 0.77 nmol/L. No testosterone or SHBG values were below the limit of detection; for estradiol concentrations among all women enrolled in the study, the number of values below the limit of detection during year 1

were: visit 1, n=7; visit 2, n=3; visit 3, n=13; visit 4, n=6. In the case of values lower than the detection limits for the assay, we used the limit of detection as the hormone value. For each hormone, concentration values measured in the blood samples collected over the four week data collection period were averaged; these mean values were then used in the analysis. One participant was excluded because she was an extreme outlier in terms of her testosterone concentrations measured from the samples collected over the four week period. The free androgen index (FAI) was calculated as: $((\text{testosterone} \times 3.467) / \text{SHBG} \times 100)^{22}$; the free estrogen index (FEI) was calculated as: $((\text{estradiol} \times 3.467) / \text{SHBG} \times 100)^{23}$.

Statistical analysis

Twelve participants were excluded from the analysis because they were missing data on age at menarche (n = 7) or data on both FEI and FAI (n = 5). An additional 11 women were excluded from the analysis because they had BMI less than 18.5 kg/m². Thus, a total of 748 women were included in the analytic dataset.

Data for all hormone variables were log-transformed to meet normality assumptions. Chi-square and Fisher's exact tests were used to compare the categorical demographic, health habit, and clinical characteristics of the overweight, obese and super obese women versus the normal weight women. Generalized linear models were conducted to examine the associations between the continuous covariates and hormone concentrations with obesity.

To evaluate the unadjusted and covariate-adjusted associations between age at menarche and BMI, linear regression models were constructed. Menopausal status was identified as a potential effect modifier *a priori*; however, unadjusted estimates (beta coefficients) of the association did not differ between pre- and peri-menopausal women and, thus, menopausal status was determined not to be an effect modifier. Covariates were considered as confounders and entered into the model if the beta coefficient for the unadjusted association between age at menarche and BMI changed by more than 5% with the potential covariate in the model. Potential confounders were all variables significantly associated with BMI at p<0.05. The subsequent models adjusted for these covariates as well as FAI or FEI to examine whether any observed significant associations between age at menarche and BMI were due to variation in free estradiol or free testosterone concentrations. To evaluate the associations between age at menarche and obesity, multinomial logistic regression models were constructed. These models allow for the calculation of odds ratios (ORs) and 95% confidence limits (95% CL) for age at menarche and the outcomes of obese and super obese compared to normal weight adjusted for covariates in a single regression model. The model building strategy for the logistic regression models was similar to that employed for the linear regression models. All analyses were conducted using SAS, Version 9.3. A p-value of <0.05 was considered statistically significant.

Results

Among the 748 women in the analytic study sample, 25.9% and 8.2% were categorized as obese and super obese, respectively. Overall, the mean age of the study sample was 48.4 years (standard deviation (SD) 2.4). The overweight, obese and super obese women were significantly more likely than the normal weight women to be of black race, to be single, and

to have less education than a college diploma (Table 1). Further, the overweight, obese and super obese women were more likely to be peri-menopausal and non-drinkers than the normal weight women. In addition, the super obese women were significantly less likely than the normal weight women to have ever been pregnant; both the overweight and obese women were more likely to be current smokers. There were no statistically significant differences in mean age between the groups.

Mean SHBG was strongly associated with BMI, with mean SHBG decreasing with increasing BMI. Further, the mean concentrations of both FEI and FAI were different among the BMI groups, with higher FEI and FAI concentrations among the overweight, obese, and super obese compared to the normal weight groups. Both FEI and FAI were weakly negatively correlated with age at menarche (FEI, $r = -0.06$, $p = 0.09$; FAI, $r = -0.04$, $p = 0.3$). Total estradiol and SHBG concentrations as well as the FEI were all significantly lower among peri- compared to pre-menopausal women (estradiol: 36.5 versus 63.5 pg/mL, $p < 0.01$; SHBG: 55.1 versus 65.8 nmol/L, $p < 0.01$; FEI: 0.25 versus 0.36; $p < 0.01$). Total testosterone was not significantly different by menopausal status (pre: 0.290 ng/mL versus peri: 0.286 ng/mL; $p = 0.8$); however, the FAI was significantly higher among peri- compared to pre-menopausal women (1.84 versus 1.55; $p < 0.01$).

In the unadjusted analyses, the mean age at menarche was significantly lower among the overweight (mean=12.8 years; SD 1.6), obese (mean=12.3 years; SD 1.5), and super obese (mean=12.3; SD 1.9) women compared to the normal weight women (mean=13.1; SD 1.6) (Table 1). After adjustment for race, menopausal status, education, marital status, weight at age 18, alcohol use, and cigarette smoking, age at menarche remained significantly and negatively associated with BMI ($\beta = -0.57$; $p < 0.0001$) (Table 2). The strength of the association was slightly attenuated after the addition of either FAI ($\beta = -0.52$; $p < 0.0001$) or FEI ($\beta = -0.48$; $p = 0.0002$) into the model; however, the association remained statistically significant in both cases. Other variables significantly associated with higher BMI were black race, peri-menopausal status, weight at age 18, being a current drinker, and being a never smoker. Additionally, both FAI and FEI were positively associated with BMI.

In the multinomial logistic regression analyses (Table 3), results showed that, after adjustment for covariates, for each year increase in age at menarche, the odds of obesity and super obesity decreased by 31% (OR 0.69; 95% CL 0.59, 0.81) and 34% (OR 0.66; 95% CL 0.52, 0.83), respectively. When FAI or FEI were entered into the model as an additional adjustment factor, the ORs remained statistically significant and similar to those in the covariate-adjusted only model. Other variables consistently and significantly associated with increased odds of being obese and super-obese were black race, peri-menopausal status, less education, and weight at 18 years of age. In addition, both FAI and FEI were significantly and positively associated with being obese and super obese; a one unit increase in FAI was associated with an increase in odds of 2.93 of being obese and an increase in odds of 6.38 of being super obese. Similarly, a one unit increase in FEI was associated with an increase in odds of 2.44 of being obese and an increase in odds of 5.95 of being super obese.

Discussion

The results of this study indicate that age at menarche is associated with midlife obesity independent of free androgen and estradiol concentrations measured in adulthood. These associations, and lack of attenuation of the risk estimates with the inclusion of the FAI or FEI variable into the model, were similar when BMI was treated as a continuous variable and when the outcomes investigated were obesity (BMI between 30 kg/m² and 34.9 kg/m²) and super obesity (BMI > 35 kg/m²). Other variables associated with higher BMI, obesity, and super obesity were black race, perimenopausal status, less education, weight at 18 years of age, and never smoking. Both FAI and FEI were positively and significantly related to midlife BMI.

Our findings of statistically significant associations between age at menarche and midlife BMI, obesity and super obesity are consistent with a number of investigations that have examined these relationships (reviewed in Prentice et al.²⁴), including those from the Framingham Heart Study⁷ and the European Prospective Investigation into Cancer and Nutrition study.⁹ Notably, in the Framingham Heart Study, researchers showed that age at menarche was associated with BMI and waist circumference, but not visceral adipose tissue or subcutaneous adipose tissue, indicating that age at menarche is associated with generalized, but not regional, body fat deposits. Although the relationship between age at menarche and midlife obesity is fairly well established, little is known about the underlying mechanism by which earlier age at menarche increases the risk of midlife obesity. In this study, the association observed was independent of circulating androgen and estradiol concentrations. These findings conflict with those of Bleil et al.¹³ which showed that the association was, in fact, driven by bioavailable circulating androgen concentrations, as the risk estimate for age at menarche and an at risk obesity phenotype was attenuated with the inclusion of the FAI into the model. It should be noted, however, that Bleil et al. investigated a different outcome – an at risk obesity phenotype (defined using BMI and number of metabolic syndrome components) – than the one examined in this study (general obesity, measured as BMI). In addition, in this study, and in the Bleil et al. study, FAI reflected circulating testosterone concentrations, and it is possible that other androgens may explain, at least partially, the association between age at menarche and adult obesity. Specifically, dehydroepiandrosterone-sulfate (DHEA-S), a major circulating steroid hormone and the sulfated form of the androgen DHEA, has been shown to be inversely associated with both obesity and body fat in women.^{25, 26} Higher DHEA-S concentrations have also been shown to be associated with earlier age at menarche.²⁷ Thus, future studies should investigate the role of other androgens, including DHEA-S, in explaining the association between age at menarche with adult obesity.

Although the underlying assumption in most investigations of the relationship between age at menarche and adult obesity is that early age at menarche is a risk factor for adult obesity, with the biological mechanism unknown, it is possible that the direction of the association is the opposite of this assumption, with adult obesity actually serving as a surrogate marker of childhood obesity. Childhood obesity has been shown in epidemiologic studies to be associated with earlier age at menarche^{28, 29} and with adulthood obesity^{11, 30}; further, several studies have shown that a significant association between age at menarche and adult

obesity was explained, in large part, by childhood BMI.^{11, 12} However, this has not been shown consistently in all studies.³¹ In the present study, weight at age 18 years was included as a covariate in the adjusted model, and, while it is recognized that this does not represent childhood BMI (BMI at age <18 years or prior to puberty), it does give some information on weight around the time of puberty. As hypothesized by Prentice et al.²⁴ it may be that the role of childhood BMI in mediating the relationship between age at menarche and adult obesity differs between individuals and populations.

It is equally as possible that earlier age at menarche and adult obesity are not directly associated, but instead share a common etiology.³² This possibility has been explored in terms of a common genetic factor by Elks et al.³³ who identified *LIN28B* as a genetic locus associated with both age at menarche and obesity such that mice overexpressing Lin28 displayed both later pubertal maturation and resistance to obesity.^{14, 33, 34} This observation has been extended to adult women; Ong et al. reported that *LIN28B* was associated with earlier age at menarche and an increase in BMI in early and mid-adulthood women (aged < 40 years).³⁵ The association observed in the Ong et al.³⁵ study was weaker in women over the age of 40 years, and the authors suggested that this result may indicate that other factors may be more important in determining BMI as a woman ages.

The present study adds to the literature investigating the association between age at menarche and midlife obesity, but several limitations should be noted. First, as stated above, no statement about the temporality or causality of the relationship between age at menarche and adult obesity can be made based on the results of this study, as all data were collected at a single time point. Second, while data on weight at age 18 years were collected and provide some information on body composition at childhood, data on childhood BMI prior to puberty were not collected, and this information is important in sorting out the seemingly complex relationship between childhood BMI, age at menarche and adult obesity. In addition, blood was not drawn on a specific day or phase of the menstrual cycle, as many of the women were having irregular menstrual periods. The lack of standardization of blood collection and hormone measurement may have introduced error in terms of the diurnal and monthly variation associated with these hormones. However, to minimize possible error, all blood draws were conducted in the morning and hormone data were pooled from up to four blood samples collected over a four week period. Further, while this study used ELISAs to measure hormone concentrations, it has been documented in the literature that at low circulating concentrations of testosterone, ELISAs have inconsistent reproducibility and inadequate sensitivity.³⁶ However, it should be noted that the testosterone concentrations used in this study were not being used for diagnostic or clinical purposes, and that, although the data may not be precise, the data should reflect ranking of high versus low testosterone concentrations. Finally, data on age at menarche were collected in midlife, and differential misclassification of exposure by obesity group could have resulted in biased estimates. However, several studies have shown a high level of agreement between data collected during adolescence and in adulthood^{37, 38}; and, further, any misclassification would likely be nondifferential and, therefore, result in an underestimation of the true association.

In conclusion, the findings from this study provide evidence that variations in circulating testosterone concentrations do not explain the significant and positive associations between earlier age at menarche and both adulthood BMI and midlife obesity and super obesity.

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Table 1

Characteristics of study sample by obesity status^a

Characteristic	Normal weight n = 286	Overweight n = 206	Obese n = 194	Super Obese n = 62
Age, years, mean (SD) ^b	48.2 (2.5)	48.7 (2.3)	48.5 (2.3)	48.6 (2.6)
Race, n (%) ^{b,c,d}				
White	241 (84.3)	127 (61.7)	96 (49.5)	23 (37.1)
Black	30 (10.5)	71 (34.5)	93 (47.9)	36 (58.1)
Other	14 (4.9)	7 (3.4)	5 (2.6)	3 (4.8)
Marital status, n (%) ^{b,c,d}				
Single	33 (11.5)	40 (19.4)	41 (21.1)	21 (33.9)
Married/living with partner	204 (71.3)	139 (67.5)	119 (61.3)	25 (40.3)
Widowed/divorced/separated	48 (16.8)	26 (12.6)	33 (17.0)	16 (25.8)
Education, n (%) ^{b,c,d}				
Some college or less	65 (22.7)	93 (45.1)	83 (42.8)	30 (48.4)
College graduate or more	221 (77.3)	112 (54.4)	109 (56.2)	32 (51.6)
BMI, kg/m ² , mean (SD) ^{b,c,d}	22.3 (1.7)	27.3 (1.5)	33.9 (2.8)	45.9 (5.5)
Weight at age 18, pounds, mean (SD) ^{b,c,d}	117.9 (14.0)	125.4 (20.8)	132.6 (26.3)	160.8 (33.9)
Smoking, n (%) ^{b,c}				
Current	21 (7.3)	24 (11.7)	25 (12.9)	5 (8.1)
Former	83 (29.0)	84 (40.8)	74 (38.1)	23 (37.1)
Never	182 (63.6)	98 (47.6)	94 (48.5)	34 (54.8)
Alcohol intake, n (%) ^{c,d}				
Current	207 (72.4)	132 (64.1)	120 (61.9)	29 (46.8)
Not current	78 (27.3)	72 (35.0)	74 (38.1)	33 (53.2)
Age at first menstrual period, years (SD) ^{b,c,d}	13.1 (1.6)	12.8 (1.6)	12.3 (1.5)	12.3 (1.9)
Menopausal status, n (%) ^{c,d}				
Pre-	206 (72.0)	133 (64.6)	120 (61.9)	31 (50.0)
Peri-	80 (28.0)	72 (35.0)	74 (38.1)	31 (50.0)
Birth control, ever, n (%)				

Characteristic	Normal weight n = 286	Overweight n = 206	Obese n = 194	Super Obese n = 62
Yes	248 (86.7)	177 (85.9)	163 (84.0)	53 (85.5)
No	38 (13.3)	28 (13.6)	31 (16.0)	9 (14.5)
Ever been pregnant, n (%) ^d				
Yes	257 (89.9)	182 (88.3)	175 (90.2)	49 (79.0)
No	29 (10.1)	24 (11.7)	19 (9.8)	13 (21.0)
Self-rated health, n (%) ^{b,c,d}				
Excellent/very good	225 (78.7)	131 (63.6)	70 (36.1)	15 (24.2)
Good	63 (22.0)	58 (28.2)	104 (53.6)	27 (43.5)
Fair/poor	8 (2.8)	17 (8.3)	19 (9.8)	20 (32.3)
SHBG, geometric mean, nmol/L, (95% CL) ^{b,c,d}	83.1 (48.5, 88.1)	61.1 (57.1, 65.5)	47.5 (44.1, 50.8)	38.4 (33.9, 43.4)
Estradiol, pg/mL, geometric mean (95% CL) ^{b,c}	57.6 (53.2, 62.3)	50.8 (46.3, 55.8)	46.3 (42.1, 50.8)	55.8 (47.2, 66.0)
FEI, geometric mean (95% CL) ^{b,c,d}	0.26 (0.24, 0.28)	0.307 (0.28, 0.34)	0.367 (0.33, 0.41)	0.537 (0.45, 0.64)
Testosterone, ng/mL, geometric mean (95% CL)	0.289 (0.27, 0.31)	0.285 (0.26, 0.31)	0.279 (0.25, 0.31)	0.333 (0.28, 0.39)
FAI, geometric mean (95% CL) ^{b,c,d}	1.22 (1.11, 1.34)	1.64 (1.47, 1.83)	2.09 (1.87, 2.34)	3.06 (2.51, 3.72)

^a p-values calculated using chi-square and Fisher's exact tests for categorical covariates and generalized linear models for continuous covariates

^b p<0.05 for comparison of overweight versus normal weight

^c p<0.05 for comparison of obese versus normal weight

^d p<0.05 for comparison of super obese versus normal weight

95% CL = 95% confidence limits; BMI = body mass index; FEI = Free Estrogen Index; FAI = Free Androgen Index; SD = standard deviation; SHBG = sex hormone-binding globulin

Table 2Unadjusted and adjusted associations between age at first menarche and body mass index^a

	unadjusted β (p-value)	covariate-adjusted β (p-value)	FAI-adjusted β (p-value)	FEI-adjusted β (p-value)
Age at menarche (years)	-0.80 (<0.0001)	-0.57 (<0.0001)	-0.52 (<0.0001)	-0.48 (0.0002)
Race (ref = white)				
Black		3.48 (<0.0001)	2.93 (<0.0001)	3.03 (<0.0001)
Other		-0.49 (0.7)	-0.60 (0.6)	-1.02 (0.3)
Peri-menopausal (ref = premenopausal)		1.68 (0.0003)	1.33 (0.002)	2.74 (<0.0001)
Less than college graduate (ref = college graduate or more)		-0.83 (0.09)	-0.64 (0.2)	-0.83 (0.07)
Single/widowed/divorced marital status (ref = married)		0.43 (0.4)	0.64 (0.2)	0.35 (0.4)
Weight at age 18 (pounds)		0.12 (<0.0001)	0.12 (<0.0001)	0.12 (<0.0001)
Alcohol drinking (ref = not current)		-1.56 (0.001)	-1.26 (0.006)	-1.43 (0.002)
Smoking (ref = never)		-0.91 (0.04)	-1.08 (0.01)	-0.93 (0.03)
FAI/FEI			2.47 (<0.0001)	2.72 (<0.0001)
r-squared	0.03	0.34	0.43	0.42

^a β s and p-values derived using linear regression

FAI = Free androgen index; FEI = Free estradiol index

Table 3

Adjusted odds ratios and 95% confidence limits for age at menarche (and covariates) and being obese or super obese^a

	Obese versus normal weight women		
	Covariate-adjusted OR (95 % CL)	Covariate and FAI-adjusted OR (95 % CL)	Covariate and FEI-adjusted OR (95 % CL)
Age at menarche (years)	0.69 (0.59, 0.81)	0.67 (0.57, 0.79)	0.68 (0.58, 0.80)
Race (ref = white)			
Black	6.98 (3.82, 12.75)	6.64 (3.46, 12.74)	6.50 (3.48, 12.14)
Other	0.79 (0.23, 2.76)	0.66 (0.18, 2.40)	0.68 (0.19, 2.44)
Peri-menopausal (ref = premenopausal)	1.73 (1.07, 2.81)	1.70 (1.01, 2.84)	2.46 (1.45, 4.17)
Less than college graduate (ref = college graduate or more)	2.01 (1.22, 3.31)	1.97 (1.15, 3.40)	2.10 (1.24, 3.55)
Single/widowed/divorced marital status (ref = married)	0.79 (0.47, 1.32)	0.84 (0.48, 1.46)	0.78 (0.46, 1.34)
Weight at age 18 (pounds)	1.05 (1.04, 1.07)	1.06 (1.04, 1.08)	1.05 (1.04, 1.07)
Alcohol drinking (ref = not current)	0.72 (0.43, 1.19)	0.73 (0.42, 1.27)	0.68 (0.40, 1.16)
Smoking (ref = never)	0.56 (0.35, 0.90)	0.48 (0.29, 0.80)	0.55 (0.34, 0.89)
FAI/FEI		2.93 (2.10, 4.08)	2.44 (1.71, 3.47)
	Super obese versus normal weight women		
	Covariate-adjusted OR (95 % CL)	Covariate and FAI-adjusted OR (95 % CL)	Covariate and FEI-adjusted OR (95 % CL)
Age at menarche (years)	0.66 (0.52, 0.83)	0.63 (0.49, 0.81)	0.67 (0.52, 0.86)
Race (ref = white)			
Black	5.24 (2.20, 12.48)	4.99 (1.96, 12.70)	5.19 (2.07, 13.03)
Other	1.06 (0.18, 6.56)	1.09 (0.17, 7.11)	0.81 (0.11, 5.77)
Peri-menopausal (ref = premenopausal)	3.73 (1.78, 7.80)	3.49 (1.58, 7.69)	6.57 (2.91, 14.81)
Less than college graduate (ref = college graduate or more)	2.55 (1.21, 5.39)	2.62 (1.16, 5.89)	2.84 (1.28, 6.32)
Single/widowed/divorced marital status (ref = married)	1.73 (0.80, 3.75)	2.20 (0.94, 5.14)	1.77 (0.78, 4.04)
Weight at age 18 (pounds)	1.09 (1.07, 1.11)	1.10 (1.07, 1.12)	1.09 (1.07, 1.11)
Alcohol drinking (ref = not current)	0.36 (0.17, 0.77)	0.41 (0.18, 0.93)	0.39 (0.17, 0.87)
Smoking (ref = never)	0.70 (0.34, 1.45)	0.57 (0.26, 1.26)	0.61 (0.28, 1.33)
FAI/FEI		6.38 (3.81, 10.68)	5.95 (3.37, 10.53)

^aOdds ratios and 95% confidence limits derived using polytomous logistic regression

95% CL = 95% confidence limits; FAI = Free androgen index; FEI = Free estradiol index; OR = odds ratio