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Relationship Between Obesity and Anti-Müllerian Hormone in Reproductive-Aged African-American Women

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Abstract

Objective—To determine whether there is an association between obesity and Anti-Müllerian hormone (AMH) amongst reproductive-aged African-American women (AAW).

Methods—1,654 AAW aged 23–35 who participated in an ongoing NIEHS study were included. Anthropometric measurements, personal health information, and serum AMH and adipokine levels were analyzed.

Results—The median body mass index (BMI) was 32.4 kg/m^2 and the median AMH was 3.18 ng/mL. Participants with obesity had AMH concentrations that were 23.7% lower than those with a BMI ≤ 25 kg/m^2 (2.9 ng/mL versus 3.8 ng/mL). In multivariable linear regression models, current BMI (β=−0.015; 95% CI −0.021, −0.009), BMI at age 18 (β=−0.016; 95% CI −0.024, −0.008), heaviest reported lifetime weight (β=−0.002; 95% CI −0.003, −0.001) and leptin (β= −0.016; 95% CI −0.025, −0.007) were inversely associated with AMH. There was no significant association between adiponectin and AMH. AMH was significantly lower (mean log=0.91, SE=0.11) in participants with obesity at age 18 and at enrollment when compared to those who were underweight or normal weight at age 18 but had obesity at enrollment (mean log=1.16, SE=0.12).

Conclusions—In reproductive-aged AAW there is a significant association between obesity and AMH, suggesting that excess adiposity may compromise ovarian reserve. Effects of obesity on AMH may be cumulative.

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Keywords

AMH; ovarian reserve; obesity; African-American; leptin; adiponectin

Introduction

In the United States the prevalence of obesity is significantly higher in women (38.3%) than men (34.3%) (1). Obesity affects all organ systems, increasing the risk of coronary heart disease (2), stroke (3), diabetes (4), cancer (5) and other comorbidities. In women it is critical not only to address the general health risks of obesity, but also to consider the impact of obesity on reproductive health. Obesity has been linked to lower spontaneous pregnancy rates (6–9), and has also been associated with poorer outcomes in women undergoing in vitro fertilization (IVF) (10). Women who have a higher BMI have decreased responses to fertility medications (11), fewer oocytes retrieved (12), and lower pregnancy and live birth rates (13) than those who have a normal BMI.

It has been suggested that obesity impairs ovarian function (14). Ovarian reserve, a term used to describe the reproductive potential of the ovaries, is correlated with ovarian function (15). Anti-Müllerian hormone (AMH), a dimeric glycoprotein and member of the transforming growth factor-beta family, is produced by granulosa cells in preantral and early antral follicles within the ovaries and is correlated with ovarian reserve (16). AMH inhibits recruitment of primordial follicles and its concentration is proportional to the number of ovarian follicles that are developing (17, 18). Clinically, AMH is used to predict outcomes with IVF as it is associated with the number of oocytes retrieved in an IVF cycle (19). AMH is also used to counsel patients who are interested in future reproduction and desire information on their reproductive lifespan as it can be used to predict timing of menopause (17). There is a well-established relationship between age and AMH, with levels declining as women grow older. However, age alone does not drive decreases in AMH, as some women have lower AMH concentrations than expected for their ages (15). It has been proposed that obesity is a factor that reduces AMH. However, this relationship has not been definitively established as certain studies have reported an inverse correlation between obesity and AMH (20–24), while others have failed to demonstrate such a relationship (25–27).

Given the current obesity epidemic coupled with the contradictions in the literature regarding the association between obesity and AMH, further investigation into this relationship is warranted. As obesity rates are higher in African-American women (AAW) than in any other racial group in the United States at a prevalence of nearly 60% (28), this is an ideal population in which to examine the relationship between obesity and AMH. The objective of this study is to examine the association between obesity and AMH in a large cohort of reproductive-aged AAW.

Methods

Study participants

The Study of Environment, Lifestyle, and Fibroids (SELF) is an ongoing prospective cohort study which is supported by the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health, in conjunction with the Henry Ford Health System (HFHS) and is being conducted in Detroit, Michigan. Recruitment of participants occurred between November 2010 and December 2012. SELF was approved by the institutional review boards of the NIEHS and HFHS, and written informed consent was provided by all study participants. The objective of SELF is to prospectively evaluate women for uterine fibroid development with a goal of identifying factors associated with incidence and growth of fibroids. Data used for this particular study were obtained at the time that participants enrolled in SELF.

Premenopausal women aged 23–34 were recruited for SELF. The study design, methods, and recruitment results have previously been described in detail (29). In order to be eligible, participants must have identified themselves as African-American or Black, and been living in the United States. Pregnant women who wanted to participate had their enrollment delayed until at least 3 months post-pregnancy. Women who had had medical treatments for cancer or autoimmune diseases such as lupus were excluded from entry into the study. This exclusion was made because these treatments can adversely affect the reproductive tract, but because these diseases will be rare in our age group the numbers would be too few to model the potential confounding effects. At enrollment participants had a clinic visit where height, weight, blood pressure, and skin reflectance were recorded. In addition a blood draw was performed, and extensive personal data were collected via questionnaires.

Assays

At the time of enrollment up to 55 mL of blood was drawn from each participant. Serum, plasma, whole blood, clot, and packed cells were stored. After all participants were enrolled, serum aliquots were sent to the Clinical Laboratory Research Core in the Pathology Department at Massachusetts General Hospital. Each stored sample of serum was barcoded and assayed for AMH. Serum AMH was measured using the picoAMH ELISA (lower limit of detection 0.0016 ng/mL, 1 ng/mL=7.14 pmol/L) (Ansh Labs, Webster, TX). Samples were run at a 1/10 dilution, then neat for the samples that were low. AMH values that were below the lower limit of detection (n=3) were assigned a value of 0.0011 ng/mL using an established formula (30). The AMH ELISA has intra- and interassay coefficients of variation (CVs) of 6.9% and 6.5% respectively.

Adiponectin and leptin were assayed on the serum of a subset of participants (n=722). Leptin/adiponectin ratios were calculated as this is a useful as a marker of insulin resistance in non-diabetic individuals (31). Adiponectin was measured using an ELISA with an intra-assay CV of 5.4%, an inter-assay CV of 5.3% and a lower limit of quantification of 0.019 ng/mL (ALPCO Diagnostics, Salem, NH). Leptin was measured using an ELISA with an intra-assay CV of <5%, an inter-assay CV of <9%, and a lower limit of quantification of 0.135 ng/mL +2SD (LINCO Research, a Division of Millipore Inc., St. Charles, MO).

Anthropometrics

Height and weight measured at enrollment were used to calculate “current BMI”. “BMI at age 18” was calculated using self-reported weight at age 18 and height measured at enrollment. Participants were also asked about their heaviest non-pregnant lifetime weight. The following definitions were used: BMI <18.5 kg/m^2= underweight, BMI ≥18.5 to 24.9 kg/m^2 = normal, BMI 25 to 29.9 kg/m^2= overweight, and BMI ≥30 kg/m^2= obese.

Covariates

Details on personal health information were obtained from participants using self-reported computer assisted telephone interviews, computer assisted web-based interviews, self-administered hard-copy questionnaires, or by obtaining responses to questions administered by the study staff at the clinic visit. A current or prior diagnosis of polycystic ovarian syndrome (PCOS), abnormal menstrual bleeding or a thyroid condition was obtained by participant self-report. To determine menstrual cycle length each participant was asked how many days generally occurred between the first day of one menstrual cycle and the first day of the next menstrual cycle over the preceding 12 months. Participants were asked about use of hormonal contraception and this was considered when cycle length was assessed as use can alter cycle regularity. Hormonal contraception included use of any oral contraceptive pill, a vaginal ring, hormonal shots, the hormonal implant, the hormonal patch, or the levonorgestrel intrauterine device.

Statistical Analysis

The distribution of AMH, the covariates of interest and relevant participant characteristics were described by means or medians (with SD or interquartile ranges) for continuous variables and proportions for categorical variables. AMH concentrations were log transformed for analysis in linear regression models, as they are not normally distributed. Spearman’s rank correlation coefficients were used to assess associations between BMI and other clinical and biochemical markers of obesity.

Given the established relationship between age and AMH, as well as the confirmed association between age and AMH in our previous analysis of this cohort (32), age-adjusted linear regression was performed to evaluate the association between obesity and its biomarkers and AMH. Age and quadratic age were both included in the model to allow for a nonlinear relationship between AMH and age. Previous analyses of this cohort demonstrated a significant relationship between AMH and current hormonal contraception use, history of a thyroid condition, abnormal menstrual bleeding, and menstrual cycles longer than 35 days (32). These covariates were included in multivariable models. Estimates of beta (β), confidence intervals, and *P* values were obtained from linear regression analysis. To explore the contribution of current obesity as compared with obesity at age 18 on AMH, we categorized participants based on their BMI at both time points and used analysis of variance to compare log-transformed AMH and calculate both least squared means and beta coefficients (SE). Statistical Analysis Software version 9.4 (SAS Institute, Cary, NC) was used to perform all analyses. Statistical significance was determined at $P<0.05$.

Results

Baseline Characteristics

Of the 1,696 women enrolled in SELF, serum was available for 1,654. Table 1 includes information on demographics, medical and reproductive history, and biomarkers of obesity for the women who had serum available for analysis. 1,645 women had height and weight recorded at enrollment allowing for calculation of current BMI. 1,633 women reported weight at age 18, allowing BMI at age 18 to be calculated.

Relationship Between BMI and AMH

Figure 1 demonstrates AMH concentrations by BMI. At enrollment 19.8% of participants were underweight or normal, 20.7% were overweight, and obesity was present in 59.5%. The median AMH concentrations were 3.8 ng/mL (IQR 1.9–5.9 ng/mL) in participants who were underweight or normal, 3.4 ng/mL (IQR 2.0–5.3 ng/mL) in those who were overweight, and 2.9 ng/mL (IQR 1.6–5.1 ng/mL) in participants with obesity.

Based on self-reported weight at age 18, 49.2% of participants were underweight or normal, 25.2% were overweight and obesity was present in the remaining 25.6%. The median AMH concentrations at enrollment were 3.4 ng/mL (IQR 1.8–5.5 ng/mL) in participants who were underweight or normal at age 18, 3.1 ng/mL (IQR 1.8–5.4 ng/mL) in those who were overweight at age 18, and 2.9 ng/mL (IQR 1.5–5.4 ng/mL) in participants with obesity at age 18.

Linear Regression Modeling

There were significant positive correlations between current BMI and BMI at age 18 (r_s= 0.73, P<.0001), weight at age 18 (r_s=0.71, P<.0001), and heaviest lifetime weight (r_s=0.89, P<.0001). Linear regression analyses were performed to assess the relationship between obesity and AMH (Table 2). When current BMI was analyzed as a continuous variable, there was a significant inverse relationship with AMH in the age-adjusted and the multivariable linear regression model. When current BMI was analyzed as a categorical variable, the beta coefficients for each BMI group increased with increasing BMI, with the strongest association between AMH and BMI being observed among those with the highest BMI, suggesting a generally linear pattern. When BMI at age 18 was analyzed as a continuous variable, there was also a significant inverse relationship with AMH in both the age-adjusted and the multivariable linear regression model. When the relationship between BMI at age 18 and AMH was analyzed as a categorical variable using the multivariable linear regression model, this association also was generally linear; AMH generally decreased as BMI increased. There was also a significant decrease in AMH with increases in heaviest lifetime weight. Sensitivity analyses were subsequently performed and participants with PCOS or long menstrual cycles were excluded. The significant relationships between AMH and both continuous and categorical BMI and BMI at age 18 persisted when these multivariable linear regression models were performed.

In adjusted models participants with obesity at both age 18 and at enrollment had significantly (P=0.0102) lower AMH concentrations (mean log AMH =0.91, SE=0.11) than

those who were underweight or normal at age 18 but with obesity at enrollment (mean log AMH =1.16, SE=0.12).

Current BMI was positively correlated with leptin (r_S=0.77, P<.0001), and negatively correlated with adiponectin (r_S=−0.28, *P*<.0001). There was a significant inverse relationship between leptin, as well as the leptin/adiponectin ratio, and AMH in both the age-adjusted and multivariable linear regression models. There was no significant association between adiponectin and AMH in either of the models.

Discussion

In this large cohort of reproductive-aged AAW, there was a significant inverse association between obesity and AMH. AMH concentrations declined as current BMI increased, and AMH was significantly lower in participants with obesity compared to those who were underweight or normal. There was also a significant inverse relationship between BMI at age 18 and AMH. Further, participants with obesity at age 18 and obesity at enrollment had significantly lower AMH concentrations than those who were underweight or normal at age 18 but had obesity at enrollment. Finally, there was a significant inverse relationship between leptin as well as the leptin/adiponectin ratio and AMH.

Previous investigations into the relationship between obesity and AMH have yielded mixed results. Dólleman et al reported that BMI was not significantly associated with age-specific AMH percentiles in women with a mean BMI of 24.3 kg/m^2 (27). Similarly, neither Sahmay and colleagues nor Halawaty et al found differences in AMH concentrations between women with and without obesity(25) (26). However, other investigators have observed associations between obesity and AMH. In a study of 36 women with a mean age of 45, Su et al reported that AMH concentrations were 77% lower in individuals with obesity compared to those of normal weight (20). Freeman and colleagues examined 122 women with a mean age of nearly 46 and reported that women with obesity had AMH concentrations that were 65% lower than women without obesity (21). Steiner et al examined 20 women with a mean age of 29 who were taking oral contraception and reported that AMH concentrations were 34% lower in women with obesity compared to normal weight women (22). Bleil and colleagues reported that AMH decreased by 1.5% with each one unit increase in BMI in a cohort of 947 women with a mean age of 35 (33). Moy et al described a negative correlation between BMI and AMH in 159 Caucasian women but not in 99 AAW(34). Buyuk et al found an inverse association between BMI and AMH in 152 women with decreased ovarian reserve, but not in 138 women with normal ovarian reserve (35). Given that in our study the strongest effects on AMH were present in the highest BMI categories, the inconsistencies in the literature may be because prior studies did not have sufficient numbers of women in very high BMI groups to capture an association with AMH.

A unique aspect of our study is that we investigated the relationship between BMI at age 18 and current AMH. The fact that participants with obesity at age 18 and at enrollment had significantly lower AMH concentrations compared to those who were underweight or normal weight at age 18 but had obesity at enrollment suggests that there may be a cumulative effect of obesity on AMH over time. Given that there are few studies examining

obesity and AMH in adolescent females, it is difficult to determine how obesity impacts AMH before a woman's prime reproductive years. Cengiz and colleagues evaluated AMH in adolescents with PCOS and found no significant association between BMI and AMH (36). However, Park et al compared AMH concentrations between adolescents with and without obesity and reported that AMH was significantly lower in individuals with obesity, both with and without PCOS (37). The relationship between BMI during adolescence and AMH in adulthood must be further explored to gain additional insight into the long-term implications of obesity on AMH.

The association between adiponectin and leptin and AMH has been assessed in several studies, but conflicting results have been reported. Olszanecka-Glinianowicz and colleagues as well as Park et al reported a significant relationship between adiponectin and AMH, but that leptin was not significantly correlated with AMH in women with and without PCOS (23) (24). Shen et al found no association between adiponectin and AMH in women with and without PCOS (38). In the only experimental study of which we are aware, Merhi and colleagues reported that AMH decreased when granulosa cells were treated with leptin, but that adiponectin treatment did not affect AMH expression (14). Our finding of an inverse association between leptin and AMH in this cohort of women with only a small prevalence of PCOS concurs with the findings of Merhi and colleagues. It seems possible that leptin plays at least a partial role in the expression of AMH and may help explain the mechanism by which AMH and BMI are inversely associated.

It has been reported that women with obesity have alterations in their ovarian follicular microenvironment (39). The results of our study demonstrate that reproductive-aged women with obesity have lower AMH concentrations, suggesting that folliculogenesis is likely impaired as BMI increases, and supporting the notion that obesity may create an altered follicular environment. A number of theories have been proposed to further explain the relationship between obesity and AMH. It is possible that insulin resistance in obese individuals impacts granulosa cells and consequently alters AMH concentration (24). There may also be lipotoxic effects on the granulosa cells (40). It is also possible that adiponectin and leptin are involved in modulating ovarian function as these adipokines play a role in reproductive processes by way of the hypothalamic-pituitary-ovarian axis (24). In addition there are receptors for adiponectin and leptin in the granulosa cells of the ovaries (14). Another possibility is that AMH may be metabolized, stored and cleared differently in obese individuals (40). Given the design of this study, the etiology for lower AMH levels in women with obesity could not be explored. While these data certainly suggest a role of obesity on AMH levels it remains unclear whether this is due to an impact on follicle number versus follicular physiology versus granulosa cell dysfunction.

This study has a number of important strengths. To our knowledge, it is one of the largest studies to date examining the association between obesity and AMH with over 1,600 participants. In addition, it is the largest study to investigate the relationship in AAW, who have the highest obesity rates amongst reproductive-aged women in the United States. Further, the participants had a mean age of 28.7 years, making results more applicable to women of peak reproductive years than some of the previous studies examining this association. In addition, this study evaluated more than just the association between current

BMI and AMH. The goal of this study was to use an epidemiologic model to gain insight into whether various obesity related factors are associated with AMH. This cohort of women was well characterized and so can provide a more thorough understanding of the relationship between obesity onset at different stages of life and AMH.

One limitation of this study is that the cross-sectional design only allowed for assessment of associations. Our study did find that BMI at age 18 was significantly associated with AMH, but this variable was self-reported. The meaning of the observed decrease in AMH with BMI at age 18 is unclear. It may be possible that high BMI in late adolescence may be particularly damaging with lasting adverse effects on the ovary. Also, those with high BMI at 18 will on average have had a longer duration with elevated BMI than those who developed a high BMI later in life; a long duration of obesity may increase adverse effects on the ovary. In addition, BMI at 18 and BMI at enrollment were quite highly correlated, so the analyses may not reflect true independent effects of each. Further detailed data collection and analyses will be needed to investigate these issues and ascertain the extent to which weight loss can reverse the reduction in AMH seen with elevated BMI. Another limitation is that we only examined the association between AMH and markers of obesity in AAW, thus potentially limiting the generalizability of these findings to other racial/ethnic groups. Finally, it was likely that PCOS was underdiagnosed in this cohort. However, the sensitivity analysis demonstrated that when we excluded women with PCOS or long menstrual cycles (a likely surrogate for subclinical or undiagnosed PCOS), results were essentially unchanged.

Conclusion

In conclusion, this large study of reproductive-aged AAW suggests that AMH is inversely associated with BMI. There was a significant association between AMH and multiple markers of obesity, including current BMI, BMI in the late teen years, and leptin. Further, AMH was significantly lower in participants with obesity at age 18 and at enrollment compared to those who were underweight or normal at age 18 but with obesity at enrollment suggesting that the effects of obesity on AMH may be cumulative. Although these findings indicate that ovarian reserve and/or folliculogenesis may be impaired in reproductive-aged AAW with obesity, additional investigation is critical to gain a fuller understanding of the relationship between obesity and AMH.

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Study Importance Questions

What is already known about this subject?

- Obesity is associated with poorer outcomes in women undergoing in vitro fertilization and the impact of obesity on ovarian reserve may play a role in these outcomes. Anti-Müllerian hormone (AMH) is a marker of ovarian reserve.
- Although several studies have reported an association between clinical measures of obesity and AMH, others have failed to demonstrate that a relationship exists.
- Previous studies investigating the relationship between biomarkers of obesity and AMH also report conflicting findings.

What does this study add?

- We found a relationship between obesity and its biomarkers and AMH in a large cohort of women in their prime reproductive years.
- We discovered an association between obesity as a late teen and AMH in adulthood, which has not been reported in any other studies of which we are aware.
- To our knowledge, this is the largest cohort of African-American women where the relationship between obesity and AMH has been studied. African-American women have the highest rates of obesity in the United States making them an optimal group to study.

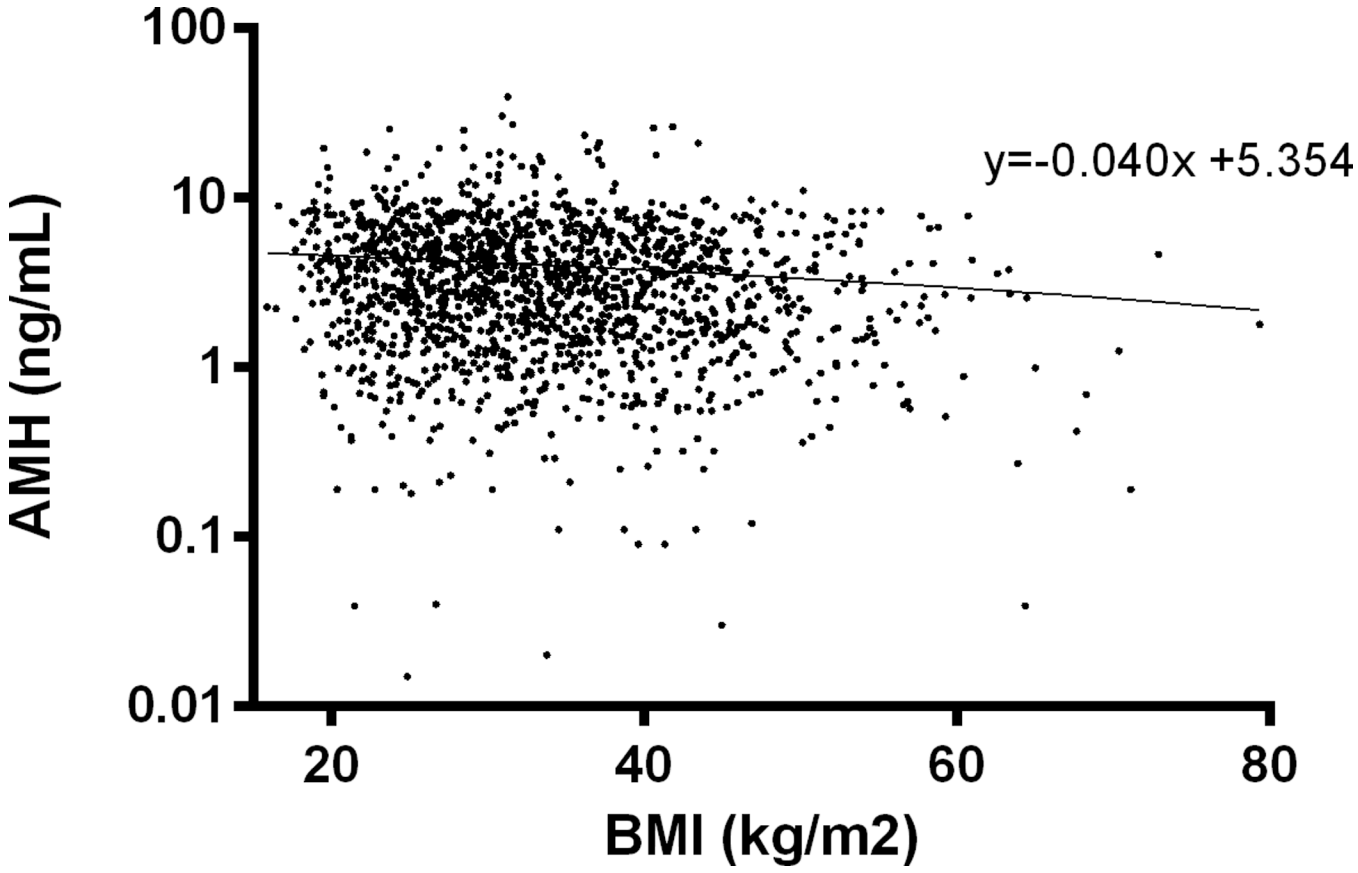

Figure 1.
Anti-Müllerian hormone (AMH) by body mass index (BMI) (n=1642; excludes 3 participants that had AMH concentrations below the limit of detection of the assay)

Table 1

Participant characteristics (n=1654)

Age, y (mean ±SD; range)	28.7 ± 3.5; 23–35 [a]
23–25	371 (22.4%)
26–28	417 (25.2%)
29–31	444 (26.8%)
32–35	422 (25.5%)
Anti-Müllerian hormone, ng/mL (median, IQR; range)	3.2, 1.7–5.3; <0.002–39.4
Current body mass index, kg/m^2 (median, IQR; range)	32.4, 26.3–39.5; 15.9–79.4
Body mass index at age 18, kg/m^2 (median, IQR; range)	25.2, 21.5–30.2; 13.5–66.1
Self reported weight at age 18, lbs (mean ±SD; range)	156.9 ± 43.8; 80–375
Heaviest reported lifetime weight, lbs (mean ±SD; range)	207.3 ± 61.8; 96–490
Adiponectin, μg/mL (median, IQR; range)[b]	4.6; 3.6–6.6; 1.5–24.7
Leptin, ng/mL (median, IQR; range)[b]	15.0, 9.0–21.2; 0.5–73.1
Education (%)	
High school or less	22.2
Some college, but no degree	37.7
Associate or technical degree	12.3
Bachelor's degree	19.4
Graduate degree	8.4
Gross annual household income (%)	
Less than $20,000	46.1
$20,001–50,000	36.8
$50,001–100,000	14.6
Over $100,000	2.5
Pregnancy history	
Never pregnant (%)	26.7
Previous pregnancy without history of a live birth (%)	14.0
Previous live birth but no history of breastfeeding (%)	21.3
Previous live birth with history of breastfeeding (%)	38.0
Current hormonal contraception use (%)	27.5
Menstrual cycle length in last 12 months[c]	
<25 days (%)	23.4
25–35 days (%)	68.4
>35 days (%)	8.2
History of polycystic ovarian syndrome (%)	3.2
History of abnormal menstrual bleeding (%)	11.5
History of a thyroid condition (%)	2.9

[a]Participants ages 23–34 were recruited, but some had turned 35 by the time that all baseline activities and enrollment were completed.

[b] Among those who had serum concentrations assayed, n= 722

[c] Among those not using hormonal contraception at any time in the last 12 months, n=953

Table 2

Associations between obesity and anti-Müllerian hormone (AMH)

	Model 1[a]		**Model 2**[b]	
Predictor	**β**[c] **(95% CI)**	***P* value**	**β**[c] **(95% CI)**	***P* value**
Current BMI[d] **(kg/m²) (Continuous)**	−0.010 (−0.016, −0.005)	**0.0003**	−0.015 (−0.021, −0.009)	**<0.0001**
Current BMI[d] **(Reference: <25 kg/m²)** (n=326)	--	0.0731	--	**0.0024**
25– <30 kg/m² (n=341)	0.006 (−0.161, 0.172)	0.9470	−0.012 (−0.185, 0.161)	0.8892
30– <35 kg/m² (n=316)	−0.024 (−0.194, 0.145)	0.7771	−0.118 (−0.295, 0.058)	0.1896
35– <40 kg/m² (n=275)	−0.053 (−0.229, 0.123)	0.5529	−0.134 (−0.319, 0.050)	0.1538
40– <45 kg/m² (n=201)	−0.188 (−0.380, 0.005)	0.0557	−0.265 (−0.465, −0.066)	**0.0091**
≥45 kg/m² (n=186)	−0.235 (−0.433, −0.038)	**0.0193**	−0.372 (−0.581, −0.163)	**0.0005**
BMI at age 18[e] **(kg/m²) (Continuous)**	−0.014 (−0.021, −0.006)	**0.0003**	−0.016 (−0.024, −0.008)	**<.0001**
BMI at age 18[e] **(Reference: <25 kg/m²)** (n=804)	--	**0.0054**	--	**0.0018**
25– <30 kg/m² (n=412)	−0.051(−0.181, 0.079)	0.4419	−0.093 (−0.229, 0.044)	0.1828
30– <35 kg/m² (n=244)	−0.171 (−0.328, −0.015)	**0.0322**	−0.213 (−0.377, −0.050)	**0.0106**
35– <40 kg/m² (n=87)	−0.258 (−0.500, −0.016)	**0.0366**	−0.308 (−0.558, −0.057)	**0.0162**
40– <45 kg/m² (n=51)	−0.360 (−0.670, −0.051)	**0.0225**	−0.385 (−0.709, −0.062)	**0.0195**
≥45 kg/m² (n=35)	−0.486 (−0.857, −0.116)	**0.0102**	−0.514 (−0.887, −0.142)	**0.0069**
BMI Groups (Reference: Underweight or normal at age 18 and underweight or normal currently) (n=294)		**0.0145**		**0.0038**
Underweight or normal at age 18 and overweight currently (n=265)	0.011 (−0.172, 0.195)	0.9045	0.001 (−0.191, 0.194)	0.9888
Underweight or normal at age 18 and obese currently (n=245)	0.059 (−0.129, 0.248)	0.5367	−0.058 (−0.257, 0.140)	0.5642
Overweight at age 18 and overweight currently	0.030 (−0.289, 0.350)	0.8529	0.011 (−0.318, 0.340)	0.9458

	Model 1[a]		Model 2[b]	
Predictor	**β [c] (95% CI)**	***P* value**	**β [c] (95% CI)**	***P* value**
(n=54)				
Overweight at age 18 and obese currently (n=331)	−0.050 (−0.224, 0.123)	0.5661	−0.146 (−0.330, 0.037)	0.1176
Obese at age 18 and obese currently (n=395)	−0.227 (−0.394, −0.061)	**0.0074**	−0.303 (−0.477, −0.128)	**0.0007**
Reported weight at age 18 (lbs)[e]	−0.003 (−0.004, −0.001)	**<0.0001**	−0.003 (−0.004, −0.001)	**<0.0001**
Heaviest lifetime weight (lbs) [f]	−0.002 (−0.002, −0.001)	**0.0002**	−0.002 (−0.003, −0.001)	**<0.0001**
Adiponectin (μg/mL)[g]	4.9×10^{-8} (-3.1×10^{-5}, 3.1×10^{-5})	0.9976	1.2×10^{-5} (-2.0×10^{-5}, 4.3×10^{-5})	0.5170
Leptin (ng/mL)[g]	−0.016 (−0.025, −0.007)	**0.0004**	−0.016 (−0.025, −0.007)	**0.0004**
Leptin/ Adiponectin Ratio	−33.131 (−60.214, −6.047)	**0.0166**	−39.610 (−66.612, −12.608)	**0.0041**

Bold font indicates statistical significance ($P<0.05$).

[a] Adjusted for age and quadratic age

[b] Adjusted for covariates demonstrated to be significantly associated with AMH in previous study of this cohort: age, quadratic age, current hormonal contraception use, history of a thyroid condition, abnormal menstrual bleeding, and menstrual cycle length.

[c] Beta coefficient (β) represents change in AMH concentration for each one unit increase in the predictor being analyzed.

[d] Analyses performed in 1645 participants who had height and weight measured at enrollment.

[e] Analyses performed in 1633 participants who self-reported weight at age 18.

[f] Analyses performed in 1638 participants who reported heaviest lifetime non-pregnant weight.

[g] Analyses performed in 722 participants who had adipokines assayed.