Published in final edited form as:

Am J Hum Biol. 2018 May ; 30(3): e23106. doi:10.1002/ajhb.23106.

Reproductive Health, Obesity, and Cardiometabolic Risk Factors among Samoan Women

H. Maredia^{1,2,*}, N. L. Hawley³, G. Lambert-Messerlian¹, U. Fidow⁴, M. S. Reupena⁵, T. Naseri⁶, and S.T. McGarvey^{2,*}

¹Departments of Pathology and Laboratory Medicine and Obstetrics and Gynecology, Alpert Medical School of Brown University, Providence, RI 02912, USA

²Department of Epidemiology and International Health Institute, Brown University School of Public Health, Providence, RI 02912, USA

³Department of Chronic Disease Epidemiology, Yale School of Public Health, New Haven, CT, 06520, USA

⁴Department of Obstetrics and Gynecology, Tupua Tamasese Meaole Hospital, National Health Service, Government of Samoa, Apia, Samoa

⁵Bureau of Statistics, Government of Samoa, Apia, Samoa

⁶Ministry of Health, Government of Samoa, Apia, Samoa

Abstract

Objectives—Obesity leads to deleterious effects on not only cardiovascular health but also on the reproductive health of women. We estimate the prevalence of menstrual irregularity and of polycystic ovarian syndrome (PCOS) in Samoan women, among whom obesity prevalence is extremely high. We explore the association of these reproductive health conditions with adiposity, cardiometabolic risk factors, and androgen levels.

Methods—A cross-sectional sample of Samoan women 25–39 years of age (n=470) from a larger population-based genome-wide association study (GWAS) of adiposity and cardiometabolic disease was assessed for the prevalence of oligomenorrhea/amenorrhea (OM/AM) using a self-reported questionnaire. Serum androgens and anti-Müllerian hormone (AMH) levels were assayed to determine hyperandrogenemia and presence of polycystic ovaries, respectively, using criterion values. PCOS was classified using NIH criteria of having at least two of the three conditions: menstrual irregularity, hyperandrogenism, and polycystic ovaries. We contrasted socio-demographic, reproductive health, and cardiometabolic risk factors between those with and without OM/AM and similarly for PCOS.

*Correspondence to: Stephen T McGarvey, PhD, MPH, International Health Institute, Brown University School of Public Health, Providence, RI 02912, USA, Tel: +1-401-863-1354, stephen_mcgarvey@brown.edu.

Author Contributions.

HM and STM did the majority of data analyses and drafted the manuscript. GLM, STM, HM and NLH developed the study hypotheses. MSR facilitated fieldwork in Samoa. NLH and STM administered surveys, collected study samples, and assembled the data sets. GLM and HM conducted androgen and AMH assays. TN and UF reviewed the report for clinical and public health implications. All authors wrote and edited the manuscript.

Results—The prevalence of OM/AM was 7.4% (95% CI: 5.1, 9.8), and women with OM/AM had significantly higher central adiposity. PCOS was estimated at 6.8% (95% CI: 4.5, 9.1), and those with PCOS were younger but had higher overall and central adiposity measures, higher triglycerides, and higher prevalence of insulin resistance than women without PCOS.

Conclusions—The prevalence of menstrual irregularity and PCOS are less than hypothesized given the high levels of adiposity in this population. Nevertheless, Samoan women with menstrual irregularity and other features of PCOS have significantly poorer metabolic health.

Keywords

menstrual irregularity; PCOS; hyperandrogenemia; Samoan; women

Introduction

As a result of nutritional, economic and social transitions, Samoa and American Samoa are characterized by very high levels of obesity (NCD Risk Factor Collaboration, 2016). A 2010 national survey in Samoa found that 91.3% of women were overweight based on the Polynesian body mass index (BMI) criteria of BMI ≥ 26 kg/m² (Hawley et al. 2014). Among women 24.5–49 years of age, mean BMI was 34.5 kg/m², with 65.2% of women above the Polynesian threshold for obesity (32 kg/m²) (Hawley et al. 2014). Similarly, in American Samoa, the 2004 WHO STEPS data indicate that 94.4% of women aged 25–64 years had a BMI ≥ 25 kg/m², and mean BMI was 36.1 kg/m² and 36.7 kg/m² among American Samoan women aged 25–34 and 35–44 years, respectively (WHO 2007).

Several studies have established that obesity increases a woman's likelihood of experiencing menstrual irregularities (Castillo-Martinez et al. 2003; Rowland et al. 2002; Brown et al. 2000; van Hooft et al. 1998; Hartz et al. 1979). Irregular menstruation can be a clinical manifestation of polycystic ovarian syndrome (PCOS). PCOS is a complex endocrine disorder that is closely linked with obesity and metabolic syndrome and is known to be the leading cause of anovulatory infertility worldwide (Baldani et al. 2013). High levels of obesity are suggested to exacerbate the onset of PCOS symptoms (irregular menstruation, acne, abnormal hair growth) but may also be a consequence of PCOS, as excessive androgens have been shown to increase body fat deposition, particularly in the abdominal area (Rosenfield 1999). Insulin as well as androgens and other factors secreted by fat cells may be involved in mediating irregular menstrual cycles among overweight and obese women (Orio et al. 2016; Pasquali et al. 2006).

The extreme levels of obesity seen in Samoans may be expected to have profound negative impacts on women's reproductive health, fecundity, and fertility. From a reproductive ecology perspective, it is important to document the consequences of the nutritional transition in Samoans on female reproductive health, and the potential interactions with their demographic and evolutionary history (Ellison 2008; Vitzthum 2009; Sherry et al. 2014). We recently found a novel genetic variant among Samoans enriched through natural selection that was positively associated with adiposity but negatively associated with fasting glucose and odds of type 2 diabetes (Minster et al. 2016). An evolutionary view of this variant suggests the importance of investigating if the generally negative influences of adiposity on

female reproductive biology and health may be somewhat attenuated in Samoans compared to other populations.

Although little is known about the reproductive health of women in Samoa, fertility patterns have been described. The total fertility rate (TFR) from the 2014 Demographic and Health Survey (DHS) is estimated at 5.1; in rural areas it is 5.2 and 4.4 among urban areas (Samoa Bureau of Statistics 2015). This represents a temporal decrease in TFR from 7.4 in the early 1970s but a recent smaller increase from 4.2 in the 2006 census (Samoa Bureau of Statistics 2015, see Figure 4.3). However, despite overall decreased fertility, older women in Samoa, and in some other Pacific nations, have remarkably high fertility compared to other world populations (House and Nasiru 1999). For example, the age-specific fertility rate among women 35 and older in Samoa in the 1970s was 79/1,000 and in the 1990s was 98/1,000, and among those 40–44 years in the 1990s was 86/1,000 (House and Nasiru 1999). Of note, the 2009 Samoa Demographic and Health Survey reported that 68.5% of women of reproductive age wanted two or more children, with 26.7% of respondents indicating wanting five or more (Samoa Ministry of Health et al. 2010).

Stimulated by anecdotal reports of infertility from physicians and some women during our ongoing studies and the literature on adiposity and women's reproductive health, we first explored menstrual irregularity in a cross-sectional study of 322 women 25–39 years of age from American Samoa and Samoa in 2002–2003, finding that 13.7% experienced menstrual irregularity, defined as oligomenorrhea/amenorrhea (OM/AM) (Lambert-Messerlian et al. 2011). In a preliminary attempt to estimate PCOS, we also found that 8% of these women had both OM/AM and elevated androgen levels. However, we did not have data on contraceptive injections, which previous studies have found are the most commonly used contraception by Samoan women (Brewis et al. 1998). Contraceptive injections can both stop menstrual cycles and alter serum androgen levels, masking the true prevalence of menstrual irregularity and hyperandrogenemia (de Aguilar et al. 1997).

In the context of the remarkably high and rising levels of adiposity among Samoan women, the purpose of this study is to update and improve upon current estimates of the prevalence of menstrual irregularity and PCOS among reproductive-aged Samoan women and to examine their associations with adiposity and cardiometabolic risk factors. Specifically, we improve the earlier study of menstrual irregularity by excluding women who report use of contraceptive injections, using a revised estimate of biochemical hyperandrogenism (Maredia et al. 2016), and applying AMH levels as a marker of polycystic ovary morphology.

Methods

Study Sample

The data for this report came from a cross-sectional genome-wide association study of adiposity and cardiometabolic risk factors among adults aged 24 – <65 years conducted in 2010 in Samoa (Hawley et al. 2014; Minster et al. 2016). Participants resided in all four census regions of Samoa including the urban and national capital region of Apia, the Northwest 'Upolu region adjacent to Apia and the international airport, the Rest of 'Upolu

(ROU) which is the rural area of 'Upolu, and Savaii, a separate island and the most rural region. As in our prior study of menstrual irregularity, we restricted the study sample to women <40 years of age, i.e., 25–39 years, $n=759$, to avoid peri-menopausal as well as postmenopausal conditions (Lambert-Messerlian et al. 2011; Rosic et al. 2014). Women who reported having their last menstrual period 12 or more months ago due to expected causes, namely pregnancy/lactation ($n = 17$), hysterectomy or oophorectomy ($n = 14$), and cancer treatment ($n = 1$), were excluded. Women who did not report their menstrual cycle data ($n = 10$) or who lacked anthropometric measurements ($n = 1$) or fasting serum samples ($n = 49$) were also excluded. Because using exogenous hormone injections for contraception can result in irregular menstruation and altered androgen levels (De Aguilar et al. 1997), we also excluded women who indicated ever using contraceptive injections ($n = 173$). Women responding “within the last 12 months” rather than choosing more specific responses of time frame for their last menstrual cycle were excluded due to ambiguity of the response ($n=24$). The final study sample size for this analysis was $n = 470$.

Measurements

We used self-reported data from the health questionnaire portion of the survey to define menstrual irregularity as oligomenorrhea (OM) or amenorrhea (AM). The questions in the survey asked: “Have you had a menstrual period in the last 12 months?” and “If YES, about how long ago was your last period?” Women answering “no” to the initial item were classified as having AM, defined as one’s last menstrual period occurring more than a year ago. OM is defined as infrequent menstrual periods, generally fewer than 6–8 periods in one year (Welt et al. 2015). Women who reported a menstrual period in the last 12 months but who selected the responses “3–6 months ago,” “6–9 months ago,” or “9–12 months ago” were therefore classified as having OM. Women reporting either type of menstrual irregularity were combined for all analyses and classified as OM/AM cases. Those selecting the response “having it now” or “1 to 3 months ago” were defined as having normal menstrual cycles.

Anthropometry, cardiometabolic factors, and androgen measurements for the sample have previously been described (Hawley et al. 2014; Maredia et al. 2016). Material lifestyle scores (MLS), an inventory of household assets, was calculated as a measure of socioeconomic position as in prior studies (Choy et al. 2016).

The variable homeostasis model assessment-estimated insulin resistance (HOMA-IR) was calculated as: $\text{HOMA-IR} = \text{fasting plasma insulin } (\mu\text{U/mL}) \times \text{glucose (mg/dL)} / 405$ (Matthews et al. 1985). Because of the general similarities in body size and adiposity of Mexican Americans and Samoans, we used, albeit cautiously, the insulin resistance cut-off of $\text{HOMA-IR} > 3.80$ recommended for Mexican Americans by Qu et al. (2011).

Type 2 diabetes was defined as either a fasting glucose level of ≥ 126 mg/dL or self-report of taking medication for diabetes. We excluded diabetic women ($n = 21$) when analyzing glucose, insulin, and HOMA-IR by reproductive health outcomes.

The free androgen index (FAI) was derived using measurements of total testosterone (TT) and sex hormone binding globulin (SHBG), using the formula: $(\text{TT} \times 100) / \text{SHBG}$. The FAI

adjusts TT values for abnormalities in SHBG, and due to TT assay variability FAI provides a better estimate of TT concentration by incorporating the more accurate results of the SHBG assays (Al Kindi et al. 2012; Rosner et al. 2007). Thus, FAI is more reliable for assessing hyperandrogenemia (HA). Measurements for TT and SHBG were performed using a chemiluminescent automated immunoassay (Immulite, Siemens Diagnostics, Los Angeles CA). SHBG levels above the 95th percentile of the population were checked to exclude heterophilic interference. In our recent paper on androgen levels in Samoan women, we defined HA using the 95th FAI percentile of the lowest BMI tertile, FAI > 8.5, and use that cutoff here (Maredia et al. 2016).

Anti-Müllerian hormone (AMH) levels estimate the number of ovarian follicles and were assayed in serum using an ultra-sensitive ELISA assay (Ansh Labs, Webster, TX). Serum AMH levels > 5.6 ng/mL have recently been proposed as a surrogate marker for ultrasound determination of polycystic ovary morphology (Dumont et al. 2015), and, in the absence of clinical examination with ultrasound of the ovaries, we use that definition as a marker of polycystic ovaries (PCO) in this study. To categorize any participant as having PCOS, we required two of the following three conditions: menstrual irregularity, biochemical hyperandrogenism, and/or high serum AMH levels as a marker of polycystic ovary morphology (NIH 2012; Lizneva et al. 2016).

Statistical Analyses

The percentages and 95% confidence intervals (CI) are presented for OM/AM and PCOS prevalence. All metabolic hormones except fasting serum glucose were log-10 transformed to obtain a normal distribution before undertaking analyses. For non-normally distributed variables, medians, the standard deviations of the log-10 transformed values, and the range of the untransformed values are shown. Mean differences of normally distributed variables between groups were analyzed using an independent samples two-tailed t-test; this includes variables transformed to normality. A Chi-squared test was used for categorical variables.

Because several socio-demographic factors were associated with OM/AM, we performed a stepwise multivariable logistic regression model with OM/AM as the dependent variable. Predictors that were significant at the level of $p < 0.10$ in bivariate analyses (Table 2) were included. To avoid issues of multicollinearity, abdominal circumference was chosen as the measure of body fat, based on the strength of the bivariate relationship with the OM/AM outcome compared to other indicators of body fat.

General linear models were used to adjust for age effects in multivariable models and to test for differences in cardiometabolic and reproductive biomarker differences by PCOS status. The potential for BMI effects to influence these differences was not modeled due to the likely developmental influence of adiposity on these biomarkers and the cross-sectional design. Pairwise exclusion was used for missing data.

We also explored differences in several socio-demographic, anthropometric, cardiometabolic, hormonal and behavioral characteristics across the four groups of women who met PCOS criteria, but we did not test for significant inter-group differences due to the small sample sizes.

Ethical approval

The Brown University Institutional Review Board and the Health Research Committee of the Samoan Ministry of Health approved the parent research protocol and informed consent process. The study, data collection protocols, and participant rights were explained verbally in Samoan by trained fieldworkers. Participants gave written consent.

Results

Menstrual irregularity

The prevalence of OM/AM was 7.4% (95% CI: 5.1, 9.8), with 4.5% of the sample classified as OM and 3.0% as AM (Table 1). Women with OM/AM had significantly lower education and MLS compared to women with normal menstrual cycles, and there was a significant difference in OM/AM percentage by census region (Table 2).

Central adiposity measurements, namely abdominal circumference, abdominal-hip ratio (AHR), and abdominal-height ratio (AHtR), were significantly higher in OM/AM compared to normally menstruating women, but there were no differences in BMI and percent body fat (Table 2). There were no significant differences in cholesterol, triglycerides, adiponectin, glucose, insulin, HOMA-IR values nor in the percentage of type 2 diabetes between normal women and those with OM/AM (Table 2). There were no differences between women with OM/AM and women with normal cycles in SHBG levels, nor in total testosterone, FAI, AMH, or in the percentage with increased serum AMH or androgens.

In a multivariable logistic regression model, the odds of OM/AM was significantly and positively associated with not completing secondary school, OR=2.9 (95% CI: 1.2 – 7.5; $p=0.02$), residing in the Rest of 'Upolu census region compared to the other regions, OR=2.9 (95% CI: 1.4 – 6.1; $p=0.005$), lower MLS score, $b=-0.19$ (SE=0.07; $p=0.009$), and higher abdominal circumference, $b=0.05$ (SE=0.01; $p=0.0002$).

PCOS

The prevalence of PCOS phenotype was 6.8% (95% CI: 4.5, 9.1). Seventy-five women, 16% (95% CI: 12.4, 19.0), were provisionally classified as having biochemical evidence of PCO morphology as determined by serum AMH levels. Women with PCOS were younger, but had higher BMI, percent body fat, and higher abdominal circumference than women without PCOS (Table 3). Without adjusting for age and BMI, women with PCOS also had higher triglycerides, fasting insulin, HOMA-IR, prevalence of insulin resistance, total testosterone, FAI and AMH levels as well as lower SHBG (Table 3). After adjusting for the effects of age, women with PCOS had significantly higher triglycerides ($p<0.001$); insulin, HOMA-IR and insulin resistance ($p<0.05$); and higher testosterone, FAI, and AMH as well as lower SHBG levels (all $p<0.001$).

There were no associations between PCOS and current alcohol use, current cigarette smoking, average minutes of moderate-vigorous exercise, nor with any socioeconomic status variables including education, census region, and MLS (data not shown).

Characteristics of the four mutually exclusive sub-groups of women that met PCOS criteria indicate that the PCO + HA phenotype was the most common (63% of women with PCOS; Table 3). Women in the OM/AM + HA or OM/AM + HA + PCO groups had the most extreme abnormalities in metabolic profile, including the highest adiposity measures (BMI, percent body fat, abdominal circumference) and highest metabolic markers (cholesterol, triglycerides, glucose). Women with OM/AM + HA only, had the highest insulin and HOMA-IR, while women with OM/AM + HA + PCO had the lowest SHBG and the highest insulin resistance prevalence and FAI.

Discussion

The prevalence of OM/AM among Samoan women of reproductive age was 7.4% (95% CI: 5.1, 9.8). Women with OM/AM had significantly more central adiposity but not higher BMI nor body fat percentage compared to normally menstruating women. PCOS was estimated to be 6.8% (95% CI: 4.5, 9.1), with PCO + HA being the most common sub-group, but the OM/AM + HA and OM/AM + HA + PCO sub-groups had the greatest degree of metabolic abnormality.

Menstrual irregularity prevalence

Adding to the limited number of population-based and ethnic-specific estimates of OM/AM, we refined the previously reported prevalence of OM/AM among Samoan and American Samoa women seen in 2002–03 by excluding women using contraceptive injections (Lambert-Messerlian et al. 2011). As a result, the present OM/AM estimate from Samoan women in 2010 was lower than that prior study's estimate of 13.7%. Varying definitions and methodologies for measuring menstrual irregularity make between-study comparisons challenging. Castillo-Martinez et al. (2003) defined OM as the absence of a cycle for 36 to 90 days, and AM as the absence of a cycle for more than 90 days. We defined our measures conservatively relative to definitions in the literature, in part because our reproductive survey questions were limited in their response options and didn't allow for this level of specificity. We defined OM as the absence of a period for 3 – 12 months and AM as the lack of a period for more than 12 months (Lambert-Messerlian et al. 2011; Berga 1998) in order to improve the potential inaccuracy of self-reported questionnaires (Weis et al. 2009). We recognize that our intent to avoid over-estimation of OM/AM may have misclassified some women with OM as normal.

A study of Greek women 17 – 45 years estimated the prevalence of menstrual irregularity as 14.6%; however, this broad age range likely included women experiencing peri-menopausal irregularity (Diamanti-Kandarakis et al. 1999). Our narrower age range reduces the potential inaccuracy stemming from including peri-menopausal women. Moreover, Diamanti-Kandarakis et al. (1999) defined menstrual irregularity as less than eight menstrual cycles per year and regular menstrual cycles as 26 to 34 days, which the authors acknowledge can lead to an overestimation of menstrual irregularity. The overall mean BMI of the study sample was not reported; however, the mean (SE) BMI was 25.9 kg/m² (0.6) in the normally menstruating group and 28.9 kg/m² (1.6) in the group with both oligomenorrhea and hirsutism.

Similarly, a study among U.S. women aged 18 – 45 years found the prevalence of menstrual irregularity to be notably higher than our estimate among Samoans: 25.1% among black women and 20.5% among white women (Azziz et al. 2004). Furthermore, in contrast to our study, the prevalence of overweight and obesity in the Azziz et al. (2004) study was lower, namely 24% were overweight (BMI: 25–29.9 kg/m²) and 32% were obese (BMI ≥ 30.0 kg/m²). Menstrual irregularity was defined by Azziz et al. (2004) as having eight or fewer menstrual cycles a year, menstrual cycles less than 26 days or more than 35 days in length, or a midluteal progesterone level less than 4 ng/ml. Thus, they included more variations of menstrual irregularity, a direct investigation of ovulation, and a larger range of ages than we did. A future, more detailed study of reproductive function might examine the prevalence of women in Samoa experiencing irregular cycle lengths or anovulation as well.

Socio-demographic factors and menstrual irregularity

OM/AM was associated independently with lower education, lower household assets, residing in the rural region of the main island of ‘Upolu, and higher central adiposity. These findings are consistent with other studies reporting that low educational attainment and economic hardship may be associated with increased rate of menstrual irregularity and entry into perimenopause, with chronic exposure to stress often postulated as an explanation (Wise et al. 2002; Geetha et al. 2016; Harlow and Campbell 2004). Geetha et al. (2016) also identified lower education and income as risk factors associated with menstrual irregularity in their recent study of rural women in India, but they found that after controlling for other confounders like menstrual hygiene, menstrual problems, and duration of menstrual flow, these associations were nullified. Women in the Rest of Upolu, the most rural region of the island of Upolu, had higher odds of having OM/AM. We further investigated patterns in interviewer, patient age, reason for menstrual irregularity, and age at last period, but we did not find significant discrepancies. Additional research is clearly needed to better understand the extent to which socioeconomic factors may be directly or indirectly contributing to this menstrual irregularity in Samoa and in other settings.

Adiposity and menstrual irregularity

Our finding that abdominal circumference, AHR, and AHtR, but not BMI nor percent body fat, are significantly larger among OM/AM women compared to normally cycling women suggests that the distribution of body fat, as opposed to total body fat, may be associated with risk for OM/AM among Samoan women. This is in contrast to our previous study of Samoan women where both a higher abdominal circumference and BMI were observed among OM/AM women compared to controls (Lambert-Messerlian et al. 2011). Our results of the association of OM/AM and central fat distribution are supported by Douchi et al. (2002), who used dual-energy X-ray absorptiometry (DXA) scans in Japanese women and found that women with OM/AM had significantly higher trunk-leg fat ratio, a measure of central obesity, compared to normally menstruating women, despite a comparable BMI and total percentage body fat. A study by Hartz et al. (1984) among U.S. and Canadian white women similarly emphasized the significance of body fat distribution, as risk of oligomenorrhea was significantly higher among women with upper body fat predominance (waist-hip ratio > 0.80) compared with women with lower body fat predominance (waist-hip ratio < 0.73).

PCOS Prevalence and Correlates

We found that 6.8% of Samoan women had PCOS based on the NIH criteria of having at least two of the three disorders: menstrual irregularity, biochemical hyperandrogenism, or elevated AMH levels, a proxy marker for PCO (NIH 2012). A recent review provides a range of PCOS prevalence from 4–21% using the alternative Rotterdam 2003 criteria across populations globally, but the review acknowledges inconsistent methods and measures and the difficulty in applying clinical gold standard assessments in population surveys (Rotterdam 2003; Lizneva et al. 2016). In our prior report in a different sample of Samoan women, with a less robust definition of HA, without control for injectable contraceptive use, and without an estimate of PCO, the frequency of having both OM/AM and HA was 8.4% (Lambert-Messerlian et al. 2011). Considering the high prevalence of obesity, type 2 diabetes (Hawley et al 2014), and high androgen levels (Maredia et al. 2016) in Samoan women 25–39 years of age, one might expect a higher prevalence of PCOS. Recent reviews emphasize the complex etiology and presentation of PCOS and the potential for ethnic diversity in prevalence and risk factors (Lizneva et al. 2016).

Women with PCOS compared to normal women were characterized by metabolic abnormalities, including higher total and central adiposity measures, triglycerides, fasting insulin and HOMA-IR, higher prevalence of insulin resistance, higher androgen levels and lower SHBG levels. These differences remained also after adjusting for age. Our findings are consistent with a pattern of higher cardiovascular disease risk factors and metabolic syndrome levels among women with PCOS (Dokras 2013, Feldman et al 2017). Despite this pattern of association, the heterogeneous presentation of PCOS must be further elucidated because cardiometabolic risk may differ across specific subgroups of PCOS (Feldman et al 2017). One recent study found that African American adolescents and women with PCOS had higher metabolic syndrome levels compared to their European ancestry counterparts with PCOS (Hillman et al 2014). Longitudinal study of PCOS among community dwelling women are needed to help disentangle socio-economic from putative biological factors and to identify components of PCOS that carry more cardiometabolic risk.

In our population-based study, the PCO + HA subgroup encompassed the majority of Samoan women with PCOS. In two case series of patients with PCOS from India (Kar et al 2013) and Croatia (Baldani et al. 2013), the most common phenotype was OM/AM + HA + PCO. The case series design of the Indian and Croatian studies may lead to strong selection bias towards study samples enriched with women with multiple reproductive disorders who are recruited at a clinic where they are seeking care based on perhaps serious reproductive health symptoms. Community level longitudinal studies are needed to describe the development of PCOS subgroups across a diversity of ethno-racial and transitioning populations.

Although small sample sizes limit our ability to compare statistical differences in the metabolic profiles across the four PCOS phenotypes, there were patterns worth commenting upon. Samoan women who had OM/AM + HA and OM/AM + HA + PCO had the highest total and central adiposity and cardiometabolic marker levels. Among the Indian women with PCOS studied by Kar et al. (2013), the hyperandrogenic phenotypes, HA + OM/AM and PCO + HA + OM/AM, had higher metabolic morbidity, including the prevalence of

metabolic syndrome, compared to PCOS phenotypes with normal androgen levels. The Kar et al. (2013) findings are consistent with our descriptive findings of more extreme abnormalities among women with OM/AM + HA and women with OM/AM + HA + PCO. In our earlier study of HA in this Samoan sample, HA was associated with greater total, central, and peripheral adiposity, and higher triglycerides, insulin, and HOMA-IR (Maredia et al. 2016). Our findings suggest an underlying pathophysiology that influences reproductive and metabolic health together, perhaps driven by HA secondary to adiposity. Studies among women of African American and European American ancestry suggest the importance of low AMH levels in metabolic syndrome, especially in young women (Feldman et al. 2017). These studies and our findings indicate that further detailed longitudinal research of metabolic profiles among the NIH phenotypes for PCOS is urgently needed given the putative heterogeneity in metabolic profiles across ethnic groups.

SHBG, insulin and adiposity

Across the four PCOS subgroups, we found the highest insulin values, relatively low SHBG values, and highest central adiposity among women with hyperandrogenemic phenotypes, specifically most pronounced in OM/AM + HA or OM/AM + HA + PCO. This is consistent with the interrelationships among adiposity, insulin, and androgens. Body fat plays a key role in altering the secretion, transportation, metabolism, and the action of androgens, and there is a reciprocal regulation by androgen hormones of body fat distribution (Pasquali et al. 2006).

Insulin may be a key mechanism in the association of obesity and the hyperandrogenemic phenotypes (Moran et al. 2012). Insulin negatively regulates SHBG; Pasquali et al. (1990) found that women with low SHBG have higher glucose-stimulated insulin. Furthermore, lower SHBG concentration in abdominally obese women has been found to be an independent risk factor for the development of type 2 diabetes (Lindstedt et al. 1991). Insulin differs significantly among women based on reproductive disorder, being highest among those with both menstrual irregularity and hyperandrogenemia (Diamanti-Kandarakis et al. 1999). Likewise, Polotsky et al. (2012) found HA, but not history of oligomenorrhea, was independently associated with risk of metabolic syndrome among pre- and perimenopausal women, while Daan et al. (2014) found that women diagnosed with hyperandrogenic PCOS had a higher prevalence of metabolic syndrome, including insulin resistance, compared to nonhyperandrogenic PCOS phenotypes. Further prospective studies are needed for mechanistic studies elucidating cardiovascular risk factors among PCOS women.

Finally, it is also important to put the Samoan population into their evolutionary and ecological contexts as we study reproductive biology and health. The demographic history of settlement and populating far-flung and ecologically vulnerable islands (Kirch 2002; Soares et al. 2011) may have left some impact on human biological and biocultural mechanisms associated with female reproductive biology, including high fertility responses to energetic shortages (McGarvey 1994), and perhaps the extended age-related fertility of female populations (House and Nasiru 1999). There may also be unique socio-cultural, genetic, and epigenetic factors associated with such reproductive traits, given the strong evolutionary

advantage of high potential for successful conception, pregnancy, and child survival. Certainly our recent finding in 21st century Samoans of a novel missense mutation in the CREBRF gene enriched by natural selection, which is positively associated with adiposity but negatively associated with glucose and diabetes (Minster et al. 2016), provides justification for conducting more detailed biocultural, including genetic, studies on reproductive health and phenotypes (Neocleous et al. 2017; Cui et al. 2015). The patterns of lower than expected menstrual irregularity and PCOS among Samoan women despite high adiposity, diabetes and androgen levels associated with the nutritional environmental changes requires more detailed research within an explicit population-specific human evolutionary reproductive biology and ecology framework.

Limitations

We estimated OM/AM using self-reported data from surveys, which are subject to several biases including recall bias, errors in translation, and variations in survey administration. Our OM/AM estimate was limited due to lack of more fine grained questions and it does not capture other definitions of menstrual irregularity in cycle length, likely leading to an underestimate (Diamanti-Kandarakis et al. 1999; Azziz et al. 2004). We may have overestimated the proportion with regular cycles because our interview did not separate women having a menstrual period 1 to 3 months ago into smaller temporal categories, and may have classified women as normal who have menstrual periods at intervals of greater than 35 days.

Similarly, for the HA estimate, clinical exams were not performed, and despite our approach to, defining HA (Maredia et al. 2016), the uniqueness of ethnic groups such as Samoans may affect the generalizability and validity of such clinical hyperandrogenemia cutoffs (Azziz et al. 2009). Our use of a cut-off value for defining high HOMA-IR was taken from Mexican Americans due to overall similarity in adiposity, and should be treated with caution. We will pursue further research on HOMA-IR values and norms among Samoans as part of our ongoing work on glucose tolerance and insulin responses. Finally, true clinical diagnosis of PCOS occurs after clinical evaluation and exclusion of related disorders, such as hyperprolactinemia, Cushing's syndrome, and androgen-secreting tumors (Wolf et al. 2014).

Given the continual temporal rise in adiposity in Samoans (Lin et al. 2016), our cross-sectional findings may also underestimate the impact of duration of adiposity on women's reproductive health. We suggest that attempts to further understand the mechanisms influencing adiposity, insulin resistance, androgen levels, menstrual regulation, and PCOS must proceed with longitudinal designs, improved biomarkers, and, if possible, clinical markers of these processes.

Conclusions

Given the high adiposity levels of Samoan women, their reproductive biology and health is of considerable concern. Despite our findings of lower than expected OM/AM and PCOS levels given the obesity, HA, and AMH levels, further studies to determine the impact of obesity on fertility, and the complex associations with cardiometabolic health are needed. In addition to the influence of overall adiposity, we found that a central adipose distribution

was associated with PCOS and the sub-groups with HA. Longitudinal studies to better estimate risks among Samoan women for adverse reproductive, cardiovascular, and metabolic conditions are needed, as well as studies of genetic influences. Our results here add to others to provide a sense of urgency about the need for interventional research to reduce the morbidity and mortality associated with these reproductive disorders (Hawley et al. 2014; Maredia et al. 2016; NCD RISC 2016).

Acknowledgments

Grant sponsorship: U.S. National Institutes of Health Grant R01-HL093093 (STM), Brown University Royce Fellowship (HM)

The authors thank the Samoan participants of the study, local village authorities and the Samoan and other field workers who helped collect the data. We acknowledge the Samoan Ministry of Health and the Samoan Bureau of Statistics for their support of this research. We also acknowledge financial support from NIH grant R01-HL093093 (S.T.M.) and the Royce Fellowship from Brown University (HM). The authors declare no conflicts of interest.

Literature Cited

- Al Kindi MK, Al Essry FS, Al Essry FS, Mula-Abed WAS. Validity of serum testosterone, free androgen index, and calculated free testosterone in women with suspected hyperandrogenism. *Oman Med J*. 2012; 27(6):471–474. [PubMed: 23226817]
- Azziz R, Woods KS, Reyna R, Key TJ, Knochenhauer ES, Yildiz BO. The prevalence and features of the polycystic ovary syndrome in an unselected population. *J Clin Endocrinol Metab*. 2004; 89(6): 2745–2749. [PubMed: 15181052]
- Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, Janssen OE, Legro RS, Norman RJ, Taylor AE, Witchel SF. Task Force on the Phenotype of the Polycystic Ovary Syndrome of The Androgen Excess and PCOS Society. *Fertil Steril*. 2009 Feb; 91(2):456–88. [PubMed: 18950759]
- Baldani DP, Skrgati L, Simuni V, Zlopasa G, Cani T, Trgovci I. Characteristics of different phenotypes of polycystic ovary syndrome based on the Rotterdam criteria in the Croatian population. *Coll Antropol*. 2013; 37(2):477–82. [PubMed: 23940993]
- Berga, SL. Amenorrhea. In: Knobil, Neill, editors. *Encyclopedia of Reproduction*. Academic press; San Diego: 1998.
- Brewis AA, McGarvey ST, Tu'u'au-Potoi N. Structure of family planning in Samoa. *Aust N Z J Public Health*. 1998; 22:424–427. [PubMed: 9659766]
- Brown WJ, Mishra G, Kenardy J, Dobson A. Relationships between body mass index and well-being in young Australian women. *Int J Obes Relat Metab Disord*. 2000; 24:1360–1368. [PubMed: 11093300]
- Castillo-Martinez L, Lopez-Alvarenga J, Villa A, Gonzalez-Barranco J. Menstrual cycle length disorder in 18- to 40-y-old obese women. *Nutrition*. 2003; 19:317–320. [PubMed: 12679164]
- Choy CC, Desai MM, Park JJ, Frame EA, Thompson AA, Naseri T, Reupena MS, Duckham RL, Deziel NC, Hawley NL. Child, maternal and household-level correlates of nutritional status: a cross-sectional study among young Samoan children. *Pub Hlth Nutr*. 2017; 20(7):1235–1247. DOI: 10.1017/S1368980016003499
- Cui L, Li G, Zhong W, Bian Y, Su S, Sheng Y, Shi Y, Wei D, Zhang W, Zhao H, Chen ZJ. Polycystic ovary syndrome susceptibility single nucleotide polymorphisms in women with a single PCOS clinical feature. *Hum Reprod*. 2015; 30:732–736. [PubMed: 25586784]
- Daan N, Louwers Y, Koster M, Eijkemans MJ, de Rijke YB, Lentjes EW, et al. Cardiovascular and metabolic profiles amongst different polycystic ovary syndrome phenotypes: who is really at risk? *Fertil Steril*. 2014; 102:1444–51e3. [PubMed: 25239303]
- De Aguilar MA, Altamirano L, Leon DA, et al. Current status of injectable hormonal contraception, with special reference to the monthly method. *Adv Contracept*. 1997; 13(4):405–17. [PubMed: 9404550]

- Diamanti-Kandarakis E, Kouli CR, Bergiele AT, Filandra FA, Tsianateli TC, Spina GG, Zapanti ED, Bartzis MI. A survey of the polycystic ovary syndrome in the Greek island of Lesbos: hormonal and metabolic profile. *J Clin Endocrinol Metab.* 1999; 84(11):4006–4011. [PubMed: 10566641]
- Dokras A. Cardiovascular disease risk in women with PCOS. *Steroids.* 2013; 78:773–6. [PubMed: 23624351]
- Douchi T, Kuwahata R, Yamamoto S, Oki T, Yamasaki H, Nagata Y. Relationship of upper body obesity to menstrual disorders. *Acta Obstet Gynecol Scand.* 2002; 81:147–150. [PubMed: 11942905]
- Dumont A, Robin G, Catteau-Jonard S, Dewailly D. Role of Anti-Mullerian Hormone in pathophysiology, diagnosis and treatment of Polycystic Ovary Syndrome: a review. *Reproductive Biology and Endocrinology.* 2015; 13:137. [PubMed: 26691645]
- Ellison PT. Energetics, reproductive ecology, and human evolution. *PaleoAnthropology.* 2008:172–200.
- Feldman RA, O'Neill K, Butts SF, Dokras A. Antimullerian hormone levels and cardiometabolic risk in young women with polycystic ovary syndrome. *Fertil Steril.* 2017; 107(1):276–281. [PubMed: 27842995]
- Geetha P, Chenchuprasad C, Sathyavathi RB, Bharathi T, Reddy SK, Kodanda RK. Effect of Socioeconomic Conditions and Lifestyles on Menstrual Characteristics among Rural Women. *J Women's Health Care.* 2016; 5:298.
- Harlow SD, Campbell OMR. Epidemiology of menstrual disorders in developing countries: a systematic review. *BJOG: an International Journal of Obstetrics and Gynaecology.* 2004; 111:6–16. [PubMed: 14687045]
- Hartz AJ, Barboriak PN, Wong A, Katayama KP, Rimm AA. The association of obesity with infertility and related menstrual abnormalities in women. *Int J Obes.* 1979; 3:57–73. [PubMed: 528119]
- Hartz AJ, Rupley DC, Rimm AA. The association of girth measurements with disease in 32,856 women. *Am J Epidemiol.* 1984; 119:71–80. [PubMed: 6691337]
- Hawley NL, Minster RL, Weeks DE, Viali S, Reupena MS, Deka R, McGarvey ST. Prevalence of adiposity and associated metabolic risk factors in the Samoan genome-wide association study. *Am J Human Biol.* 2014; 26(4):491–501. [PubMed: 24799123]
- Hillman JK, Johnson LN, Limaye M, Feldman RA, Sammel M, Dokras A. Black women with polycystic ovary syndrome (PCOS) have increased risk for metabolic syndrome and cardiovascular disease compared with white women with PCOS. *Fertil Steril.* 2014; 101:530–5. [PubMed: 24382375]
- House WJ, Nasiru I. Fertility Patterns of Adolescent and Older Women in Pacific Island Countries: Programme Implications. *Asia-Pacific Population Journal.* 1999; 14(2):3–22.
- Kar S. Anthropometric, clinical, and metabolic comparisons of the four Rotterdam PCOS phenotypes: A prospective study of PCOS women. *J Hum Reprod Sci.* 2013; 6(3):194–200. [PubMed: 24347934]
- Kirch, P. *On the Road of the Winds; An Archaeological History of the Pacific Islands before European Contact.* Univ of California Press; 2002.
- Lambert-Messerlian G, Roberts MB, Urlacher SS, et al. First assessment of menstrual cycle function and reproductive endocrine status in Samoan women. *Hum Reprod.* 2011; 26:2518–24. [PubMed: 21677061]
- Lizneva D, Suturina L, Walker W, Brakta S, Gavrilova-Jordan L, Azziz R. Criteria, prevalence, and phenotypes of polycystic ovary syndrome. *Fertil Steril.* 2016; 106(1):6–15. [PubMed: 27233760]
- Lindstedt G, Lundberg P, Lapidus L, Lundgren H, Bengtsson C, Bjorntorp P. Low Sex-Hormone-Binding Globulin Concentration as Independent Risk Factor for Development of NIDDM: 12-Yr Follow-Up of Population Study of Women in Gothenburg, Sweden. *Diabetes.* 1991; 40(1):123–128. [PubMed: 2015967]
- Lin S, Linhart C, Morrell S, Taylor R, McGarvey ST, Magliano DJ, Zimmet P. Trends in diabetes and obesity in Samoa over 35 years, 1978–2013. *Diabetic Medicine.* 2016:654–661. [PubMed: 27505623]

- Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985;412–419. [PubMed: 3899825]
- Maredia H, Lambert-Messerlian G, Palomaki GE, Viali S, Hawley NL, McGarvey ST. Cut-off levels for hyperandrogenemia among Samoan women: An improved methodology for deriving normative data in an obese population. *Clin Biochem*. 2016; 49(10–11):782–6. [PubMed: 26908216]
- McGarvey ST. The thrifty gene concept and adiposity studies in biological anthropology. *Jl Polynesian Society*. 1994; 103:29–42.
- Ministry of Health [Samoa], Bureau of Statistics [Samoa], and ICF Macro. Samoa Demographic and Health Survey 2009. Apia, Samoa: Ministry of Health, Samoa; 2010.
- Minster RL, Hawley NL, Su CT, Sun G, Kershaw EE, Cheng H, Buhule OD, Lin J, Reupena MS, Viali S, Tuitele J, Naseri T, Urban Z, Deka R, Weeks DE, McGarvey ST. A thrifty variant in CREBRF strongly influences body mass index in Samoans. *Nat Genet*. Sep; 2016 48(9):1049–54. [PubMed: 27455349]
- Moran C, Arriaga M, Rodriguez G, Moran S. Obesity Differentially Affects Phenotypes of Polycystic Ovary Syndrome. *International Journal of Endocrinology*. 2012
- NCD Risk Factor Collaboration (NCD-RisC). Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. *Lancet*. 2016; 387:1377–1396. [PubMed: 27115820]
- National Institutes of Health. [Accessed January 31, 2017] Evidence-based methodology workshop on polycystic ovary syndrome, December 3–5, 2012. Executive summary. Available at: <https://prevention.nih.gov/docs/programs/pcos/FinalReport.pdf>
- Neocleous V, Fanis P, Toumba M, Phedonos AAP, Picolos M, Andreou E, Kyriakides TC, Tanteles GA, Shammam C, Phylactou LA, Skordis N. Variations in the 3'UTR of the CYP21A2 Gene in Heterozygous Females with Hyperandrogenaemia. *Int J Endocrinol*. 2017 Epub 2017 Apr 12.
- Orio F, Muscogiuri G, Nese C, Palomba S, Savastano S, Tafuri D, Colarieti G, La Sala G, Colao A, Yildiz BO. Obesity, type 2 diabetes mellitus and cardiovascular disease risk: an uptodate in the management of polycystic ovary syndrome. *Eur J Obstet Gynecol Reprod Biol*. 2016 Aug 12.
- Pasquali R, Casimirri F, Platè L, et al. Characterization of obese women with reduced sex hormone-binding globulin concentrations. *Horm Metab Res*. 1990; 22:303–306. [PubMed: 2189819]
- Polotsky AJ, Allshouse A, Crawford SL, Harlow SD, Khalil N, Santoro N, et al. Relative contributions of oligomenorrhea and hyperandrogenemia to the risk of metabolic syndrome in midlife women. *J Clin Endocrinol Metab*. 2012; 97:E868–77. 25. [PubMed: 22466350]
- Qu HQ, Li Q, Rentfro AR, Fisher-Hoch SP, McCormick JB. The definition of insulin resistance using HOMA-IR for Americans of Mexican descent using machine learning. *PLoS One*. 2011:e21041. [PubMed: 21695082]
- Rosner W, Auchus RJ, Azziz R, Sluss PM, Raff H. Utility, limitations and pitfalls in measuring testosterone: an Endocrine Society Position Statement. *J Clin Endocrinol Metab*. 2007; 92:405–413. [PubMed: 17090633]
- Rosenfield RL. Ovarian and adrenal function in polycystic ovary syndrome. *Endocrinol Metab Clin North Am*. 1999; 28:265–293. [PubMed: 10352919]
- Rosic S, Rosic M, Samardzic R, Kendic S. Receptive functions at childbearing age, perimenopause and postmenopause. *Mater Sociomed*. 2014:49–50. [PubMed: 24757402]
- Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Fertil Steril*. 2004; 81:19–25.
- Rowland AS, Baird DD, Long S, et al. Influence of medical conditions and lifestyle factors on the menstrual cycle. *Epidemiology*. 2002; 13:668–674. [PubMed: 12410008]
- Samoa Bureau of Statistics. 2012. <http://www.sbs.gov.ws/index.php/economic-statistics/key-statistics>
- Samoa Ministry of Health, Bureau of Statistics [Samoa], and ICF Macro. Samoa Demographic and Health Survey 2009. Apia, Samoa: Ministry of Health, Samoa; 2010.
- Sherry DS, McGarvey ST, Sesepasara ML, Ellison PT. Ovarian function in Samoan women shows stronger association with signals of energy metabolism than fat reserves. *Am J Human Biology*. 2014; 26:95–98.

- Soares P, Rito T, Trejaut J, Mormina M, Hill C, Tinkler-Hundal E, Braid M, Clarke DJ, Loo JH, Thomson N, et al. Ancient voyaging and Polynesian origins. *American journal of human genetics*. 2011; 88(2):239–247. [PubMed: 21295281]
- UNICEF. [Accessed May 1, 2017] Samoa. Statistics. 2017. Available at: https://www.unicef.org/infobycountry/samoa_statistics.html
- van Hooff MHA, Voorhorst FJ, Kaptein MBM, Hirasing RA, KoppelIndaal C, Schoemaker J. Relationship of the menstrual cycle pattern in 14–17 year old adolescents with gynaecological age, body mass index and historical parameters. *Hum Reprod*. 1998; 13:2252–2260. [PubMed: 9756306]
- Vitzthum VJ. The ecology and evolutionary endocrinology of reproduction in the human female. *AJPA Yrbook of Phys Anthro*. 2009; 140(Suppl S49):95–136.
- Weis S, Schmidt MD, Dwyer T, Norman RJ, Venn AJ. Obesity and menstrual irregularity: associations with SHBG, testosterone and insulin. *Obesity*. 2009; 17:1070–1076. [PubMed: 19180069]
- Welt, Corrine. Patient education: Absent or irregular periods (Beyond the Basics). In: Crowley, WF., Jr, Martin, KA., editors. UpToDate. UpToDate; Waltham, MA: [Accessed November 16, 2016]
- WHO. American Samoa NCD Risk Factors STEPS Report. Suva; Fiji: 2007.
- Wise LA, Krieger N, Zierler S, Harlow BL. Lifetime socioeconomic position in relation to onset of perimenopause. *J Epidemiol Community Health*. 2002; 56:851– 860.
- Wolf, J., Barnes, CL., Aubuchon, M. Polycystic Ovarian Syndrome: A Diagnosis of Exclusion. In: Pal, Lubna, editor. Polycystic Ovary Syndrome: Current and Emerging Concepts. New York: Springer; 2014.

Table 1

Prevalence of Oligomenhorrea or Amenorrhea (OM/AM)

Last Period	n	Prevalence (%)	Menstrual Pattern
Having it now	177	37.7	Normal Cycle
1–3 months ago	258	54.9	Normal Cycle
3–6 months ago	16	3.4	OM
6–9 months ago	0	0.0	OM
9–12 months ago	5	1.1	OM
More than 12 months ago	14	3.0	AM
Total OM/AM	35	7.4 [*]	OM/AM

^{*} Difference in sums of percentages and total OM/AM prevalence due to rounding.

Table 2

Comparison of Normally Menstruating Women and those with Oligomenhorrea or Amenorrhea (OM/AM)

	Normally Menstruating (n=435)	OM/AM (n=35)
Socio-Demographic Characteristics		
Age (years) [mean (SD)]	32.2 (4.6)	32.8 (3.9)
Age Group		
25.0 – 25.9 (%)	37.0 *	22.9
30.0 – 34.9 (%)	30.6	48.6
35.0 – 39.9 (%)	32.4	28.6
Education		
Less than Secondary School (%)	8.5 **	22.9
Secondary School Completed (%)	91.5	77.1
Census Region		
Apia Urban Area (%)	21.4 **	8.6
Northwest Upolu (%)	31.7	31.4
Rest of Upolu (%)	23.2	45.7
Savai'i (%)	23.7	14.3
Material Lifestyle Score [mean (SD)] ^a	4.4 (2.4) ***	3.2 (2.2)
History of Oral Contraceptive use (%) ^b	12.4	16.0
Behavioral Factors		
Current Cigarette Smoker (%)	25.5	34.3
Current Alcohol Consumer (%) ^c	3.7	2.9
Average Minutes of Moderate-Vigorous Physical Activity Per Day [mean (SD)]	39.3 (95.6)	43.8 (73.7)
Anthropometric Characteristics		
BMI (kg/m ²) [mean (SD)]	34.0 (6.8) *	36.3 (6.8)
BMI Classification		
Normal (<26 kg/m ²) (%)	11.7	2.9
Overweight (26 – 32 kg/m ²) (%)	27.4	28.6
Obese (>32 kg/m ²) (%)	60.9	68.6
Percent Body Fat (BIA) ^d [mean (SD)]	36.1 (12.0) *	41.9 (13.0)
Abdominal Circumference (cm) [mean (SD)]	104.2 (14.0) ***	112.2 (15.8)
Abdominal-Hip Ratio [mean (SD)]	0.91 (0.06) ***	0.95 (0.06)
Abdominal-Height Ratio [mean (SD)]	0.64 (0.08) ***	0.69 (0.09)
Arm Circumference (cm) [mean (SD)]	36.8 (5.5) **	39.1 (5.7)
Hip Circumference (cm) [mean (SD)]	114.0 (12.1) *	118.0 (12.6)
Calf Circumference (cm) [mean (SD)]	42.9 (4.7)	43.6 (4.5)
Cardiometabolic Factors		
Cholesterol (mmol/L) ^e	4.7 (0.07) * [2.7–7.7]	4.8 (0.07) [3.2–6.9]
Triglycerides (mmol/L) ^e	0.9 (0.2) [0.2–5.1]	1.1 (0.2) [0.5–3.1]

	Normally Menstruating (n=435)	OM/AM (n=35)
Adiponectin (µg/ml) ^e	5.0 (0.2) [1–20]	4.9 (0.2) [2–15]
Glucose (mmol/L) [mean (SD)] ^f	4.6 (0.6)	4.6 (0.7)
Insulin (µU/ml) ^{e, f}	13.1 (0.3) [1.9–141.9]	12.9 (0.3) [2.6–107.1]
HOMA-IR ^{e, f, g}	2.7 (0.4) [0.3–33.7]	2.2 (0.4) [0.5–27.2]
Type 2 Diabetes Prevalence (%)	4.1 *	11.8
Reproductive Hormones		
Total Testosterone (ng/dl) ^e	44.2 (0.2) [20–274]	50.0 (0.2) [20–128]
Sex Hormone Binding Globulin (nmol/L) ^e	45.4 (0.3) [9.9–566.0]	55.3 (0.4) [10.9–516.0]
Free Androgen Index (FAI) ^e	3.4 (0.4) [0.14–42.5]	2.6 (0.5) [0.2–23.6]
Hyperandrogenemia (%) ^h	13.6	20.0
Anti-Mullerian Hormone (AMH) (ng/mL) ^e	2.0 (0.5) [0.08–25.8]	1.8 (0.6) [0.08–13.9]
PCO (%) ⁱ	15.4	22.9

Asterisks denote significant differences between groups based on t-test or Chi-square tests:

*
p<0.1,

**
p<0.05,

p<0.001.

^aThe Material Lifestyle Score (MLS) is a measure of socioeconomic status, based on household assets; a higher MLS indicates higher socioeconomic status.

^bIndicates whether participants had ever used oral contraceptives; 42 participants were missing data for this variable.

^cParticipants were considered current alcohol consumers if they had consumed at least one alcoholic drink in the past 12 months.

^dBIA= bioelectrical impedance.

^emedian, (s.d.) of log 10 transformed values and [range];

^fIndividuals with type 2 diabetes were not included in between-group comparisons of fasting glucose, insulin and HOMA-IR.

^gHOMA-IR = homeostasis model assessment-estimated insulin resistance;

^hHyperandrogenemia is based on a Samoan-specific cutpoint (FAI>8.5; Maredia et al. 2016).

ⁱPCO defined as AMH >5.6 ng/mL (Dumont et al. 2015).

Table 3

Anthropometric, Cardiometabolic and Sex Hormone contrasts by PCOS Criteria

	Normal (not PCOS) versus PCOS Contrasts		PCOS Criteria (Groups are mutually exclusive; % of women with PCOS)			
	Normal (n=438)	PCOS (n=32)	OM/AM + PCO ^a n=5 (16%)	OM/AM + HA ^b n=4 (13%)	PCO + HA n=20 (63%)	OM/AM + HA + PCO n=3 (9%)
Percent of study sample (%)	93.2	6.8				
Demographic Characteristics (Mean (SD) unless otherwise stated)						
Age	32.4 (4.5)	30.0 (3.7) **	31.2 (0.8)	32.7 (5.2)	29.4 (3.8)	28.4 (1.0)
Anthropometric Characteristics						
BMI (kg/m ²)	33.9 (6.8)	38.0 (6.0) ***	31.9 (3.1)	41.6 (1.4)	37.2 (5.0)	48.6 (2.3)
Percent Body Fat (BIA ^c)	35.9 (12.1)	44.3 (11.0) ***	33.7 (6.8)	52.9 (3.3)	42.3 (8.9)	62.1 (4.8)
Abdominal Circumference (cm)	104.1 (14.1)	113.9 (13.6) ***	102.0 (7.7)	126.3 (9.5)	110.9 (10.3)	137.5 (4.2)
Cardiometabolic Factors						
Cholesterol (mmol/L) ^d	4.7 (0.1) [2.7–7.7]	4.9 (0.1) [3.7–6.6]	4.8 (0.1) [4.0–5.9]	5.6 (0.1) [4.3–6.2]	4.9 (0.1) [3.7–6.6]	5.3 (0.1) [4.6–6.1]
Net Triglycerides (mmol/L) ^d	0.9 (0.2) [0.2–5.1]	1.3 (0.2) ** [0.7–3.1]	1.2 (0.2) [0.7–2.0]	1.4 (0.2) [0.7–1.5]	1.2 (0.1) [0.7–2.1]	1.9 (0.2) [1.5–3.1]
Adiponectin (µg/ml) ^d	5.0 (0.2) [1–20]	5.0 (0.1) [2–9]	5.0 (0.1) [4–7]	4.0 (0.2) [4–8]	5.0 (0.2) [2–9]	4.0 (0.1) [3–4]
Glucose (mmol/L) ^e	4.6 (0.6)	4.6 (0.7)	4.2 (0.6)	4.9 (1.6)	4.6 (0.7)	5.1 (0.5)
Insulin (µU/ml) ^{d,e}	12.6 (0.3) [1.9–141.9]	19.2 (0.3) ** [5.5–65.7]	7.3 (0.1) [5.5–8.4]	39.4 (0.5) [13.1–65.7]	20.9 (0.1) [13.2–45.7]	21.6 (0.01) [21.1–22.1]
HOMA-IR ^{d,e}	2.6 (0.3) 0.3–33.7]	3.8 (0.3) ** [0.8–17.8]	1.5 (0.1) [0.8–1.6]	10.1 (0.6) [2.2–17.8]	4.8 (0.2) [2.3–9.9]	4.9 (0.03) [4.6–5.1]
Insulin Resistance (%) ^f	31.2	52.8 **	0	50	61	100
Type 2 Diabetes (%)	4.6	6.9	0	33.3	0	33.3
Reproductive Hormones						
Total Testosterone (ng/dl) ^d	43.1 (0.2) [20–214]	90.9 (0.2) **** [28.5–274]	37.5 (0.2) [28.5–115]	73.5 (0.1) [67.1–128]	104.5 (0.2) [36.9–274]	96.5 (0.1) [74–118]
SHBG (nmol/L) ^d	47.3 (0.28) [9.9–566.0]	24.0 (0.31) ** [10.9–417.0]	73.7 (0.46) [24.9–417.0]	26.7 (0.16) [17.0–41.0]	22.3 (0.16) [11.2–40.4]	15.0 (0.10) [10.9–17.5]
HA (%)	8.9	84.4 ***	0	100	100	100
Free Androgen Index (FAI) ^d	3.1 (0.4) [0.1–31.3]	12.2 (0.4) **** [1.0–42.5]	1.8 (0.3) [1.0–4.3]	10.8 (0.1) [8.6–13.7]	15.4 (0.2) [8.9–42.5]	23.4 (0.01) [22.3–23.6]
AMH (ng/mL) ^{d,g}	1.9 (0.5) [0.8–16.8]	8.2 (0.4) **** [0.3–25.8]	7.4 (0.1) [6.8–13.9]	0.9 (0.5) [0.3–3.9]	8.8 (0.2) [6.1–25.8]	9.5 (0.09) [8.1–12.1]

	Normal (not PCOS) versus PCOS Contrasts		PCOS Criteria (Groups are mutually exclusive; %s of women with PCOS)			
	Normal (n=438)	PCOS (n=32)	OM/AM + PCO ^a n=5 (16%)	OM/AM + HA ^b n=4 (13%)	PCO + HA n=20 (63%)	OM/AM + HA + PCO n=3 (9%)
History of Oral Contraceptive Use ^h (%)	13.4	0 **	0	0	0	0

Asterisks denote significant differences between the PCOS group versus Normal based on t-test or Chi-square tests:

* p<0.1,

**

p<0.05,

p<0.001.

Comparative analyses were not undertaken for PCOS phenotypes.

^aPCO – Polycystic ovaries is based on serum anti-Müllerian hormone > 5.6 ng/mL (Dumont et al. 2015);

^bHA - Hyperandrogenemia is based on a Samoan-specific cutpoint (FAI>8.5; Maredia et al. 2016);

^cBIA= bioelectrical impedance;

^dmedian, (s.d.) of log 10 transformed values & [range]. T-tests on log 10 transformed values;

^eIndividuals with type 2 diabetes were not included in between-group comparisons of fasting glucose, insulin and HOMA-IR. Sample sizes for each group (left to right) were as follows, n=342, n=26, n=52 and n=4;

^fInsulin Resistance defined as HOMA-IR > 3.80 (Qu. et al. 2011);

^gAMH = anti-Müllerian hormone;

^hIndicates whether participants had ever used oral contraceptives; 42 participants were missing data for this variable.