Comparison of metabolic syndrome elements in White and Asian women with polycystic ovary syndrome: results of a regional, American cross-sectional study

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Objective: To examine differences in metabolic dysfunction between White, East Asian, and South Asian women with polycystic ovary syndrome (PCOS) living in the San Francisco Bay Area, California.
Design: Cross-sectional study.
Setting: Referral clinic at an academic center.
Patient(s): A total of 243 White, 25 South Asian, and 38 East Asian women with PCOS, according to the Rotterdam criteria, aged 14–57 years, were recruited from May 2006 to May 2017.
Intervention(s): None.
Main Outcome Measure(s): Fasting and 2-hour insulin and glucose, homeostasis model assessment of insulin resistance, and fasting lipids. Metabolic syndrome and its five individual components were defined according to the National Cholesterol Education Program Adult Treatment Panel guidelines.
Result(s): Median baseline body mass index (25.9 vs. 24.8 vs. 24.0 kg/m^2) and age (28.3 vs. 25.2 vs. 29.4 years) did not differ between White, South Asian, and East Asian women. Two-hour insulin levels were elevated in East and South Asian women at >25–30 and >30 years, respectively, compared with White women in the same age groups. Two-hour glucose level was also elevated in East Asian women compared with White women at age >30 years. No other differences were detected in continuous metabolic markers or in the risk of metabolic syndrome and its components across the three race categories.
Conclusion(s): White, South Asian, and East Asian women with PCOS living in the same geographic region have comparable metabolic profiles to one another, although Asian women have higher 2-hour insulin levels and East Asian women, in particular, have higher 2-hour glucose levels. (Fertil Steril Rep® 2020;1:305–13. ©2020 by American Society for Reproductive Medicine.)
Key Words: Metabolic syndrome, insulin resistance, race, polycystic ovary syndrome

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Polycystic ovarian syndrome (PCOS) is an endocrine disorder affecting 6%–10% of reproductive-aged women worldwide. The prevalence largely depends on the diagnostic criteria used in identifying women with PCOS, as well as on the geographic place of residence (1, 2). The most widely accepted diagnostic criteria for research purposes, but not without limitations, are the 2003 Rotterdam criteria (3). Polycystic ovarian syndrome under these set of criteria can be diagnosed with the presence of two of the three cardinal features, as follows: [1] chronic or oligoovulation and anovulation, [2] biochemical and/or clinical hyperandrogenism, and [3] polycystic ovaries as viewed on ultrasound or using alternative imaging techniques after exclusion of other endocrinopathies (4). In addition to reproductive dysfunction, metabolic disturbances are often present. Insulin

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resistance characterized by decreased insulin clearance and increased insulin secretion is the key pathogenic mechanism for the additional risk observed in women with PCOS for metabolic syndrome, type 2 diabetes, and cardiovascular disease (5, 6). Although metabolic syndrome and type 2 diabetes share underlying etiologies of insulin resistance and impaired glucose tolerance with PCOS, the higher prevalence and earlier onset of metabolic syndrome and type 2 diabetes compared with the general population are important to note in women with PCOS (7–9). Furthermore, race and ethnicity, obesity, and age have all been shown to influence the heterogeneity in the prevalence of these two complications in the PCOS population (10).

Metabolic syndrome is defined by a constellation of metabolic abnormalities, also commonly observed in PCOS, and can differ in presentation across race and ethnic groups. Apridonidze et al. (9) reported the prevalence of metabolic syndrome in women with PCOS to be twice that of the general population (43% vs. 24%) when matched for body mass index (BMI) and age in women who were generally between the ages of 30 and 39 years. Other studies reported the prevalence of metabolic syndrome in PCOS populations to be comparable (33%–46%) (8, 11, 12). In addition to the overall increased prevalence of metabolic syndrome in women with PCOS, the syndrome and its components—elevated fasting serum glucose, elevated fasting serum triglycerides, elevated waist circumference, low high-density lipoprotein cholesterol (HDL-C), and hypertension—differ by race and ethnicity, despite lack of agreement in some findings between studies (8, 11, 13–18). Independent of obesity, African American and Hispanic women with PCOS have been identified as higher risk race groups compared with White women with increased prevalence of hypertension and insulin resistance, respectively (11, 13). Two more high-risk race groups explored in our study include South and East Asian women, which are commonly grouped together due to small numbers (8, 16, 18). South Asian women with PCOS have increased risk of metabolic syndrome secondary to central obesity (15, 19), elevated fasting glucose, and decreased HDL-C (14). In addition, type 2 diabetes is more prevalent in this group (20) with insulin resistance observed at lower BMI and waist circumferences (21). Similarly, East Asian women with PCOS have more central obesity (22) and lower HDL-C (23), which accounts for increased rates of metabolic syndrome. However, most of these studies (15, 19, 21–23) have been conducted natively and few are multiracial cohort studies (14, 20), although none have been strictly conducted in the United States exploring South and East Asian population groups separately. In general, investigations of racial and ethnic differences in metabolic end points in a US PCOS cohort are somewhat limited, although findings have largely been reported among African American and Hispanic populations (11, 13). Furthermore, metabolic syndrome and its components have not been studied in exposure groups with more rigorous Asian definitions. In addition, although East Asian women present with a milder hyperandrogenic phenotype, South Asian women have some of the highest rates of hirsuitism (24, 25). Due to different clinical manifestations and metabolic abnormalities associated with PCOS observed in the two Asian populations, it is imperative to recognize the value of treating South and East Asians as two distinct groups.

To our knowledge no PCOS studies investigating metabolic outcomes have evaluated South and East Asian women as separate groups originating from a single community in the United States. With sampling from the same region, we may better reveal genetic and racial influences of metabolic abnormalities. Therefore, the aim of this study was to examine the risk of metabolic syndrome and its components, along with associated metabolic and cardiovascular end points, between White, East Asian, and South Asian women with PCOS from a single regional cohort.

MATERIALS AND METHODS

Study Population

This was a cross-sectional study in which patients were recruited from a multidisciplinary PCOS clinic at the University of California at San Francisco between May 2006 and May 2017. Patients were referred to the clinic by their providers for further evaluation and confirmatory diagnosis of PCOS based on the 2003 Rotterdam criteria (3), one of the main inclusion criteria for our study. Specific to the components of the Rotterdam criteria, chronic or oligoovulation and anovulation were defined as an average menstrual cycle length of $\geq$35 days and/or $<$8 menstrual cycles per year without oral contraceptive pill use. Biochemical hyperandrogenism was defined as abnormally elevated serum levels of total testosterone, free testosterone, androstenedione, or dehydroepiandrosterone based on site-dependent laboratory thresholds, and values were taken before the baseline visit. Patients also completed a self-administered questionnaire, which captured demographics and review of symptoms. During the baseline visit, trained specialists recorded anthropometric, ultrasonographic, and dermatologic measurements. A dermatologist conducted a physical examination to assess the degree of terminal hair growth on nine regions of the body using the Ferriman-Gallwey scoring method (26). Clinical hyperandrogenism was defined as a mean Ferriman-Gallwey total score $\geq$8 with or without androgenic alopecia and/or severe acne. In addition, patients were assessed for cutaneous manifestations of hyperinsulinemia (i.e., acanthosis nigricans). A transvaginal ultrasound scan using a Shizmadzu SDU-450XL scanner and 4- to 8-mHz transducer by either examiner (H.G.H. or M.I.C.) was used to detect the presence or absence of polycystic ovaries. Polycystic ovary was defined as $\geq$12 follicles per ovary, 2–9 mm in diameter, and/or an ovarian volume $>$10 cm^3 (4). Thyroid-stimulating hormone, prolactin, 17-hydroxyprogesterone, follicle-stimulating hormone, and estradiol were ordered additionally to rule out endocrinopathies other than PCOS. We limited our study population to include only women who reported being White, East Asian, or South Asian (n = 306) and excluded participants who reported mixed race or ethnicity (i.e., Asian-White, White-Native American). All participants provided written and informed consent, and the study was approved by the Committee for Human Research at the University of California at San Francisco.

Racial Groups

Race and ethnicity were reported on the self-administered questionnaire completed before the baseline visit for all patients with PCOS. Women were asked about their own ancestry ("What is your ancestry?") and their parents' ancestry ("What is your mother's ancestry? What is your father's ancestry?"). The answers were provided as checkboxes and participants were instructed to check all that apply. The possible selections included specific race categories (i.e., African American, Native American, Ashkenazi Jewish, Middle Eastern, and African) along with Asian and White race categories broken down by nationality or region (i.e., Asian-Chinese, Asian-Japanese, Asian-Korean, Asian-Indian, Asian Filipino, Asian-Vietnamese, White-Northern European, White-Russian, and White-Southern European). Women were also given a chance to select "Other" and further specify country of origin (i.e., Pacific Islander, Asian-Other). Ethnicity, defined as Hispanic or non-Hispanic, was also included as an answer selection for these three questions (i.e., Hispanic-Mexican, Hispanic-South American, Hispanic-Central American, and Hispanic-Spain).

Patient's ancestry information was ascertained using parental race queried from the questionnaire to form race groups for analysis. In addition, we excluded patients with discordant self and parental race and ethnicity, as well as mixed race and ethnicity to form clean groups. For our research purposes, we chose to focus on three "single" race categories—South Asian, East Asian, and White-European. South Asians were defined as women who selected either Asian-Indian or Asian-Other, specifying Pakistan as the country of origin. East Asians were defined as those who selected one or more of the other Asian categories from the questionnaire (i.e., Asian-Chinese, Asian-Japanese, Asian-Korean, Asian-Indian, Asian Filipino, Asian-Vietnamese) or specified a country of origin that included Thailand, Nepal, Cambodia, and Indonesia. All White race categories (i.e., White-Northern European, White-Russian, and White-Southern European), in addition to Ashkenazi Jewish, were grouped as European ancestry.

Metabolic End Points

Insulin resistance and metabolic dysfunction were assessed from baseline levels of fasting insulin and glucose, 2-hour insulin and glucose (from 75-g, 2-hour oral glucose tolerance test), the homeostasis model assessment of insulin resistance (HOMA-IR), and fasting lipids. The HOMA-IR was calculated using the following formula: HOMA-IR = {fasting plasma insulin [μIU/mL] $\times$ fasting plasma glucose [mg/dL]} /405 (27, 28). Serum assessment of fasting lipids included total cholesterol, triglycerides, HDL-C, and low-density lipoprotein cholesterol. C-reactive protein (CRP) was also measured and indicates cardiovascular disease risk (29). Metabolic syndrome was defined according to the National Cholesterol Education Program Adult Treatment Panel guidelines, which requires the presence of three of the five risk factors: [1] waist circumference >88 cm; [2] hypertension (systolic blood pressure $\geq$130 mmHg and/or diastolic blood pressure $\geq$85 mmHg); [3] elevated fasting triglycerides ($\geq$150 mg/dL); [4] elevated fasting glucose ($\geq$100 mg/dL); and [5] low fasting HDL-C (<50 mg/dL) (30). A modified elevated waist circumference threshold of >80 cm was used in a sensitivity analysis to account for the race-specific definition of central obesity in Asian women (31).

Biochemical Assays

Intra-assay and interassay coefficients of variation for the metabolic end points are not reported as biomarkers were measured at one of several laboratories, dependent on the patient's insurance. Serum samples of fasting insulin were restricted to those women who obtained testing at one of three commercial laboratories and levels were adjusted by regression to control for assay-dependent differences, as detailed in a prior publication (32).

Statistical Analyses

Baseline characteristics were evaluated using Kruskal-Wallis, χ^2, and Fisher's exact tests as appropriate. For analysis purposes, age was split into three groups, as follows: $\leq$25, >25–30, and >30 years. Continuous outcomes, such as fasting insulin and glucose, 2-hour insulin and glucose, HOMA-IR, CRP, and fasting lipids, were evaluated using an age-stratified Kruskal-Wallis model. Dichotomous outcomes (i.e., metabolic syndrome, elevated waist circumference, elevated fasting glucose, elevated triglycerides, low HDL-C, and hypertension) were tested using a logistic regression model controlling for age. All testing was performed at the .05 level of statistical significance, and a Bonferroni adjustment was used for pairwise comparisons as appropriate. Statistical analyses were performed using SAS version 9.4, 32-bit (SAS Institute).

RESULTS

Of the 306 women with PCOS in our study, 79% were White or of European ancestry, 8% were South Asian, and 12% were East Asian (Table 1). Women of each race did not differ from one another in age, BMI, and other anthropometric measurements. In addition, attainment levels of education and income had similar distributions across all groups. With respect to clinical manifestations of PCOS, women across groups were similar in reported polycystic ovaries, oligoamenorrhea or amenorrhea, and hyperandrogenism, with one exception, total mean Ferriman-Gallwey. South Asian women had higher total mean modified Ferriman-Gallwey scores compared with White and East Asian women (overall $P<.01$; pairwise P values were .0002 and <.0001, respectively). The PCOS phenotypes defined using the 2003 Rotterdam criteria did not differ by race. South Asian (50%) and East Asian (44.4%) women were noted to have acanthosis nigricans compared with White (23.4%) women ($P = .02$).

Continuous measures of metabolic markers stratified by age were reported as median and 25th–75th interquartile ranges (IQRs) across race groups (Table 2). The 2-hour insulin levels were significantly different across race groups in two of the three age categories, as follows: >25–30 and >30 years (overall $P = .03$ in both age groups). Furthermore,

TABLE 1

Baseline demographic and clinical characteristics [n (%)] by race of polycystic ovarian syndrome study participants.

Characteristics	No. of observations	White women (n = 243)	South Asian women (n = 25)	East Asian women (n = 38)	KW *P* value
Age (y)[a]	306	28.3 (24.6–31.5)	25.2 (22.9–28.8)	29.4 (24.0–33.9)	.10
BMI (kg/m^2)[a]	303	25.9 (22.8–32.9)	24.8 (21.6–27.7)	24.0 (20.5–31.5)	.09
Waist circumference (cm)[a]	282	81.3 (71.1–96.5)	73.7 (68.6–88.9)	81.3 (68.6–91.4)	.18
Systolic BP (mmHg)[a]	299	110.0 (102.0–120.0)	109.0 (100.0–120.0)	104.0 (100.0–118.0)	.06
Diastolic BP (mmHg)[a]	299	70.0 (66.0–79.0)	70.0 (65.0–74.0)	70.0 (66.0–79.0)	.77
Household income ($)					.64[e]
<25,000	49	40 (18.4)	3 (15.8)	6 (16.7)	
25,000–<50,000	42	35 (16.1)	2 (10.5)	5 (13.9)	
50,000–<75,000	45	34 (15.7)	3 (15.8)	8 (22.2)	
75,000–<100,000	46	40 (18.4)	1 (5.3)	5 (13.9)	
100,000–200,000	68	53 (21.8)	8 (32.0)	7 (19.4)	
>200,000	22	15 (6.9)	2 (10.5)	5 (13.2)	
Highest education level					.44[e]
7th–8th grade	2	2 (0.9)	0 (0.0)	0 (0.0)	
9th–12th grade	11	8 (3.6)	1 (5.0)	2 (5.7)	
Some college	52	41 (18.4)	1 (5.0)	10 (28.6)	
College graduate	117	97 (43.5)	9 (45.0)	11 (31.4)	
Post-graduate	96	75 (33.6)	9 (45.0)	12 (34.3)	
Have children	20	14 (6.2)	2 (10.0)	4 (11.4)	.36[e]
Not US born	49	20 (10.6)	10 (62.5)	19 (59.4)	<.01[e]
Smoking status					.61[e]
Nonsmoker	250	201 (89.3)	17 (85.0)	32 (88.9)	
Previous smoker	9	6 (2.7)	1 (5.0)	2 (5.6)	
Current smoker	22	18 (8.0)	2 (10.0)	2 (5.6)	
PCO	269	214 (91.8)	22 (95.7)	33 (86.8)	.50[e]
Oligoamenorrhea and amenorrhea	246	194 (82.6)	17 (73.9)	35 (92.1)	.32[e]
Clinical or biochemical hyperandrogenism	271	211 (89.0)	25 (100.0)	35 (94.6)	.15[e]
Only clinical hyperandrogenism	77	62 (27.8)	9 (37.5)	6 (17.6)	.24
Only biochemical hyperandrogenism	43	33 (14.8)	3 (12.5)	7 (20.6)	.63[e]
Total mFG[a]	301	7.0 (4.0–11.0)[c]	13.0 (8.0–17.0)[cd]	4.5 (3.0–9.0)[d]	<.01
PCOS phenotypes[b]					
O + H + P	179	138 (62.4)	14 (66.7)	27 (73.0)	.45
O + H	23	17 (7.7)	1 (4.8)	5 (13.5)	.44[e]
H + P	49	40 (18.1)	6 (28.6)	3 (8.1)	.12[e]
O + P	26	24 (10.9)	0 (0.0)	2 (5.4)	.20[e]
Acne	208	164 (69.8)	16 (64.0)	28 (75.7)	.61
Androgenic alopecia	89	70 (30.4)	10 (43.5)	9 (25.0)	.31
Acanthosis nigricans	82	54 (23.4)	12 (50.0)	16 (44.4)	<.01

Note: BMI = body mass index; BP = blood pressure; H = hyperandrogenism; KW = Kruskal-Wallis; mFG = mean Ferriman-Gallwey score; O = oligoamenorrhea and amenorrhea; P = polycystic ovaries; PCO = polycystic ovary; PCOS = polycystic ovarian syndrome.

[a] Data are presented as n (%) with the following exceptions: age (y), BMI (kg/m^2), diastolic BP (mmHg), systolic BP (mmHg), total mFG, and waist circumference are reported as median (25th–75th percentile).

[b] PCOS phenotypes were defined using the 2003 Rotterdam criteria.

[c,d] Significant differences for within row comparisons among Asian and White women with PCOS.

[e] Fisher's exact *P* values used in the case of small sample sizes.

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East Asian women had elevated 2-hour insulin levels at >25–30 years (median 107.3, IQR 62.0–217.2 μIU/mL vs. median 35.1, IQR 21.9–45.0 μIU/mL; pairwise $P = .03$), whereas South Asian women had elevated 2-hour insulin levels at >30 years (median 166.7, IQR 82.9–320.1 μIU/mL vs. median 34.0, IQR 13.1–57.6 μIU/mL; pairwise $P = .024$) compared with White women. Other continuous metabolic end points (i.e., fasting glucose, HOMA-IR, total cholesterol, low-density lipoprotein cholesterol, triglycerides, and CRP) did not differ across race groups. Two-hour glucose, fasting insulin, and HDL-C levels were shown to approach statistical significance across race groups at >30 years (overall $P = .05$, $P = .09$, and $P = .08$, respectively), with statistically significant pairwise comparisons of increased 2-hour glucose levels in East Asian women compared with White women (median 118.0, IQR 97.0–142.0 mg/dL vs. median 92.0, IQR 79.0–114.0 mg/dL; pairwise $P = .04$).

There was no increased risk for metabolic syndrome or its components (i.e., elevated waist circumference, elevated fasting glucose, elevated triglycerides, low HDL-C, and hypertension) between race groups in age-adjusted pairwise comparisons (Table 3). In the sensitivity analysis, results were similar and nonsignificant between race and the modified elevated waist circumference (data not shown).

TABLE 2

Comparison of metabolic end points by race of age-stratified polycystic ovarian syndrome participants.

Metabolic end points	Age, y	White women (n = 243)	South Asian women (n = 25)	East Asian women (n = 38)	KW *P* value
Fasting glucose (mg/dL)					
N	≤25	60	11	10	
Median (25th–75th percentile)		84.5 (79.0–91.5)	83.0 (76.0–88.0)	80.5 (74.0–91.5)	.39
N	>25–30	91	6	9	
Median (25th–75th percentile)		85.0 (79.0–91.0)	85.5 (73.0–89.0)	91.0 (85.0–100.0)	.23
N	>30	76	6	18	
Median (25th–75th percentile)		89.0 (83.0–93.0)	84.5 (79.0–88.0)	86.5 (78.0–94.0)	.22
2-hour glucose (mg/dL)					
N	≤25	50	11	8	
Median (25th–75th percentile)		90.0 (76.0–115.0)	107.0 (97.0–118.0)	96.5 (80.5–128.0)	.19
N	>25–30	89	6	9	
Median (25th–75th percentile)		90.0 (74.0–104.0)	98.5 (79.0–110.0)	115.0 (90.0–126.0)	.15
N	>30	73	6	16	
Median (25th–75th percentile)		92.0 (79.0–114.0)[a]	100.5 (80.0–121.0)	118.0 (97.0–142.0)[b]	.05
Fasting insulin (μIU/mL)					
N	≤25	27	5	7	
Median (25th–75th percentile)		6.0 (4.8–12.5)	6.0 (5.4–6.9)	3.2 (1.7–7.1)	.32
N	>25–30	53	3	5	
Median (25th–75th percentile)		4.6 (2.5–8.7)	4.8 (4.7–5.0)	6.8 (4.4–7.7)	.96
N	>30	45	3	11	
Median (25th–75th percentile)		4.4 (3.0–10.0)	19.7 (7.6–245.5)	6.9 (3.0–17.1)	.09
2-hour insulin (μIU/mL)					
N	≤25	32	2	7	
Median (25th–75th percentile)		41.5 (30.0–88.8)	53.5 (46.0–61.0)	74.0 (25.2–252.3)	.73
N	>25–30	41	2	4	
Median (25th–75th percentile)		35.1 (21.9–45.0)[a]	176.7 (27.6–325.7)	107.3 (62.0–217.2)[b]	.03[c]
N	>30	32	5	4	
Median (25th–75th percentile)		34.0 (13.1–57.6)[a]	166.7 (82.9–320.1)[b]	40.7 (24.0–52.7)	.03[c]
HOMA-IR					
N	≤25	27	5	7	
Median (25th–75th percentile)		1.17 (0.94–2.28)	1.15 (1. 13–1.41)	0.62 (0.34–1.22)	.20
N	>25–30	51	3	5	
Median (25th–75th percentile)		0.86 (0.48–2.17)	1.04 (0.96–1.10)	1.69 (0.81–1.73)	.91
N	>30	43	3	11	
Median (25th–75th percentile)		0.94 (0.58–2.15)	4.34 (1.48–52.14)	1.85 (0.58–3.76)	.11
Total cholesterol (mg/dL)					
N	≤25	54	10	9	
Median (25th–75th percentile)		179.0 (157.0–208.0)	162.0 (154.0–192.0)	183.0 (174.0–191.0)	.60
N	>25–30	89	7	9	
Median (25th–75th percentile)		179.0 (156.0–199.0)	160.0 (153.0–197.0)	171.0 (159.0–190.0)	.87
N	>30	77	6	17	
Median (25th–75th percentile)		185.0 (168.0–221.0)	189.0 (173.0–206.0)	181.0 (166.0–197.0)	.92
HDL-C (mg/dL)					
N	≤25	56	10	10	
Median (25th–75th percentile)		54.5 (46.5–70.5)	59.0 (49.0–68.0)	71.5 (56.0–76.0)	.32
N	>25–30	86	7	8	
Median (25th–75th percentile)		61.5 (47.0–74.0)	49.0 (44.0–59.0)	54.5 (51.0–62.0)	.35
N	>30	76	6	17	
Median (25th–75th percentile)		62.0 (48.5–74.0)	49.0 (41.0–56.0)	53.0 (40.0–63.0)	.08
LDL-C (mg/dL)					
N	≤25	59	9	10	
Median (25th–75th percentile)		101.0 (86.0–116.0)	90.0 (80.0–114.0)	100.5 (91.0–153.0)	.82
N	>25–30	85	6	9	
Median (25th–75th percentile)		98.0 (79.0–115.0)	87.0 (78.0–103.0)	101.0 (89.0–117.0)	.72
N	>30	76	6	15	
Median (25th–75th percentile)		106.5 (85.5–133.5)	93.5 (89.0–138.0)	101.0 (84.0–127.0)	.91
Triglycerides (mg/dL)					
N	≤25	55	10	9	
Median (25th–75th percentile)		76.0 (49.0–130.0)	76.0 (50.0–100.0)	72.0 (53.0–110.0)	.79
N	>25–30	87	7	9	
Median (25th–75th percentile)		68.0 (48.0–99.0)	97.0 (61.0–156.0)	106.0 (75.0–113.0)	.15
N	>30	75	6	17	
Median (25th–75th percentile)		85.0 (55.0–122.0)	112.5 (94.0–189.0)	73.0 (63.0–106.0)	.28
CRP (mg/dL)					
N	≤25	29	3	4	

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TABLE 2

Continued.

Metabolic end points	Age, y	White women (n = 243)	South Asian women (n = 25)	East Asian women (n = 38)	KW *P* value
Median (25th–75th percentile)		0.8 (0.2–2.0)	1.3 (0.1–1.6)	1.5 (0.15–4.2)	.89
N	>25–30	38	3	4	
Median (25th–75th percentile)		0.3 (0.1–2.3)	0.11 (0.10–0.68)	0.55 (0.10–8.51)	.89
N	>30	30	5	6	
Median (25th–75th percentile)		1.05 (0.16–2.9)	1.9 (0.8–4.6)	1.3 (0.9–3.15)	.70

Note: CRP = C-reactive protein; HDL-C = high-density lipoprotein cholesterol; HOMA-IR = homeostasis model assessment of insulin resistance; KW = Kruskal-Wallis; LDL-C = low-density lipoprotein cholesterol.
[a,b] Significant differences for within row comparisons are denoted by different letters.
[c] KW *P* value < .05.

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DISCUSSION

This study evaluated metabolic dysfunction as measured by markers of insulin resistance (i.e., fasting and 2-hour glucose and insulin levels, HOMA-IR), cardiovascular risk, and metabolic syndrome and its components in South Asian, East Asian, and White women with PCOS of a single region in the United States. Our results indicate that South and East Asian women with PCOS living in the same geographic region do not largely differ in their metabolic and cardiovascular risk profiles compared with White women or one another, although evidence of a more adverse metabolic profile may be suggested by differences in 2-hour insulin and 2-hour glucose levels.

As our study sought to compare metabolic differences between race groups residing in the same country and furthermore, in the same urban community, we controlled for environment to reveal genetic and racial influences in women with PCOS. East and South Asian women with PCOS have been demonstrated to have metabolic dysfunction when compared with controls (15, 23). Recent evidence supports the strong role of genetic factors in clinical manifestations of PCOS between various racial and ethnic groups (24). Furthermore, another study (33) demonstrated racial and ethnic differences in metabolic response (among women with PCOS). As a result, there is reason to believe South and East Asian women may differ in metabolic function from each other and White women residing in the same region. Prior to this study it was unclear whether South and East Asian women with PCOS residing in this geographic region of the United States would demonstrate clinical phenotypes similar to each other or White American women with PCOS. However, our findings did not indicate any differences in metabolic syndrome and its components between races. This may be the result of sample size limitations or the possibility that region or place of residence is a more substantial driver in metabolic dysfunction compared with genetic and racial influences. Furthermore, the metabolic changes commonly associated with PCOS may not become apparent until the third and fourth decades of life when the disease clinically manifests as metabolic disturbances, which limits our ability to discern racial differences in younger PCOS individuals with predominant reproductive abnormalities.

Although race and ethnicity are not accounted for in the diagnosis of PCOS, increasing evidence suggests that compared with White women, South and East Asian women can present with different clinical manifestations (24, 25, 34). For example, clear racial differences exist with respect to hirsutism rates as East Asian and White women have been shown to have a lower prevalence and decreased total mean Ferriman-Gallwey scores compared with South Asian women with PCOS. This was demonstrated in our study as well as by previous investigators (35, 36). Sensitivity to circulating free androgens and activity of 5-alpha reductase, a dermal enzyme that converts testosterone to dihydrotestosterone, which is directly responsible for the clinical manifestations of hirsutism, have been shown to differ by race whereby East Asian women have lower sensitivity and decreased enzyme levels (37). More recently, a cross-sectional study (33) in the United States investigating metabolic dysfunction in nondiabetic African American, Hispanic, White, and Asian women with PCOS using similar measures of insulin resistance (i.e., fasting and 2-hour glucose and insulin, HOMA-IR), along with more specific measures of beta-cell function (i.e., HOMA-β%), found that Asian women demonstrated a lower insulin response to circulating glucose, suggesting possible beta-cell dysfunction. Similar to our findings, Asian women differed in their metabolic response with higher mean 2-hour glucose levels compared with White women with PCOS. Such investigations of racial differences in metabolic abnormalities associated with PCOS could contribute to further insight on the underlying physiologic processes driving endocrine disruption.

Consistent with previous literature, our results of elevated 2-hour insulin and 2-hour glucose levels in South and East Asian women >25 years of age suggest Asian women with PCOS may be at higher risk for insulin resistance and its downstream consequences, such as type 2 diabetes, compared with White women. Such findings likely support an interaction between race and PCOS metabolism in Asian women. Other studies (16, 38) also investigating markers of insulin resistance in populations with PCOS reported increased fasting insulin levels in Asians, which is inconsistent with our findings. However, our results of increased 2-hour glucose levels in Asian women and no differences in HOMA-IR and

TABLE 3

Metabolic outcomes by race comparisons in polycystic ovarian syndrome participants.

Metabolic end points	No. of observations	Paired race groups	aOR[a] (95% CI)
Metabolic syndrome[b]	281	White vs. South Asian	0.30 (0.02, 3.64)
		White vs. East Asian	1.01 (0.29, 3.58)
		East vs. South Asian	3.41 (0.22, 51.77)
Elevated waist circumference (>88 cm)	282	White vs. South Asian	0.63 (0.23, 4.99)
		White vs. East Asian	0.68 (0.26, 1.79)
		East vs. South Asian	1.08 (0.23, 4.99)
Elevated fasting glucose (≥100 mmHg)	287	White vs. South Asian	0.38 (0.3, 4.71)
		White vs. East Asian	1.41 (0.43, 4.69)
		East vs. South Asian	3.70 (0.25, 54.45)
Elevated triglycerides (≥150 mmHg)	275	White vs. South Asian	1.37 (0.33, 5.71)
		White vs. East Asian	0.70 (0.18, 2.75)
		East vs. South Asian	0.51 (0.08, 3.28)
Low HDL-C (<50 mg/dL)	276	White vs. South Asian	1.84 (0.63, 5.39)
		White vs. East Asian	0.92 (0.35, 2.44)
		East vs. South Asian	0.50 (0.13, 1.96)
Hypertension (>130 and/or >85 mmHg)	299	White vs. South Asian	0.36 (0.03, 4.37)
		White vs. East Asian	0.62 (0.14, 2.87)
		East vs. South Asian	1.74 (0.11, 30.09)

Note: aOR = adjusted odds ratio; CI = confidence interval; HDL-C = high-density lipoprotein cholesterol; OR = odds ratio.
[a] Analyses controlled for age as a categorical variable using three groups: ≤25, >25–30, and >30 years. Pairwise multiple comparisons were adjusted using Bonferroni correction.
[b] Metabolic syndrome is defined as having ≥3 of 5 criteria listed in the Table.

Chahal. Metabolic syndrome, race, and PCOS. Fertil Steril Rep 2020.

fasting levels are in agreement with a more recent study (33) conducted in the United States. Although Asian women with PCOS in our study had more degrees of insulin resistance, they did not have an increased risk of metabolic syndrome or any of its five components. It is possible that these few notable differences of insulin resistance between Asian and White women with PCOS may represent early signs of intrinsic physiologic differences driven by race that takes time to manifest clinically as metabolic syndrome (8). Alternatively, lifestyle factors, such as diet and exercise, may prevent progression of subtle metabolic disturbances into metabolic syndrome that requires presence of at least three of the five components. On the contrary, the increased insulin levels may represent the true burden of insulin resistance as a direct effect of PCOS metabolism without clear evidence of the role of metabolic syndrome.

According to previous literature, South and East Asian women with PCOS are at increased risk for metabolic syndrome compared with their same-race, non-PCOS counterparts (15, 21, 23) and White women with PCOS (14, 20, 38). A cross-sectional study (14) performed across five outpatient clinics in different countries (United States, India, Brazil, Finland, and Norway) found Indian women to have the highest age- and BMI-adjusted prevalence of metabolic syndrome—driven by increased fasting glucose and low HDL-C—when compared with US White women with PCOS. In contrast, we did not observe associations between metabolic syndrome or its five components and race. Similarly, in a multicenter study (8) comparing prevalence of metabolic syndrome and its components across races, no differences were noted in Asian, Hispanic, and mixed race women with PCOS when compared with White and African American women. Direct comparisons between the two studies (8, 14) and ours, however, remain limited due to differences in outcome measurements (prevalence vs. risk), settings (multiregional vs. single region), and definition of exposure groups. Studies performed in indigenous South Asian (15, 21) and East Asian (22, 23, 39) populations have reported an increased risk of metabolic syndrome in women with PCOS compared with the general population. Some studies (15, 23) in particular attributed the increased risk to central obesity that is defined at lower proposed Asian cutoffs for overweight BMI and elevated waist circumference (BMI ≥23–25 kg/m^2 and waist circumference ≥80 cm). We also accounted for the race-specific definition of central obesity in Asian women in our sensitivity analysis (31). However, even after the use of a modified elevated waist circumference threshold, no differences were detected. It is less likely that the risk of metabolic syndrome, along with the risk of elevated waist circumference, are underestimated in South and East Asian women in our study. More likely environmental influences may predominate genetic and racial factors in the metabolic complications of PCOS.

Multiracial cohort studies performed in other countries (18, 20), the United States (40), or both (17) also sought to characterize differences in insulin resistance and metabolic risk profiles between Asian and White women with PCOS. Although some studies (18, 20, 40) demonstrated findings supporting decreased insulin sensitivity and higher prevalence of type 2 diabetes in Asian women, others (17) did not. An observational study (17) in Icelandic and Boston, Massachusetts, racial groups did not find differences in

fasting glucose, insulin, or HOMA-IR between countries or races, and the few notable differences observed in non-Asians were explained by weight and BMI. There was also no difference in the prevalence of metabolic syndrome across races, but Asian women living in Boston (n = 21) were more likely to have increased triglyceride levels compared with White, African American, and Hispanic women with PCOS in Boston. Consistent with the findings in the Boston subjects, we also did not detect differences in fasting glucose, insulin, HOMA-IR, and risk of metabolic syndrome across race groups residing in a single region. Despite comparable baseline characteristics, such as age and BMI, across groups in our study, Asian women had increased 2-hour insulin and glucose. Our findings of more insulin resistance in Asian women closely mirror those of a Danish population (18). In Denmark, Middle Eastern women with PCOS were shown to have decreased insulin sensitivity, as marked by increased area under the curve insulin and 2-hour glucose without changes in fasting levels (18). In the present study, Asian women also demonstrated decreased insulin sensitivity with increased 2-hour insulin levels. East Asian women in particular demonstrated increased 2-hour glucose. However, Glintborg et al. (18) reported increased prevalence of elevated waist circumference, systolic and diastolic blood pressures in Whites versus Middle Eastern Danish women, whereas we found no differences in the individual components of metabolic syndrome among American race groups. Again, these few differences in insulin sensitivity may not render an increased risk of metabolic syndrome or its components in Asian women with PCOS and instead point to smaller scale physiologic differences as a result of PCOS metabolism that take time to develop and contribute to lifetime cardiovascular risk and morbidity.

Furthermore, no differences were detected in the cardiovascular risk profile between Asian and White women with PCOS after controlling for age in our study, as reported previously in some studies (17, 20), but not others (18, 40). Nonetheless, caution must be taken in drawing conclusions in racial differences of cardiovascular risk in our study population, as we did not exclude or report on the prevalence of type 2 diabetes, a known cardiovascular risk factor and comorbid condition (6). In addition, Asian women with PCOS were more likely to have diabetes compared with their more obese, White counterparts in a large study using integrated healthcare system data in Northern California (n = 11,035) (40). Therefore, race and ethnicity-guided screening and management in the complications associated with PCOS are necessary in clinical practice. Our results of increased 2-hour insulin and glucose in Asian women living in the Bay area represent changes in normal metabolism and endocrine function secondary to PCOS that likely predispose them and increase their risk for diabetes and adverse cardiovascular outcomes long term.

Strengths and Limitations

Our study is strengthened by the evaluation of women of multiple races (i.e., South Asian, East Asian, and White) with PCOS living in the same geographic location—San Francisco Bay area. In addition, we used clean exposure groups by querying parental ancestry and excluded participants who reported mixed race and ethnicity. However, our study is not without limitations. We cannot rule out referral bias in our study population as a select group of women presented to the clinic who were referred by their primary-care providers due to suspicion of underlying reproductive or endocrine abnormality; therefore, our results may not be generalizable to the rest of the population. Self-reporting of race and ethnicity is subject to reporting bias, and subsequently may result in misinterpretation of classifications. However, we used ascertainment of patient's race and ethnicity with parental information to limit such error. Results should be interpreted with caution due to small number of participants in the Asian groups. The use of multiple laboratory sites to retrieve metabolic end points may also impact the ability to detect meaningful differences across groups. Furthermore, the high frequency of missing data in our main outcomes introduces bias and once again warrants caution in the interpretation of our results, as there is loss of power to detect change.

In conclusion, South Asian, East Asian, and White women with PCOS from a single region in the United States appear to have similar metabolic and cardiovascular risk profiles with no increased risk of metabolic syndrome or its components by race after also controlling for age. Apart from elevated 2-hour insulin levels in South and East Asian women >25 years and increased 2-hour glucose levels in East Asian women >30 years, continuous metabolic markers did not differ by race. The minor differences in insulin resistance in Asian women may be a direct result of racial variation seen with PCOS metabolism. Environmental factors may be important confounders for racial differences in metabolic dysfunction in women with PCOS as it is a disease brought on by the interplay between genetics and the environment. The racial differences in insulin resistance and metabolic abnormalities associated with PCOS remain unclear. Prospective studies following women in larger, regional, multiracial cohorts are needed to determine the impact and importance of race and ethnicity in the screening and management of metabolic abnormalities in women with PCOS. Following larger numbers of East and South Asian women can help to determine whether the findings of insulin resistance found in this study are meaningful and to provide further insight on the metabolic dysfunction associated with race in women with PCOS over time.

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