GLOBAL VOICES

Sex differences in global electrical heterogeneity: The Hispanic Community Health Study/Study of Latinos

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Vectorcardiographic (VCG) global electrical heterogeneity (GEH) is helpful in the prediction of sudden cardiac death and life-threatening sustained ventricular tachyarrhythmias.[1] Sex differences in GEH have been reported in white and African American populations.[2–4] The Hispanic population is characterized by the exceptionally high prevalence of cardiovascular risk factors. The age-standardized prevalence of metabolic syndrome exceeds 70% for Hispanic women at 70–74 years of age.[5] The GEH phenotype highlighted distinctive latent profiles in Hispanic/Latino populations, perhaps reflecting the range of susceptibility or resilience to harmful cardiovascular risk factor exposure.[6,7] However, sex differences in GEH among Hispanic/Latino adults have not been previously explored. In this ancillary study within the Hispanic Community Health Study/Study of Latinos (HCHS/SOL), we aimed to compare VCG GEH in Hispanic/Latino male and female adults with and without cardiovascular disease (CVD). We hypothesized that sex modifies the association of prevalent CVD with GEH.

KEYWORDS Electrophysiology; ECG; Vectorcardiography; Cardiovascular risk; Hispanic/Latino; Sex differences; Women (Heart Rhythm O2 2025;6:97–102)

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The research reported in this article adhered to the Declaration of Helsinki. The study was approved by the institutional review board at each participating institution, and all participants signed informed consent before joining the study. The article was reviewed and approved by the HCHS/SOL publication committee. The HCHS/SOL study was designed as a multicenter, community-based longitudinal cohort study of cardiovascular risk factors in self-identified Hispanic/Latino adults aged 18–74 years. This cross-sectional study included HCHS/SOL participants with available 10-second digital 12-lead electrocardiograms (ECGs) recorded at rest. Figure 1A shows the study flowchart. Major and minor ECG abnormalities (including ECG diagnosis of myocardial infarction) were classified at the EPICARE Center (Wake Forest School of Medicine, Winston Salem, NC) and coded using the Minnesota code.[8] The raw digital ECG signal was analyzed in a fully blinded manner.[9,10] The GEH phenotype was measured using 5 VCG metrics: area-based spatial QRS-T angle (QRSTa), spatial ventricular gradient (SVG) vector direction (SVG azimuth [SVGaz] and SVG elevation [SVGel)], SVG magnitude [SVGmag] (Figure 1B), and sum absolute QRST integral (SAIQRST) (Figure 1C).[1]

Prevalent CVD was defined as a self-reported history of coronary heart disease or stroke. Coronary heart disease history included a self-reported history of myocardial infarction, coronary artery bypass grafting, or percutaneous coronary

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KEY FINDINGS

- This cross-sectional analysis of the largest (N = 15,684; mean age 41 years; female subpopulation 53% (95% confidence interval (CI) 51.2%–53.4%); 6% (95% CI 5.2–6.3) with known cardiovascular disease [CVD]) community-based survey of diverse Hispanic/Latino individuals in the United States (Hispanic Community Health Study/Study of Latinos) showed substantial sex differences in vectorcardiographic (VCG) global electrical heterogeneity (GEH). The female spatial ventricular gradient (SVG) vector is smaller than the male SVG vector, and it points farther downward and posteriorly. The female spatial QRS-T angle and sum absolute QRST integral (SAIQRST) are smaller than the male metrics.
- Sex modifies an association of prevalent CVD with SVG magnitude and SAIQRST. SAIQRST and SVG are smaller in men with CVD than in CVD-free men. In contrast, SAIQRST and SVG are larger in women with CVD than in CVD-free women.
- Female reproductive health history (age of menarche and menopause, parity, use of hormone replacement therapy) is associated with differences in VCG GEH phenotype.

intervention. Definitions of clinical covariates have been provided elsewhere.[6,7] Female-specific cardiovascular risk factors included the age when menses began, age of menopause, number of pregnancies and live births, use of birth control medications, and female hormones other than birth control pills. Postmenopausal women were identified via questionnaire and included both natural menopause and post-hysterectomy with removal of both ovaries. Pregnant women were identified via a questionnaire.

The HCHS/SOL study sample was selected through a stratified 2-stage area probability sample design.[11] To determine whether sex and CVD are independently associated with GEH, we developed linear regression models with GEH metrics as outcome variables (one by one) and adjusted for known confounders (age, Hispanic/Latino background, education attainment, hypertension, diabetes, smoking, hypercholesterolemia/dyslipidemia, height, obesity, chronic kidney disease, level of physical activity, and diet quality), type of median beat, and average R-R' interval. A separate set of models included an interaction term of sex with prevalent CVD status. Statistical analysis was performed using STATA MP 17.0 (StataCorp LP, College Station, TX); code is provided at https://github.com/Tereshchenkolab/statistics. To account for the testing of 12 hypotheses, a P value of <.004 was considered statistically significant.

The female subpopulation accounted for 53.3% (95% confidence interval [CI] 51.2%–53.4%). The population had a mean age of 41.1 years (95% CI 40.6–41.6 years). CVD was more prevalent in male subpopulation than in female subpopulation (7.1%; 95% CI 6.2%–8.2% vs 4.4%; 95% CI 3.8%–5.2%). A comparison of male and female population characteristics is presented in Table 1. Female subpopulation was slightly older than male subpopulation. The most striking difference was in physical activity level: only 59% of female subpopulation achieved the 2008 physical activity guidelines recommended level as compared with 76% of male subpopulation. Female population had a higher prevalence of obesity but a lower prevalence of hypercholesterolemia than did male population.

In the female subpopulation, 61.8% (95% CI 60.1%–63.3%) were fertile and 38.2% (95% CI 36.6%–39.8%) were postmenopausal. In total, 76.2% (95% CI 73.8%–78.4%) of female subpopulation reported being peri- or postmenopausal. The mean age when menses began was 12.5 years (95% CI 12.4–12.6 years), and menopause was reached at the age of 44.4 years (95% CI 43.8–44.9 years). Nearly a third of the female population (30.2%; 95% CI 28.1%–32.4%) underwent hysterectomy. A hysterectomy history with removal of both ovaries was reported by 15.1% (95% CI 13.4%–17.0%) and without removal of both ovaries by another 11.9% (95% CI 10.4%–13.6%). The mean age at hysterectomy was 42.3 years (95% CI 41.4–43.1 years). On average, a Hispanic/Latino woman was pregnant 3.9 times (95% CI 3.7–4.1 times) and had 2.9 live births (95% CI 2.7–3.1 live births). There were 14 pregnant women participating in the study (1.2%; 95% CI 0.6%–2.4%). The history of birth control pill use was reported by 59.1% (95% CI 57.3%–60.9%) of female subpopulation, and only 2.5% (95% CI 2.1%–3.0%) reported current use of female hormones for other than birth control reasons.

After adjustment for the prevalence of CVD, demographic characteristics, height, and cardiovascular risk factors, women had a faster heart rate, smaller QRSTa (adjusted difference −13.0°; 95% CI −14.6° to −11.3°; $P < .0001$), smaller SVGmag (adjusted difference −12.6 mV·ms; 95% CI −14.5 to −10.8 mV·ms; $P < .0001$), and smaller SAIQRST (adjusted difference −32.5 mV·ms; 95% CI −35.4 to −29.6 mV·ms; $P < .0001$) than did men. The SVG vector pointed farther downward (adjusted difference −5.1°; 95% CI −5.9° to −4.3°; $P < .0001$) and posteriorly (adjusted difference +13.6°; 95% CI +12.3°–+14.9°; $P < .0001$) in women than in men.

In fully adjusted models, adults with CVD had a significantly greater QRSTa (+12.2°; 95% CI 8.8°–15.6°; $P < .0001$) and smaller SVGmag (−6.9 mV·ms; 95% CI −10.0 to −3.8 mV·ms; $P < .0001$) than did CVD-free adults. Sex significantly ($P < .0001$) modified an association of SVGmag and SAIQRST with CVD (Figure 2). Women with CVD had a larger SAIQRST than did those without CVD, but an opposite association was observed in men: smaller SAIQRST in men with CVD than in CVD-free men. Similarly, men (but not women) with CVD had a smaller SVGmag than did CVD-free men.

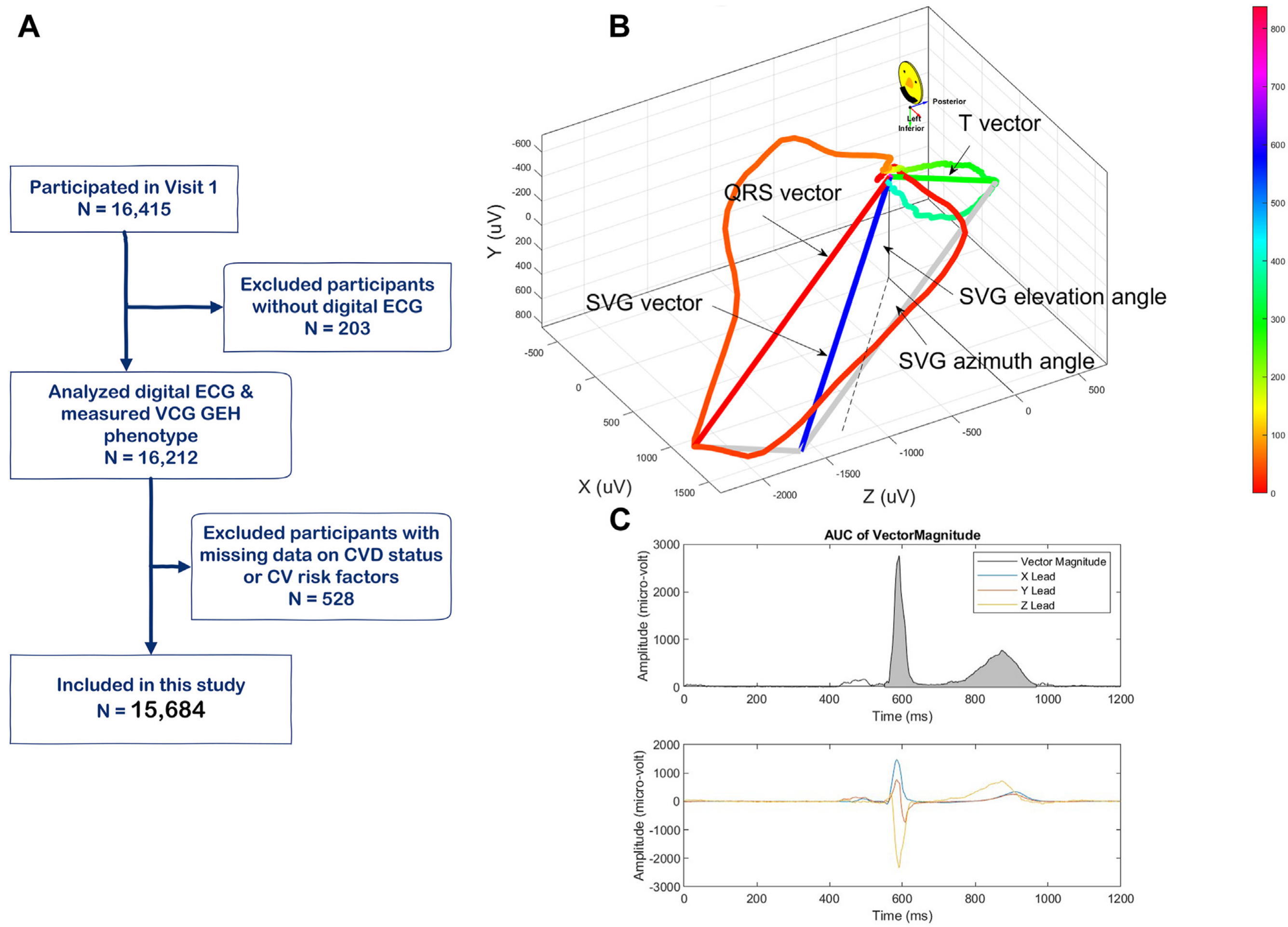

Figure 1 **A:** Study flowchart. **B:** Representative example of vectorcardiographic (VCG) and measured global electrical heterogeneity (GEH) variables: spatial QRS-T angle and spatial ventricular gradient (SVG) magnitude and direction (azimuth and elevation). SVG elevation reflects SVG's position relative to a horizontal plane on a Y axis, upward from zero. SVG azimuth reflects SVG's position relative to a frontal plane on a Z axis, with positive backward and negative forward values. **C**. Representative example of sum absolute QRST integral (SAIQRST). SVG's scalar SAIQRST is an absolute QRST integral on orthogonal XYZ leads or an area under the curve (AUC) on a vector magnitude signal divided by 0.62. CV = cardiovascular; CVD = cardiovascular disease; ECG = electrocardiogram.

After adjustment, female-specific characteristics were associated with GEH metrics (Table 2). A larger number of pregnancies, greater parity, and later onset of menarche were associated with smaller SVGmag and SAIQRST. Age of menarche was associated with a slightly more positive (ie, backward-directed) SVGaz, and age of menopause was associated with a higher SVGel. Greater parity and later onset of menopause were associated with a higher SVGel. The use of any hormone replacement therapy (including the use of contraceptives) was associated with a smaller QRSTa, whereas later onset of menopause was associated with a greater QRSTa.

Thus, our study revealed significant sex differences in cardiac electrophysiology manifested by the VCG GEH phenotype. The female QRSTa, SAIQRST, and SVG are smaller than the male metrics. The female SVG vector points farther downward and posteriorly than the male SVG vector. Sex modifies an association of prevalent CVD with SVGmag and SAIQRST. In male subpopulation, CVD manifests by smaller SAIQRST and SVGmag. In contrast, in female subpopulation, CVD manifests by larger SAIQRST and SVGmag. Notably, in other race and ethnicity subpopulations,[2–4] the degree of sex differences in GEH is similar to that observed in the present study, suggesting the paramount importance and strength of sex differences. Sex differences dominate race/ethnicity differences in GEH.[6,7]

Age of menarche and menopause, parity, and use of hormone replacement therapy are associated with the VCG GEH phenotype. The study limitations should be considered. While we adjusted for the history and treatment of hypertension, we have not accounted for the presence of left ventricular hypertrophy. GEH can be easily and reliably measured on an inexpensive, noninvasive 12-lead ECG. Future studies are needed to determine dynamic changes in GEH that can be revealed at higher heart rates (under stress or exercise) and the influence of sex hormones on GEH.

Table 1 Characteristics of male and female populations

Characteristic	Category	Men (n = 6254) (%)	Women (n = 9430) (%)
Age category (age range 18–76 y)	18–44 y	61.9 (60.1 to 63.7)	57.8 (56.1 to 59.5)
	45–64 y	30.6 (29.1 to 32.1)	32.8 (31.4 to 34.3)
	≥65 y	7.5 (6.6 to 8.5)	9.4 (8.5 to 10.4)
Background group	Dominican	8.1 (6.8 to 9.7)	11.5 (10.0 to 13.3)
	Central American	7.4 (6.2 to 8.8)	7.4 (6.4 to 8.6)
	Cuban	22.0 (18.6 to 25.9)	18.4 (15.4 to 21.8)
	Mexican	37.1 (33.6 to 40.7)	38.5 (35.3 to 41.9)
	Puerto Rican	16.4 (14.6 to 18.3)	14.9 (13.3 to 16.6)
	South American	4.7 (4.1 to 5.5)	5.2 (4.5 to 6.0)
	Mixed/other/unknown	4.3 (3.6 to 5.2)	4.1 (3.4 to 5.0)
Attained education level category	Less than high school	31.7 (29.9 to 33.5)	32.6 (30.9 to 34.3)
	High school or equivalent	30.6 (28.9 to 32.3)	26.5 (25.0 to 27.9)
	Some college	10.9 (9.7 to 12.3)	13.4 (12.4 to 14.5)
	University or college	26.8 (25.0 to 28.7)	27.5 (25.7 to 29.4)
Cigarette use category	Never used	51.6 (49.8 to 53.5)	70.6 (69.1 to 72.2)
	Former user	21.8 (20.5 to 23.2)	13.1 (12.1 to 14.1)
	Current user	26.6 (25.0 to 28.3)	16.3 (15.0 to 17.7)
Diet quality category	Healthy diet	45.5 (43.1 to 47.9)	44.9 (42.9 to 47.0)
2008 Physical activity guidelines	Does meet the level criteria	75.8 (74.2 to 77.3)	58.9 (57.3 to 60.4)
Obesity category	BMI <30 kg/m^2	63.4 (61.6 to 65.2)	57.6 (55.9 to 59.3)
	BMI ≥30 kg/m^2	36.6 (34.8 to 38.4)	42.4 (40.7 to 44.2)
Hypercholesterolemia/dyslipidemia	Present	50.5 (48.8 to 52.2)	35.3 (33.8 to 36.8)
Diabetes category	Nondiabetic	46.6 (44.8 to 48.5)	51.1 (49.2 to 52.7)
	Prediabetic	38.5 (36.9 to 40.3)	32.6 (31.2 to 34.0)
	Diabetic	14.8 (13.7 to 16.1)	16.3 (15.2 to 17.5)
HTN stage	Normal BP <120/80 mm Hg	40.0 (38.1 to 41.9)	57.2 (55.4 to 58.9)
	Elevated BP 20–129/<80 mm Hg	18.2 (16.9 to 19.6)	7.4 (6.6 to 8.3)
	Untreated HTN stage 1: BP 30–139/80–89 mm Hg	18.2 (16.9 to 19.7)	10.6 (9.7 to 9.9)
	Untreated HTN stage 2: BP ≥140/90 mm Hg	8.9 (7.9 to 9.9)	6.5 (5.9 to 7.2)
	Treated HTN	14.8 (13.6 to 16.1)	18.4 (17.2 to 19.8)
Chronic kidney disease		9.1 (8.2 to 10.0)	10.6 (9.7 to 11.5)
Cardiovascular disease		7.1 (6.2 to 8.2)	4.4 (3.8 to 5.2)
Major ECG abnormalities		8.6 (7.8 to 9.6)	6.9 (6.1 to 7.7)
Minor ECG abnormalities		55.1 (53.3 to 56.8)	34.2 (32.8 to 35.7)
Myocardial infarction on the ECG		2.9 (2.4 to 3.6)	1.7 (1.3 to 2.3)
Spatial QRS-T angle (deg)		54.4 (53.3 to 55.4)	43.4 (42.5 to 44.4)
SVG azimuth angle (deg)		−26.3 (−27.0 to −25.7)	−12.2 (−12.9 to −11.5)
SVG elevation angle (deg)		65.3 (64.9 to 65.6)	60.4 (59.9 to 60.8)
SVG magnitude (mV·ms)		91.1 (89.9 to 92.3)	71.1 (70.3 to 71.9)
SAIQRST (mV·ms)		184.3 (182.3 to 186.3)	139.9 (138.8 to 141.0)
R-R′ interval (ms)		990.0 (984.7 to 994.8)	957.7 (953.2 to 962.3)
Atrial fibrillation		0.25 (0.13 to 0.46)	0.06 (0.03 to 0.12)
Ventricular pacing		0.15 (0.08 to 0.30)	0.03 (0.01 to 0.10)
Use antiarrhythmic medications		0.17 (0.07 to 0.48)	0.09 (0.03 to 0.29)
Use lipid-lowering medications		8.5 (7.6 to 9.4)	9.9 (8.9 to 10.9)
Use antihypertensive medications		12.1 (11.0 to 13.2)	13.4 (12.4 to 14.6)

Values are presented as population-weighted mean (95% confidence interval [CI]) for continuous variables. Unadjusted categorical prevalence estimates for the representative Hispanic/Latino population were calculated using survey logistic regression conditional margins and reported as weighted proportion (95% CI).

BMI = body mass index; BP = blood pressure; ECG = electrocardiogram/electrocardiographic; HTN = hypertension; SAIQRST = sum absolute QRST integral; SVG = spatial ventricular gradient.

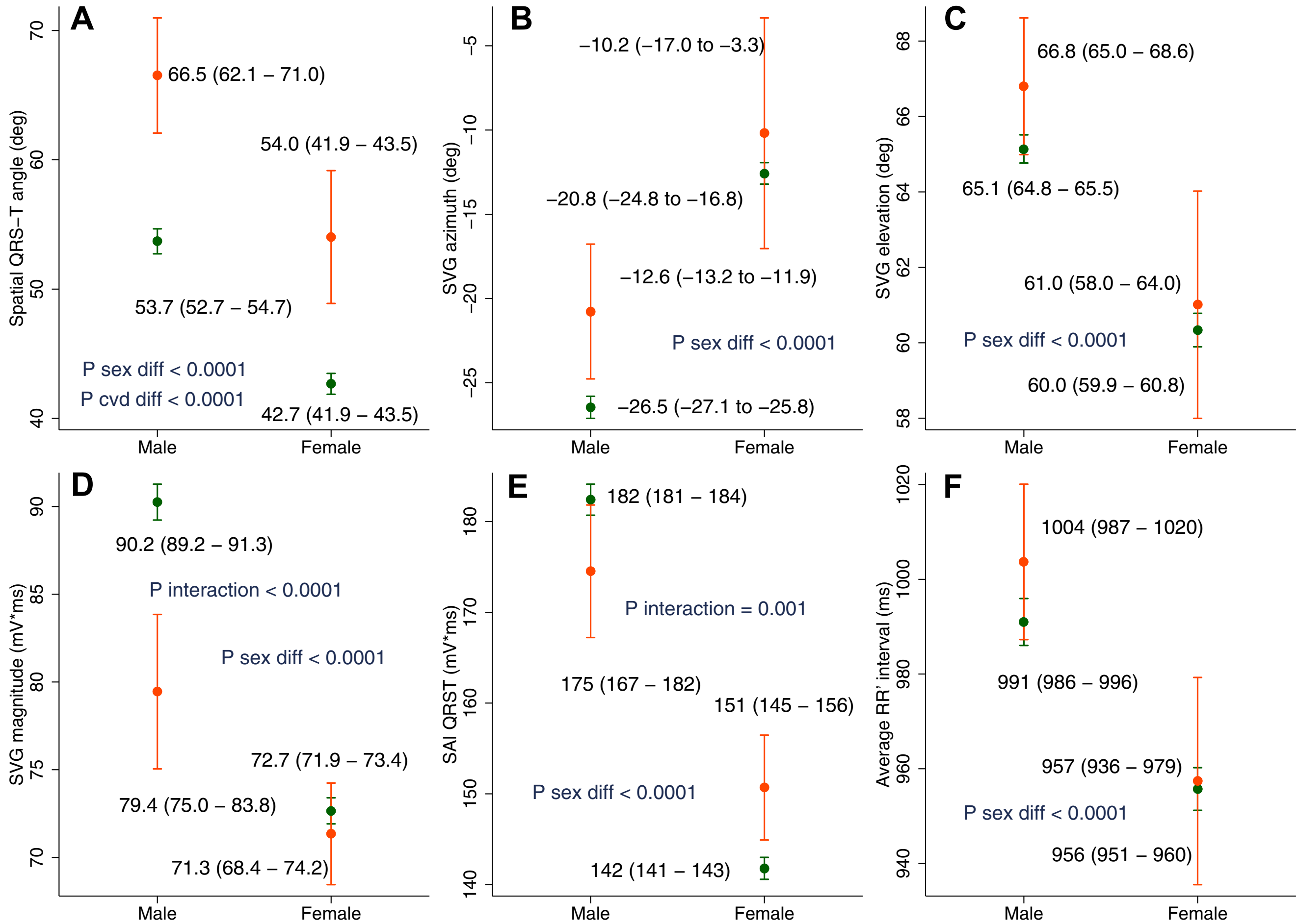

Figure 2 Estimated adjusted marginal (least-squares) means and 95% confidence intervals (CIs) of (**A**) spatial QRS-T angle, (**B**) spatial ventricular gradient (SVG) azimuth, (**C**) SVG elevation, (**D**) SVG magnitude, (**E**) sum absolute QRST integral (SAIQRST), (**F**) average R-R' interval in male and female participants with (*orange*) and without (*green*) prevalent cardiovascular disease. All models were adjusted for age, sex, Hispanic/Latino background, education attainment, hypertension, diabetes, smoking, hypercholesterolemia/dyslipidemia, obesity, chronic kidney disease, level of physical activity, diet quality, type of median beat, and average R-R' interval.

Table 2 Association of female-specific characteristics with VCG global electrical heterogeneity variables

Characteristic	Spatial QRS-T angle (deg)	SVG azimuth (deg)	SVG elevation (deg)	SVG magnitude (mV·ms)	SAIQRST (mV·ms)
Age menses began (per 1 year increase)	+0.07 (−0.3 to +0.5)	**+0.6 (0.1 to 0.8)**	+0.1 (−0.04 to +0.3)	**−0.6 (−1.0 to −0.2)**	**−1.0 (−1.6 to −0.4)**
Age menopause reached (per 1 year increase)	**+0.3 (0.1 to 0.6)**	+0.1 (−0.2 to +0.3)	**+0.2 (0.02 to 0.5)**	−0.1 (−0.3 to +0.02)	−0.2 (−0.5 to +0.03)
Currently pregnant (yes versus no)	+20.0 (−14.0 to +53.9)	+11.5 (−6.8 to +29.8)	+4.7 (−3.8 to +13.2)	−6.5 (−16.2 to +3.3)	+13.5 (−26.4 to +53.4)
Currently postmenopausal (yes versus no)	+2.2 (−0.1 to +4.4)	−0.2 (−1.7 to +1.2)	+0.8 (−0.2 to +1.7)	−1.2 (−3.3 to +0.8)	−1.3 (−4.7 to +2.0)
Number of times pregnant (per 1 pregnancy increase)	+0.4 (−0.1 to +0.9)	+0.3 (−0.2 to +0.8)	**+0.3 (0.01 to 0.6)**	**−0.5 (−0.8 to −0.2)**	**−0.7 (−1.3 to −0.04)**
Number of live births (per 1 live birth increase)	+0.4 (−0.01 to +0.7)	+0.2 (−0.01 to +0.5)	+0.1 (−0.1 to +0.3)	**−0.5 (−0.9 to −0.2)**	**−0.6 (−1.0 to −0.1)**
Current hormone replacement therapy (yes versus no)	**−3.8 (−7.5 to −0.1)**	+0.4 (−2.1 to +3.0)	−1.0 (−2.3 to +0.4)	+0.6 (−3.1 to +4.3)	−0.8 (−6.3 to +4.7)

Values are presented as adjusted change (95% confidence interval) in the outcome variable (QRSTa, SVGaz, SVGel, SVGmag, SAIQRST) per one unit of increase in exposure variable. Linear regression models were adjusted for age, Hispanic/Latino background, education attainment, hypertension, diabetes, smoking, hypercholesterolemia/dyslipidemia, height, obesity, chronic kidney disease, level of physical activity, diet quality, type of median beat, and average R-R′ interval.

Bold indicates statistically significant: $P < .004$.

SAIQRST = sum absolute QRST integral; SVG = spatial ventricular gradient; VCG = vectorcardiographic.

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Ethics Statement: The research reported in this article adhered to the Declaration of Helsinki. The study was approved by the institutional review board at each participating institution.

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