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ORIGINAL ARTICLE
Cardiovascular signal processing

Latent profiles of global electrical heterogeneity: the Hispanic Community Health Study/Study of Latinos

Larisa G. Tereshchenko [1,2,3,*], Kazi T. Haq[4], Stacey J. Howell[5], Evan C. Mitchell[6], Jesús Martínez[7], Jessica Hyde[7], Genesis Briceno[7], Jose Pena[7], Edvinas Pocius[7], Akram Khan[7], Elsayed Z. Soliman[8], João A.C. Lima[3], Samir R. Kapadia [2], Anita D. Misra-Hebert[1], Michael W. Kattan [1], Mayank M. Kansal[9], Martha L. Daviglus[9], and Robert Kaplan[10,11]

[1]Quantitative Health Sciences, Lerner Research Institute, Cleveland Clinic, 9500 Euclid Ave, JJN3-01, Cleveland, OH 44195, USA; [2]Heart, Vascular & Thoracic Institute, Cleveland Clinic, 9500 Euclid Ave, JJN3-01, Cleveland, OH 44195, USA; [3]Department of Medicine, Cardiovascular Division, Johns Hopkins School of Medicine, Baltimore, MD, USA; [4]Sheikh Zayed Institute for Pediatric Surgical Innovation, Children's National Hospital, Washington, DC, USA; [5]Section of Electrophysiology, Division of Cardiology, University of California San Francisco, San Francisco, CA, USA; [6]Department of Surgery, Brown University School of Medicine, Providence, RI, USA; [7]School of Medicine, Oregon Health & Science University, Portland, OR, USA; [8]Epidemiological Cardiology Research Center, Division of Public Health Sciences and Department of Medicine, Cardiology Section, Wake Forest School of Medicine, Winston Salem, NC, USA; [9]Department of Medicine, University of Illinois at Chicago, Chicago, IL, USA; [10]Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, New York, NY, USA; and [11]Public Health Sciences Division, Fred Hutch Cancer Center, Seattle, WA, USA

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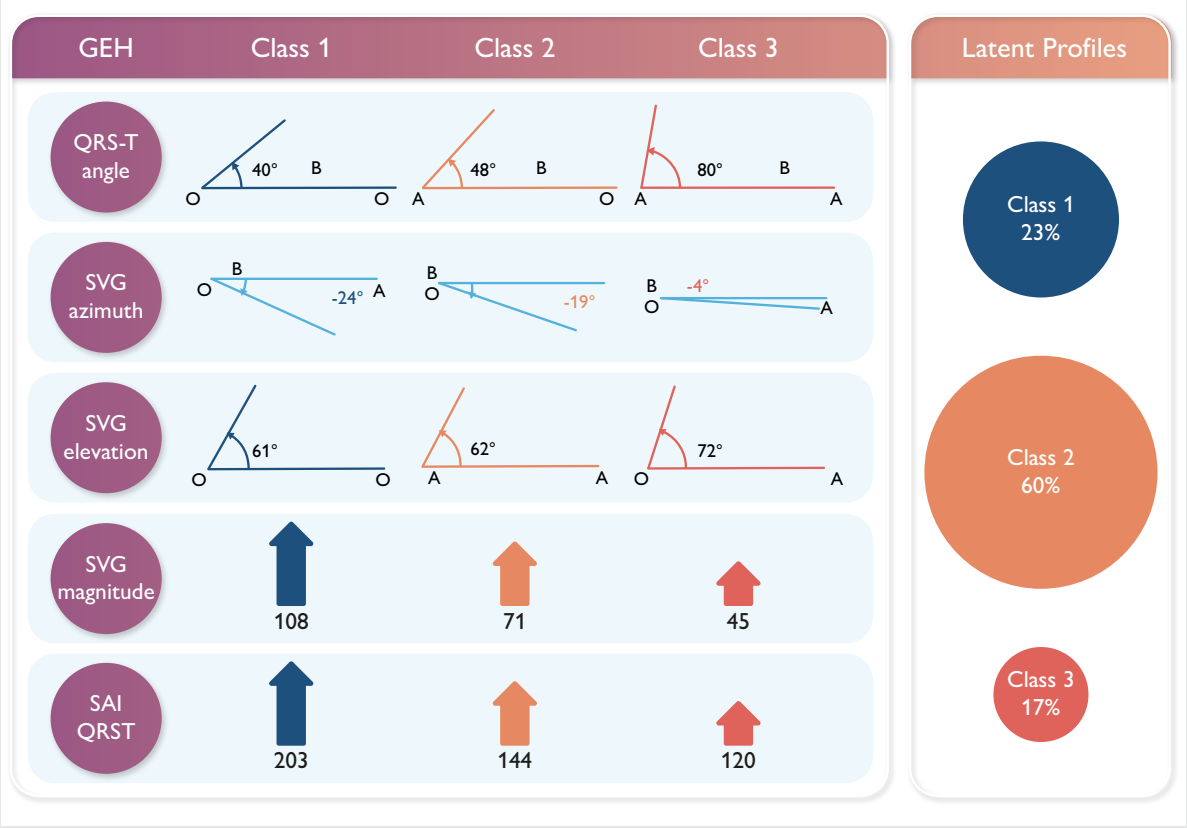
Aims Despite the highest prevalence of stroke, obesity, and diabetes across races/ethnicities, paradoxically, Hispanic/Latino populations have the lowest prevalence of atrial fibrillation and major Minnesota code–defined ECG abnormalities. We aimed to use Latent Profile Analysis in the Hispanic Community Health Study/Study of Latinos (HCHS/SOL) population to obtain insight into epidemiological discrepancies.

Methods and results We conducted a cross-sectional analysis of baseline HCHS/SOL visit. Global electrical heterogeneity (GEH) was measured as spatial QRS-T angle (QRSTa), spatial ventricular gradient azimuth (SVGaz), elevation (SVGel), magnitude (SVGmag), and sum absolute QRST integral (SAIQRST). Statistical analysis accounted for the stratified two-stage area probability sample design. We fitted a multivariate latent profile generalized structural equation model adjusted for age, sex, ethnic background, education, hypertension, diabetes, smoking, dyslipidaemia, obesity, chronic kidney disease, physical activity, diet quality, average RR' interval, median beat type, and cardiovascular disease (CVD) to gain insight into the GEH profiles. Among 15 684 participants (age 41 years; 53% females; 6% known CVD), 17% had an increased probability of likely abnormal GEH profile (QRSTa 80 ± 27°, SVGaz −4 ± 21°, SVGel 72 ± 12°, SVGmag 45 ± 12 mVms, and SAIQRST 120 ± 23 mVms). There was a 23% probability for a participant of being in Class 1 with a narrow QRSTa (40.0 ± 10.2°) and large SVG (SVGmag 108.3 ± 22.6 mVms; SAIQRST 203.4 ± 39.1 mVms) and a 60% probability of being in intermediate Class 2.

Conclusion A substantial proportion (17%) in the Hispanic/Latino population had an increased probability of altered, likely abnormal GEH profile, whereas 83% of the population was resilient to harmful risk factors exposures.

* Corresponding author. Tel: 216 444 2445, Email: tereshl@ccf.org

Graphical Abstract



Keywords Electrophysiology • ECG • Vectorcardiogram • Cardiovascular risk • Hispanic or Latino ethnicity • Latent class analysis

Introduction

The Hispanic/Latino population is the fastest-growing ethnic group in the USA and is characterized by the high prevalence of cardiovascular risk factors. The age-adjusted prevalence of obesity and metabolic syndrome in the Hispanic/Latino population (~50%) is among the highest in the USA.[1] Age-adjusted incidence of stroke is higher in Hispanic than non-Hispanic White adults.[2] However, the prevalence and incidence of atrial fibrillation (AF) are lower in Hispanic than non-Hispanic White adults.[3,4] Furthermore, it is known that the development of cardiovascular disease (CVD) in metabolic syndrome is frequently asymptomatic, which is consistent with the data reporting low awareness of CVD in Hispanic individuals.[5,6] An electrocardiogram (ECG) is especially useful in detecting silent myocardial infarction (MI).[7] However, the prevalence of ECG MI in Hispanic adults is relatively low.[8,9] The reasons behind discrepant epidemiological findings are unclear.

A vectorcardiogram (VCG) carries additional, complementary to 12-lead ECG information,[10] and, hypothetically, it can help to reconcile discrepancies in epidemiological findings. Vectorcardiogram phenotype global electrical heterogeneity (GEH)[11] is associated with sudden cardiac death,[12] ventricular tachyarrhythmias,[13–15] stroke,[16] and cardiac structure and function abnormalities.[17] The GEH phenotype is comprised out of five metrics: spatial ventricular gradient (SVG) azimuth (SVGaz), SVG elevation (SVGel), and magnitude (SVGmag), sum absolute QRST integral (SAIQRST), and spatial QRS-T angle (QRSTa). Individual features of the GEH phenotype have been shown to be associated with the range of cardiovascular outcomes. The QRSTa has been shown to be associated with sudden cardiac death, ventricular arrhythmias, cardiovascular mortality, and broadly defined CVD.[12,16,18–21] Importantly, SVG and SAIQRST carry additional, complementary predictive value to the QRSTa.[12–14,22] Furthermore, VCG GEH is in part genetically determined and can characterize a genetic predisposition to CVD[23,24] and reflect a burden of cardiac memory.[25,26]

In all previous studies, five GEH features were considered separately, one by one. However, advancements in analytical approaches demonstrated the value of latent profile analysis for many biomarkers. For example, linear growth curve modelling revealed three different trajectories in pulse-wave velocity change during the COVID-19 pandemic, providing insight into cardiovascular health.[27] To capitalize on modern statistical methodology, we conducted the study to uncover latent profiles in GEH phenotype while jointly modelling all five GEH metrics at once, using multivariate analysis. We hypothesized that after adjustment for demographic and clinical characteristics, there is unobserved heterogeneity in GEH in Hispanic/Latino adults from several underlying background groups (possibly genetically determined and/or reflecting the unmeasured burden of paroxysmal arrhythmia).

Methods

We conducted a cross-sectional analysis of the baseline visit for the Hispanic Community Health Study/Study of Latinos (HCHS/SOL). The multicentre study was approved by the Institutional Review Board at each participating institution, and all participants signed informed consent before joining the study.

Study population

The HCHS/SOL is a multicentre, community-based longitudinal cohort study of cardiovascular risk factors in Hispanic/Latino adults aged 18–74 years.[28–30] Participants were enrolled in four communities: Bronx (New York), Chicago (Illinois), Miami (Florida), and San Diego (California), between March 2008 and June 2011. The HCHS/SOL design combined the intentional selection of Hispanic/Latino community areas and the random selection of households within those areas, aiming to include participants of Mexican, Cuban, Puerto Rican, Dominican, Central American, and South American origin. Geographic clusters were stratified by the proportion of residents ≥ 25 years of age with at least a high school education based on the 2000 Census. The targeted over-representation of persons 45–74 years of age was achieved by subsampling according to age.

This cross-sectional study included HCHS/SOL participants with available digital 12-lead ECG recordings ($n = 16\,212$ out of 16 415). After the exclusion of those with missing data on CVD status or cardiovascular risk factors ($n = 528$), the remaining 15 684 participants (96% of the study population) were included in this study.

Electrocardiogram and vectorcardiogram analysis: global electrical heterogeneity measurements

The resting 12-lead ECG recording in HCHS/SOL has been previously described.[9] The EPICARE Center (Wake Forest School of Medicine, Winston Salem, NC, USA) detected major and minor ECG abnormalities as defined in the Minnesota Code.[9]

The Tereshchenko Laboratory analysed fully de-identified ECG signals in a blinded manner. After at least two physician investigators (S.J.H., E.C.M., and L.G.T.) manually labelled each cardiac beat, the 12-lead ECG was transformed into XYZ ECG using Kors transformation. The time-coherent global median beat was constructed using only one (dominant) type of beat, and the origin of the heart vector was identified.[31] In this study, we included three categories of median beats. The normal (N) category included normal sinus, atrial paced, junctional, and ectopic atrial median beat. The ventricular paced (VP) category included VP median beat. The supraventricular (S) category included median beat of AF or atrial flutter with consistently one type of ventricular conduction.

The GEH was measured as previously described (*Figure 1*) and reported in the Supplementary material. Two investigators (K.T.H. and E.C.M.) performed quality control of automated ECG analysis with the aid of a visual display. The MATLAB (MathWorks, Natick, MA, USA) code is provided at https://physionet.org/physiotools/geh and https://github.com/Tereshchenkolab/Origin.

Prevalent cardiovascular disease and cardiovascular risk factors definitions

Prevalent CVD was defined as a self-reported history of stroke or coronary heart disease, which included a history of MI, coronary artery bypass grafting, or percutaneous coronary intervention. Hypertension was defined according to the 2017 American Heart Association/American College of Cardiology guidelines and the use of antihypertensive medications. Untreated hypertension categories included normal blood pressure (BP) if <120/80 mmHg, elevated BP (120–129/<80 mmHg), and hypertension I (130–139/80–89 mmHg), hypertension II (≥140/90 mmHg). Treated hypertension comprised a separate category. The use of antiarrhythmic drugs included the use of Class 1 or 3 antiarrhythmics, beta-blockers, calcium channel blockers, or digoxin. Diabetes was defined according to the American Diabetes Association as fasting plasma glucose ≥ 126 mg/dL, 2-h post-prandial plasma glucose ≥ 200 mg/dL, HbA1c ≥ 6.5%, self-reported diabetes diagnosis, or self-reported use of antihyperglycaemic medications. Hypercholesterolaemia/dyslipidaemia was defined as total cholesterol ≥ 240 mg/dL, LDL cholesterol ≥ 160 mg/dL, HDL cholesterol < 40 mg/dL, or receiving lipid-lowering medication.[32] Obesity was defined as a body mass index (BMI) ≥ 30 kg/m^2. Diet quality was assessed by a score according to the sex-specific quintile of daily intake of saturated fatty acids, potassium, calcium, and fiber, with the score of 5 representing the most favorable quintile (i.e. lowest quintile of intake for saturated fatty acids and highest quintile of intake for potassium, calcium, and fiber).[33] The four scores were summed, and the higher 40 percentile was considered a healthier diet.[32] Physical activity in a typical week was assessed according to the 2008 guidelines,[34] as meeting or not the guidelines level for moderate/heavy intensity work and leisure activities. The estimated glomerular filtration rate (eGFR) was calculated from serum creatinine and cystatin C using the new CKD-EPI creatinine–cystatin C equation fitted without race. Chronic kidney disease (CKD) was defined as urinary albumin to creatinine ratio (UAC) ≥ 30 or $eGFR_{cr\text{-}cys(AS)}$ < 60 mL/min/1.73 m^2. Post-menopausal females were identified via questionnaire and included both natural menopause and post-hysterectomy with removal of both ovaries.

Statistical analysis

Survey design and analysis aspects

The HCHS/SOL study sample was selected using a stratified two-stage area probability sample design.[29] We used the normalized weight that sums to the enrolled study participants from all four field centres ($n = 16\,415$) so that the degrees of freedom from the sum of the weights were not inflated when conducting statistical tests of significance. Generalized linear model analysis of complex survey data used Taylor linearization-based variance estimators. The primary sampling unit clustering variable was a combination of the Field Center and selected block group identifier. The stratum was a combination of the Field Center, Hispanic/Latino Household Proportion (high and low), and socio-economic status (high and low). The HCHS/SOL sampling weights (age, gender, and Hispanic/Latino background) were calibrated to the US 2010 Census within the specific HCHS/SOL target areas. In this study, we analysed the subpopulation of the HCHS/SOL study participants who met the eligibility criteria. As required by the survey study analytical standards, excluded participants were still assumed to be a part of the target population and, therefore, contributed to the variance calculations. We estimated population means and 95% confidence intervals (CIs) for continuous variables. Population means of circular variables were normally distributed and included in the analysis without transformations to facilitate the interpretation of the results. Unadjusted categorical prevalence estimates for the target Hispanic/Latino population in the four HCHS/SOL communities were calculated using survey logistic regression conditional margins.

Latent profile analysis models

To gain insight into spatial 3D SVG vector direction and magnitude (described by five continuous GEH variables) range, we fitted a multivariate, latent class/profile analysis, generalized structural equation model, and modelling joint probabilities (multiple responses) of five continuous GEH variables distributions (QRSTa, SVGaz, SVGel, SVGmag, and SAIQRST) as a mixture of three normal distributions (Gaussian family; identity link function). To determine how many latent profiles should be defined, we compared Akaike's information criterion and Bayesian information criterion of models describing one, two, and three latent profiles (see Supplementary material online, *Table S1*). The best fit was achieved by the model describing three latent profiles of GEH variables. The model used the multinomial logistic distribution to model the probabilities for the latent class and a linearized variance estimator for survey data estimation.

To obtain an insight into the potential nature of the unobserved heterogeneity, we included in the generalized structural equation model covariates characterizing demographic characteristics (age, sex, and ethnic background category), prevalent CVD, cardiovascular risk factors (hypertension, diabetes, smoking, hypercholesterolaemia/dyslipidaemia, obesity, CKD, level of physical activity, and diet quality), and attained education level (less than high school, high school or equivalent, greater than high school with some college, and university or college). Cigarette smoking was categorized as former, current, or never. All models were also adjusted for the type of median beat (N, S, or VP) and average RR interval. We obtained predicted posterior probabilities for each latent class for every study participant and categorized participants into three GEH profile groups. Membership in a

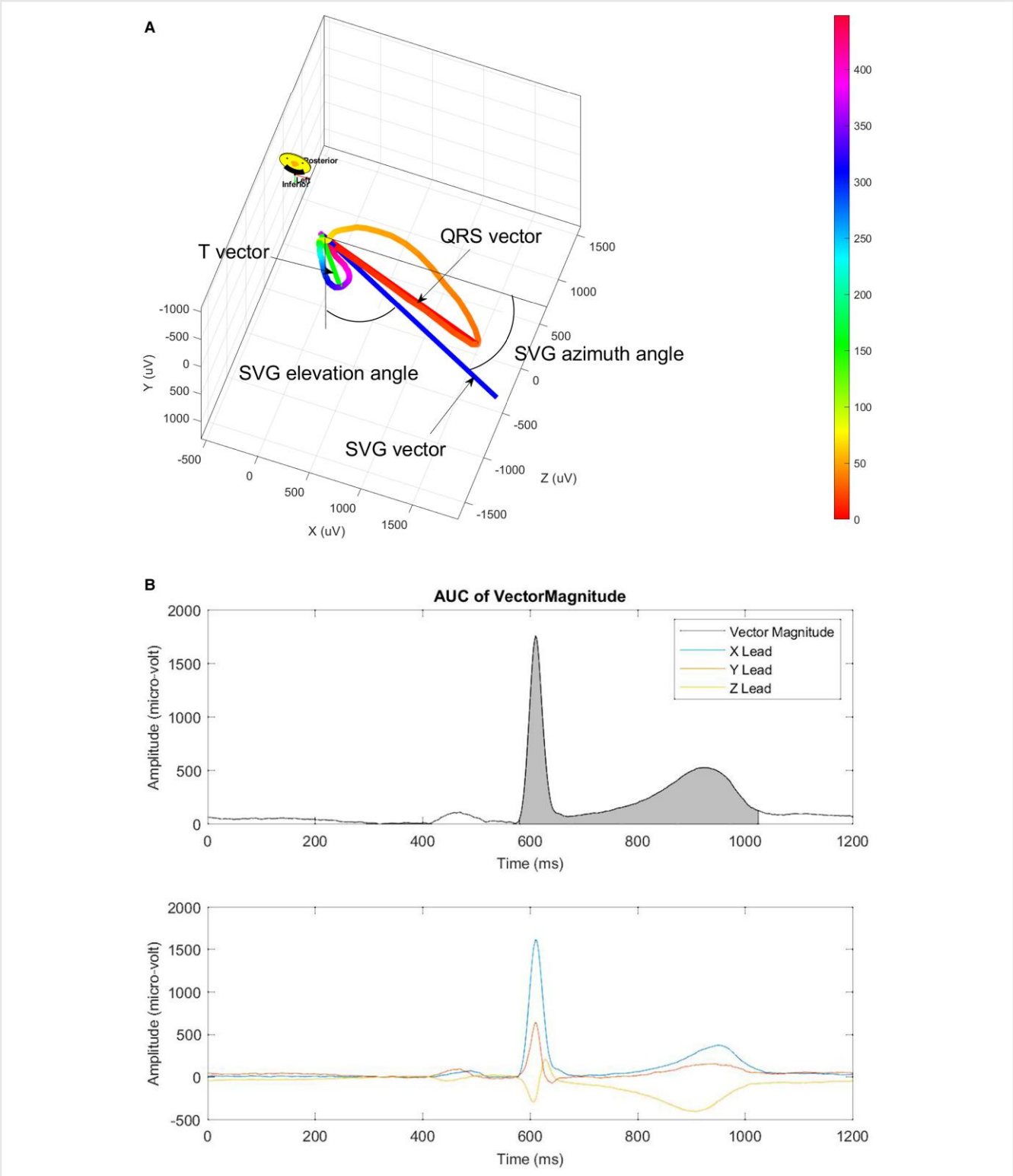


Figure 1 Representative example of vectorcardiogram (*A*) and measured global electrical heterogeneity phenotype, presented by five metrics: spatial QRS-T angle, 3D spatial ventricular gradient magnitude and direction (azimuth and elevation), and spatial ventricular gradient scalar sum absolute QRST integral (*B*). A 3D spatial ventricular gradient vector is a QRST integral on orthogonal XYZ leads. Spatial ventricular gradient scalar sum absolute QRST integral is an absolute QRST integral on orthogonal XYZ leads or a vector magnitude signal. VMQTi = 0.62 ∗ SAIQRST. Spatial ventricular gradient elevation indicates spatial ventricular gradient direction relative to a horizontal plane on a *Y*-axis, upward from 0. Spatial ventricular gradient azimuth indicates spatial ventricular gradient direction relative to a frontal plane on a Z-axis, with positive backward and negative forward values. AUC, area under the curve; SVG, spatial ventricular gradient.

Table 1 Latent class probabilities and descriptive statistics of global electrical heterogeneity variables

Predicted posterior probability, %	Class 1 23	Class 2 60	Class 3 17
Spatial QRS-T angle (°) population mean ± SD. Median (95% CI)	40.0 ± 10.2 38.6 (26.6–57.4)	47.7 ± 13.2 46.1 (30.8–69.9)	80.2 ± 26.8 74.6 (44.6–129.2)
SVG azimuth (°) population mean ± SD. Median (95% CI)	−23.8 ± 6.7 −23.2 (−34.5 to −14.2)	−19.1 ± 11.0 −17.4 (−32.6 t −6.0)	−4.0 ± 20.9 −5.1 (−31.9 to +38.9)
SVG elevation (°) population mean ± SD. Median (95% CI)	61.4 ± 4.1 61.5 (54.7–68.0)	61.8 ± 3.9 61.8 (56.3–67.9)	72.0 ± 11.6 69.3 (58.0–96.7)
SVG magnitude (mVms) population mean ± SD. Median (95% CI)	108.3 ± 22.6 107.7 (72.3–147.2)	71.4 ± 17.8 71.2 (42.9–101.8)	45.1 ± 11.9 44.5 (26.8–65.6)
SAIQRST (mVms) population mean ± SD. Median (95% CI)	203.4 ± 39.1 201.3 (143.3–272.1)	143.9 ± 31.2 142.2 (97.6–197.1)	120.1 ± 22.5 117.4 (86.5–157.4)
Average RR' (ms) population mean ± SD. Median (95% CI)	971 ± 132 970 (756–1192)	970 ± 132 967 (754–1198)	974 ± 141 978 (733–1210)

CI, confidence interval; SD, standard deviation.

latent class was defined by a non-overlapping probability of belonging to that class exceeding 50%. Next, we plotted histograms of five GEH variables for three latent class profiles. To gain insight into relationships between CVD and known cardiovascular risk factors with GEH, first, we compared unadjusted population means and proportions of demographic and clinical characteristics using ordered probit (assuming ordered latent classes) and multinomial logistic (assuming no natural ordering in latent classes) regression. Next, we compared the adjusted strength of association of CVD and cardiovascular risk factors with five GEH variables across three GEH profiles, with all covariates included in the model (age, sex, Hispanic background category, education attainment, prevalent CVD, hypertension, diabetes, smoking, hypercholesterolaemia/dyslipidaemia, obesity, CKD, level of physical activity, diet quality, type of ECG median beat, and average RR' interval). In addition, unadjusted relationships between continuous exposure variables (age, BMI, and height) and response GEH variables were explored using polynomial fit for the three latent class populations.

As previous studies showed significant sex differences in GEH in White and African American populations,[35–37] we compared population means (of the age when menses began, age of menopause, and number of alive births) and proportions (of currently pregnant and postmenopausal) across latent classes, in a subpopulation of women.

Statistical analysis was performed using STATA MP 17.0 (StataCorp LP, College Station, TX, USA); code is provided at https://github.com/Tereshchenkolab/statistics. Adjusted for multiple (10) hypotheses testing, $P < 0.005$ was considered statistically significant, which, nevertheless, should be interpreted with caution. The width of 95% CI represents descriptive statistics and should not be used in place of a hypothesis test.

Results

Study population

The population had a mean age of 41.1 years (95% CI 40.6–41.6), and 53.3% (95% CI 51.2–53.4) were females. The prevalence of CVD was 5.7% (95% CI 5.2–6.3), major ECG abnormalities 7.7% (95% CI 7.1–8.4), and ECG MI 2.3% (95% CI 2.0–2.7). Less than 1% used Class 1 or 3 antiarrhythmics (0.13%; 95% CI 0.06–0.28) and digoxin (0.18%; 95% CI 0.11–0.31), whereas 5.7% (95% CI 5.2–6.2) used beta-blockers.

Global electrical heterogeneity profiles

The latent profile analysis revealed that in the HCHS/SOL population (*Table 1*), there was a 23% probability for a participant of being in Class 1 with a narrow QRSTa (~40°) and large SVG magnitudes (SVGmag ~110 mVms; SAIQRST ~200 mVms), a 60% probability of being in Class 2 with an intermediate QRSTa (~50°) and intermediate magnitudes (SVGmag ~70 mVms; SAIQRST ~140 mVms), and a 17% probability that a participant would be in Class 3 with wide QRSTa (~80°) and small magnitudes (SVGmag ~45 mVms; SAIQRST ~120 mVms). There was a statistically significant difference in the probabilities of belonging to each class ($P < 0.0001$). The narrow QRSTa and large SVG profile (Class 1) was characterized by an SVG vector pointing more anteriorly and having the largest SVGmag and scalar value (SAIQRST), as shown in *Figure 2*. The wide QRSTa and small SVG profile (Class 3) was characterized by an SVG vector pointing more posteriorly and upward and having the smallest SVGmag and SAIQRST. The intermediate profile (Class 2) had an intermediate QRSTa and other GEH metrics. Spatial ventricular gradient elevation in Classes 1 and 2 was nearly identical.

Differences across global electrical heterogeneity profiles in association with cardiovascular disease and cardiovascular risk factors

The unadjusted association of prevalent CVD with latent classes was U shaped (*Table 2*). The lowest CVD prevalence was in Class 2, whereas both Classes 1 and 3 had a higher prevalence of CVD, major ECG abnormalities, and ECG MI. Interestingly, the prevalence of several risk factors had linear associations with latent classes. Class 1 had the highest prevalence of older age, hypertension, smoking, and use of antiarrhythmic drugs. However, latent Class 1 individuals were taller, with mean height gradually declining from Class 1 to Class 3.

Figure 3 and Supplementary material online, *Table S2* show the adjusted associations of demographic and clinical characteristics of HCHS/SOL participants with GEH metrics for each latent profile. Across all latent classes, Class 3 had the strongest association with CVD and its risk factors. In participants with Class 3 profile, prevalent CVD association with greater (pointing backward, towards left ventricle) SVGaz [+30° (95% CI 9–51)]. Untreated Stage 2 hypertension, similar to treated hypertension, had the strongest association with spatial QRSTa, which was wider by 32° (95% CI 26–56) in Class 3, by 12° (95% CI 6–17) in Class 2, and only by 6° (95% CI 3–10) in

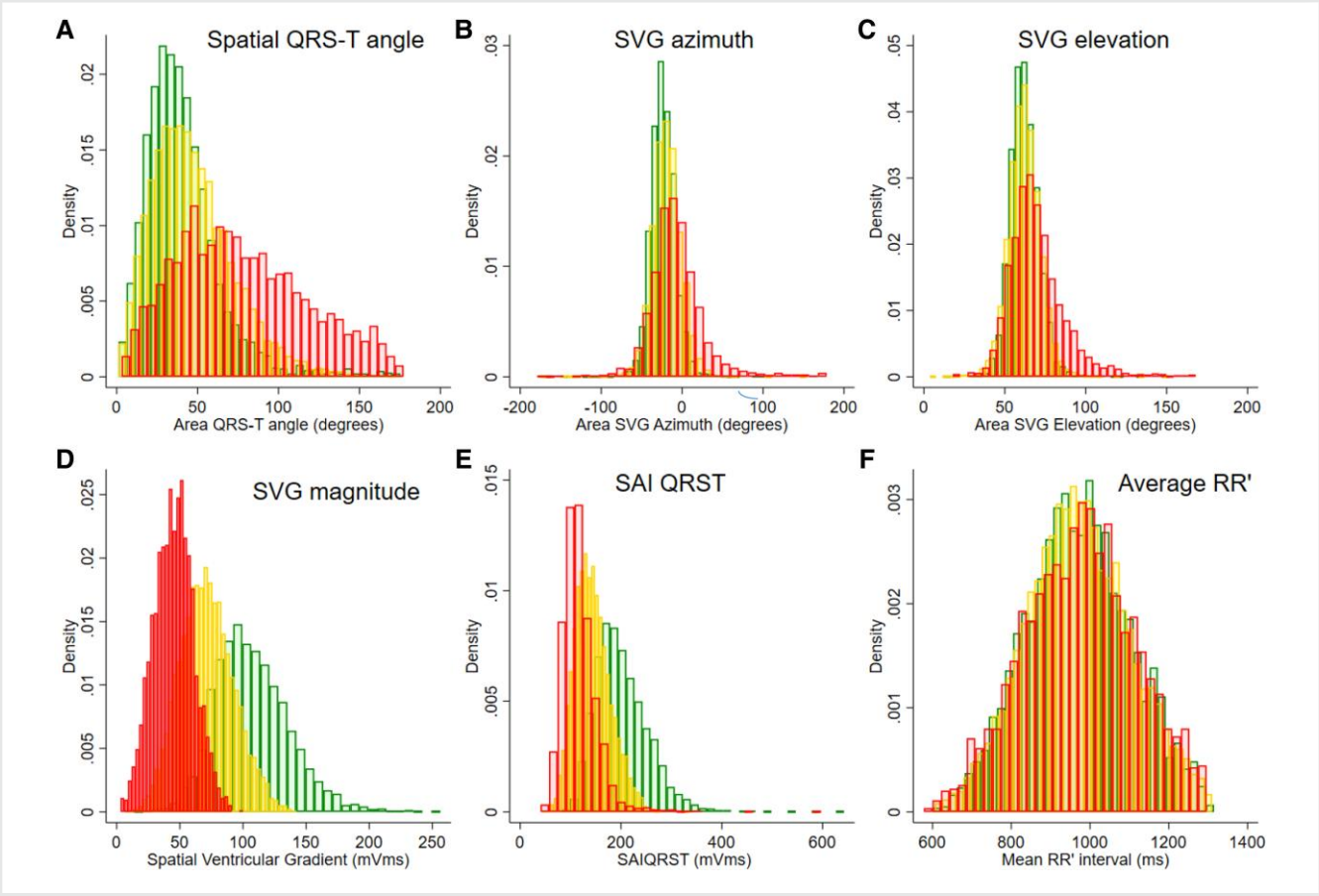


Figure 2 Predicted three latent profiles of global electrical heterogeneity variables. Histograms of (*A*) Spatial QRS-T angle, (*B*) spatial ventricular gradient azimuth, (*C*) spatial ventricular gradient elevation, (*D*) spatial ventricular gradient magnitude, (*E*) sum absolute QRST integral, and (*F*) average RR' interval in non-overlapping three classes of participants with a posterior probability > 0.5 of belonging to Class 1 (green), Class 2 (yellow), and Class 3 (red). SAIQRST, sum absolute QRST integral; SVG, spatial ventricular gradient.

Class 1, as compared with persons with normal BP. Major ECG abnormalities were observed in 15.3% (95% CI 13.4–17.5) of participants with Class 3 GEH profile, in contrast to only 7.0% (95% CI 6.0–8.2) in Class 1 and 5.9% (95% CI 5.3–6.7) in Class 2. Myocardial infarction was detected on ECG twice more frequently in participants with Class 3 profile [4.0% (95% CI 2.7–5.6), vs. 1.9% (95% CI 1.6–2.4) in Class 2 and 2.2% (95% CI 1.6–3.0) in Class 1]. There was no difference in minor ECG abnormalities proportions across GEH profiles [51.4% (95% CI 48.7–54.0) in Class 1; 40.1% (95% CI 38.5–41.6) in Class 2; 50.0% (95% CI 46.8–52.5) in Class 3].

Participants from Class 3 profile had a nonlinear association of age with SVG direction and QRSTa, as compared with participants from Class 1 and 2 profiles. After the age of 40, QRSTa rapidly increased and the SVG vector rapidly turned backward and upward in Class 3 population, in strike contrast to Class 1 and 2 populations, in whom QRSTa and SVG direction did not appreciably change with age (*Figure 4A–C*). As compared with 18–44 years of age adults, adults ≥ 65 years of age had a wider QRSTa by 8° (95% CI 2–14) in Class 1, by 14° (95% CI 9–17) in Class 2, and by 39° (95% CI 21–57) in Class 3 (see Supplementary material online, *Table S2*). Class 3 exhibited a greater increase in QRSTa, SVGaz, and SVGel across the range of BMI values, in contrast to Class 1 and 2 behaviour, showing minimal changes in QRSTa and SVG direction across the BMI distribution (*Figure 4*).

Some cardiovascular risk factors had a stronger association with GEH metrics in Class 1 population, as compared with Classes 2 and 3. Diabetes and hyperlipidaemia/dyslipidaemia had the strongest association with SAIQRST and SVGmag in Class 1 GEH profile, as compared with Classes 2 and 3. Class 1 population had a U-shaped association of BMI with SVGmag and SAIQRST, in contrast to Class 2 and 3 populations, demonstrating more linear relationships (*Figure 4*). Interestingly, in background groups with relatively high CVD prevalence (Puerto Ricans, Cubans, and Dominicans) compared with Mexicans, Hispanic/Latino background was associated with a narrower QRSTa and smaller SVGel but larger SVGaz in Class 1 and 2 populations (with QRSTa of 40–50°). Compared with Mexican, Cuban ethnic background was associated with larger SAIQRST and SVGmag across all latent classes (see Supplementary material online, *Table S2*).

Differences across global electrical heterogeneity profiles in association with female-specific risk factors

Sex differences in QRSTa and SVG direction were more prominent in Class 3 profile than Class 1 or 2 profile. However, sex differences in SVGmag and SAIQRST were more prominent in Class 1 profile. There was an apparent 'dose-dependent effect' of latent class membership on the strength of association of sex with GEH (*Figure 3*). In a fully adjusted model, SVGaz in females was more positive (i.e. pointing more posteriorly) than in males by 10° (95% CI 9–12) in Class 1,

Table 2 Demographic and clinical characteristics of participants in three latent classes

	Class 1 ($n = 3532$)	Class 2 ($n = 9675$)	Class 3 ($n = 2472$)	*P*
Age 18–44 years	57.4 (55.0–59.8)	59.2 (57.5–60.8)	65.3 (62.4–68.0)	0.015
Age ≥ 65 years	10.7 (9.3–12.4)	8.6 (7.8–9.4)	5.2 (3.7–7.2)	<0.0001
Mean age, years	40.0 (39.2–40.9)	41.3 (40.8–41.9)	41.7 (40.9–42.5)	0.002
Females	50.9 (48.5–53.4)	52.4 (51.0–53.7)	53.8 (50.8–56.8)	0.126
Education: university/college	29.8 (27.6–32.0)	27.1 (25.2–29.0)	24.2 (21.6–27.0)	0.019
Obesity	36.9 (34.5–39.4)	40.3 (38.7–41.9)	40.9 (37.8–44.0)	0.031
Mean BMI, kg/m^2	29.0 (28.7–29.3)	29.5 (29.2–29.7)	29.6 (29.2–30.0)	0.010
Height, cm	164.6 (164.1–165.1)	163.5 (163.2–163.8)	162.8 (162.2–163.4)	<0.0001
Never smokers	58.6 (56.1–61.1)	62.7 (61.2–64.1)	61.4 (58.4–64.2)	0.003
Diabetes	16.6 (14.9–18.4)	15.4 (14.3–16.5)	14.9 (12.9–17.0)	0.138
Physical activity meets guidelines	69.6 (67.3–71.4)	66.2 (64.6–67.8)	66.1 (63.3–68.9)	0.037
Treated hypertension	18.2 (16.5–20.0)	17.2 (16.0–18.3)	12.7 (10.8–15.0)	<0.0001
Untreated Stage 2 hypertension	9.7 (8.5–11.2)	7.4 (6.7–8.1)	5.5 (4.5–6.7)	<0.0001
Prevalent CVD	6.3 (5.2–7.8)	5.0 (4.5–5.6)	7.3 (5.8–9.3)	0.004
Use of any antiarrhythmic drug	9.5 (8.3–10.9)	8.7 (7.9–9.6)	8.2 (6.6–10.2)	0.794
Use of beta-blockers	6.7 (5.7–7.8)	5.5 (4.9–6.1)	5.1 (4.1–6.3)	0.029
Major ECG abnormalities	7.0 (6.0–8.19)	5.9 (5.3–6.7)	15.3 (13.4–17.5)	<0.0001
Minor ECG abnormalities	51.4 (48.7–54.0)	40.1 (38.5–41.6)	49.7 (46.8–52.5)	<0.0001
Myocardial infarction on ECG	2.2 (1.6–3.0)	1.9 (1.6–2.4)	3.9 (2.7–5.6)	0.001

Estimated proportions are reported as percentage with a 95% CI. *P*-value is from unadjusted ordered probit or multinomial logistic regression for survey data. $P < 0.005$ was considered statistically significant.
BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; ECG, electrocardiogram.

by 14° (95% CI 12–15) in Class 2, and by 21° (95% CI 16–26) in Class 3. As compared with males, SAIQRST was smaller in females by −51 mVms (95% CI −59 to −43) in Class 1, by −36 mVms (95% CI −40 to −32) in Class 2, and by −27 mVms (95% CI −32 to −22) in Class 3.

There was an association of latent class with female-specific cardiovascular risk factors, including post-menopause (*Table 3*). In Class 3, menses began at a slightly older age.

Discussion

This first multivariate latent profile analysis, conducted in the largest community-based cross-sectional study of diverse Hispanic/Latino adults in the USA, described three distinct GEH profiles. Exposure to cardiovascular risk factors had different effects on GEH phenotype in these three profiles/classes.

The wide QRSTa and small SVG (Class 3) GEH profile demonstrated the strongest association of CVD and cardiovascular risk factors with well-established biomarkers of adverse cardiovascular outcomes: wide QRSTa, SVG vector pointing upward and posteriorly (toward left ventricle), and small SVG (of both vectorial amplitude, SVGmag, and SAIQRST).[12,16,18,19,21,22,25,26,36,38–43] We observed a substantial portion of the study population (17%) with more than a 50% probability of having such a Class 3 GEH profile (wide QRSTa and small SVG). Notably, the proportion of the Hispanic/Latino population with Class 3 GEH profile (17%) exceeded the previously reported proportion of the study population with major ECG abnormalities (~8%),[9] diagnosed AF (~1%),[44] and systolic or diastolic dysfunction on echocardiogram (<10%).[45] Our study finding is consistent with previous epidemiological data, reporting a wide prevalence of cardiovascular risk factors in Hispanic/Latino adults.[2,46]

Notably, the vast majority of the HCHS/SOL population (60%) belonged to the intermediate, second class, which characterized the population that was resilient to exposure to cardiovascular risk factors. In second class population, exposure to risk factors had almost no (or very little) effect on GEH phenotype. This finding supports the notion that the Hispanic/Latino population is exceptionally resilient to cardiovascular risk factors.[28–30]

Nearly a quarter of the HCHS/SOL population was classified into the first GEH profile (narrow QRSTa and large SVG). The first profile, in contrast to the second profile, had significantly greater exposure to known cardiovascular risk factors (age, smoking, and hypertension), while manifesting by similar VCG GEH phenotype, which can be interpreted as especially resilient to the risk factors exposure profile. The remarkable resilience of latent Class 1 implies possible differences either in the genetic composition of Profile 1 population (e.g. via height)[47] or unmeasured differences in the exposures, e.g. due to the unmeasured burden of paroxysmal arrhythmias.[25,26,48] The cross-sectional nature of the present study limits the interpretation of observed differences between the first and second latent profiles. Further prospective studies will be needed for a better understanding of the observed differences between latent classes.

Global electrical heterogeneity is a 3D VCG phenotype of the well-known 'dispersion of repolarization'. Global electrical heterogeneity describes five features of a single 3D SVG vector, pinpointing the direction and magnitude of the greatest inhomogeneity in total recovery time.[11] Therefore, multivariate modelling of all five GEH features jointly, as a single phenotype, provides the most meaningful analytical framework.

Global electrical heterogeneity is associated with sudden cardiac death,[12,22] cardiovascular mortality,[38] left ventricular dysfunction,[17] and stroke.[16] In this study, we, for the first time, conducted a multivariate analysis of all five GEH variables together as a single response

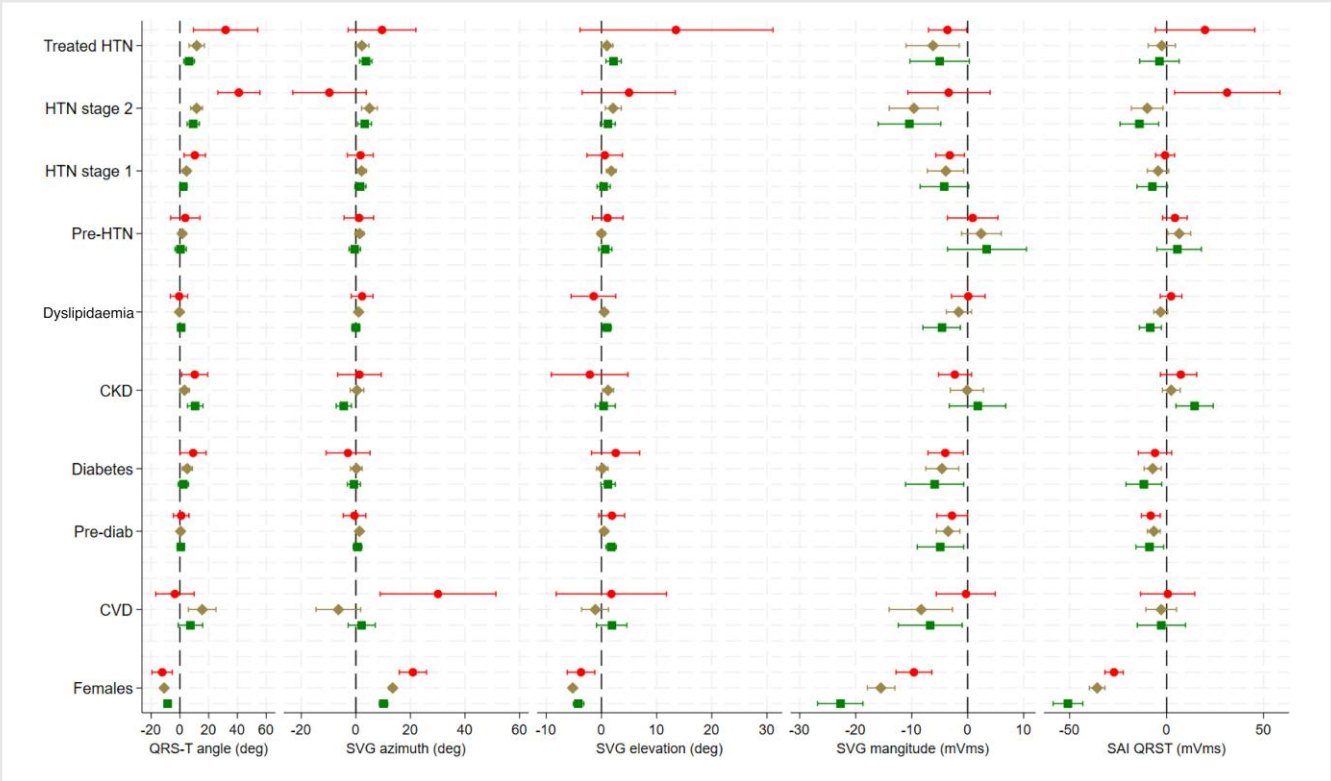


Figure 3 Estimated adjusted (for age, sex, Hispanic/Latino background, education attainment, hypertension, diabetes, smoking, dyslipidaemia, obesity, chronic kidney disease, physical activity, diet quality, average RR' interval, median beat type, and cardiovascular disease prevalence) differences and 95% confidence interval of global electrical heterogeneity variables, associated with demographic and clinical cardiovascular risk factors and prevalent cardiovascular disease as compared with a reference category in non-overlapping three classes of participants with a posterior probability > 0.5 of belonging to Class 1 (green square), Class 2 (brown diamond), and Class 3 (red circle). CKD, chronic kidney disease; CVD, cardiovascular disease; HTN, hypertension; SVG, spatial ventricular gradient.

phenotype. Our results confirmed previously observed complementary prognostic values of five GEH variables combined into the GEH risk score.[12] Interestingly, in this study, the third GEH profile included the lower tail of SVGmag distribution (45.1 ± 11.9 mVms), which was similar to SVGmag in mostly non-Hispanic systolic heart failure patients, recipients of primary prevention implantable cardioverter defibrillators (41.1 ± 24.6 mVms),[13] supporting the interpretation of latent Class 3 profile as likely abnormal. In African-American participants of the Jackson Heart Study,[35] SVGmag (69.6 ± 28.5 mVms) was within the intermediate (Class 2; 71.4 ± 17.8 mVms) range, consistently with the interpretation of latent Class 2 profile as 'resilient'. In all these studies, ECGs were recorded using the same manufacturer's ECG recording equipment and analysed by an identical analytical approach, suggesting that the comparison across populations is meaningful.

The interpretation of the latent Class 3 (wide QRSTa and small SVG) in this study is based on a large body of evidence accumulated over 20 years of research on QRSTa, which proved that a wide QRSTa is associated with sudden cardiac death, ventricular tachyarrhythmias, increased cardiovascular, and total mortality.[12,18,19,39–43,49] On the other hand, latent Classes 1 and 2 are novel endophenotypes. Future studies are needed to determine the clinical significance of latent Classes 1 and 2. Possibly, latent Class 1 reflects especially strong resilience manifested by minimal changes in VCG GEH phenotype despite greater exposure to CV risk factors. Joint modelling of five GEH features permits nuanced characterization of electrophysiological substrates, which requires further study.

Our finding of a considerable portion of the study participants with an elevated probability of having a Class 3 GEH profile is consistent with other HCHS/SOL studies reporting a high burden of CV risk factors (70–80% of the population with at least one major CV risk factor).[30] Nearly one out of every five Hispanics/Latinos in our study had an increased probability of carrying an altered electrophysiological substrate, which contradicted the previously reported low prevalence of clinically detected paroxysmal arrhythmia in the Hispanic population.[3,4,44] Long-term continuous ECG monitoring using an ECG patch explained discrepancies in the prevalence of clinically detected and monitor-detected arrhythmia in Hispanics,[48] which corroborated our findings.

An important unmeasured covariate contributing to latent GEH heterogeneity is the burden of paroxysmal (frequently undiagnosed) arrhythmias. Global electrical heterogeneity phenotype is significantly affected by cardiac memory.[16,23,25] In this study, membership in a latent GEH profile was associated with graded or U-shaped response in the strength of an association of known cardiovascular risk factors with GEH features, supporting biological plausibility. It is known that cardiovascular risk factors (age, hypertension, dyslipidaemia, and smoking) are associated with cardiac arrhythmia burden.

Last but not least, our findings suggest that GEH reflects female-specific cardiovascular risk factors. In this study, a shorter fertile life (from menarche to menopause) was associated with a wide QRSTa and small SVG (Class 3) GEH profile, carrying unfavourable cardiovascular risks.

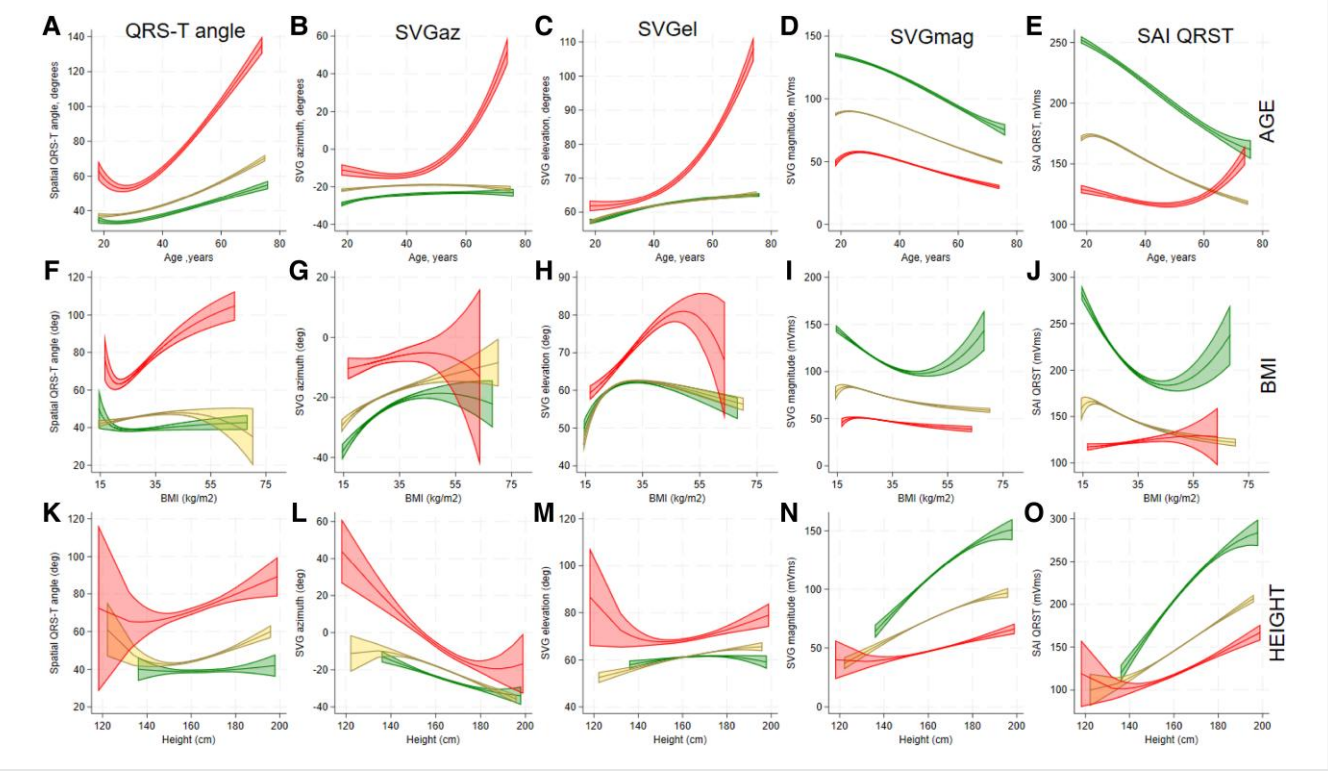


Figure 4 Fractional polynomial fit with 95% confidence interval of age (*A–E*), body mass index (*F–J*), and height (*K–O*) for prediction of spatial QRS-T angle (*A*, *F*, *K*), spatial ventricular gradient azimuth (*B*, *G*, *L*), spatial ventricular gradient elevation (*C*, *H*, *M*), spatial ventricular gradient magnitude (*D*, *I*, *N*), and sum absolute QRST integral (*E*, *J*, *O*). Unadjusted relationships between continuous variables age, body mass index, height (*X*-axes), and vectorcardiogram global electrical heterogeneity variables (*Y*-axes) are illustrated for populations of the latent Class 1 (green), Class 2 (brown and yellow), and Class 3 (red). BMI, body mass index; SAIQRST, sum absolute QRST integral; SVGaz, spatial ventricular gradient azimuth; SVGel, spatial ventricular gradient elevation; SVGmag, spatial ventricular gradient magnitude.

Table 3 Women-specific cardiovascular risk factors across latent classes

Characteristic	Class 1 ($n = 2155$)	Class 2 ($n = 5813$)	Class 3 ($n = 1456$)	*P*-value
Age of menarche, population mean (95% CI)	12.27 (12.15–12.39)	12.47 (12.40–12.54)	12.56 (12.40–12.71)	0.002
Age of menopause, population mean (95% CI)	46.41 (45.80–47.03)	46.18 (45.78–46.57)	45.75 (44.01–47.47)	0.428
Number of live births, population mean (95% CI)	2.61 (2.49–2.72)	2.56 (2.48–2.64)	2.54 (2.42–2.66)	0.206
Postmenopausal women, proportion (95% CI)	47.1 (43.9–50.3)	36.3 (34.5–38.1)	32.7 (34.5–38.1)	<0.0001
Currently pregnant women, proportion (95% CI)	0	0.91 (0.44–1.85)	0.33 (0.07–01.61)	<0.0001

CI, confidence interval.

Strengths and limitations

The study's main strength is the unique, large population of diverse Hispanic/Latino individuals. The study utilizes a robust design: a stratified two-stage area probability sample and is built on comprehensive phenotyping of cardiovascular risk.[30] The study uses a novel analytical approach (multivariate latent profile analysis, jointly modelling responses of five continuous GEH variables).

However, the study limitations have to be taken into consideration. Due to the cross-sectional study design, the causality of observed associations cannot be determined. Future studies will be needed to determine whether observed in this study three latent profiles, and the interpretation of their associations can be validated in different populations. In this study, CVD was self-reported and may be under- or mis-diagnosed.

Conclusions

In summary, our large study of more than 15 000 Hispanic males and females with diverse origin backgrounds (Mexican, Cuban, Puerto Rican, Dominican, Central and South American, and mixed) showed a substantial prevalence (17%) of individuals with a high probability of having an abnormal GEH profile (wide QRSTa, SVG vector pointing

upward, and posteriorly diminished magnitudes of SVG and SAIQRST), likely developed in response to the unmeasured burden of paroxysmal cardiac arrhythmias and/or subclinical CVD. Further studies of GEH are needed to validate its clinical value as the measure of subclinical CVD and cardiac memory in response to paroxysmal arrhythmia burden. Notably, 83% of the Hispanic/Latino population demonstrated GEH profiles suggesting resilience to cardiovascular risk factors exposure. Further studies of genetic architecture behind latent GEH profiles may help uncover underlying biological mechanisms of resilience and susceptibility to harmful exposures.

Supplementary material

Supplementary material is available at *European Heart Journal – Digital Health*.

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Conflict of interest: none declared.

Data availability

The data underlying this article were provided by the HCHS/SOL. Data requests are considered by the HCHS/SOL Coordinating Center.

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