Population Prevalence and Correlates of Prolonged QT Interval

Cross-Sectional, Population-Based Study From Rural Uganda

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ABSTRACT

Objectives: We aimed to estimate the prevalence and correlates of QT interval prolongation in rural Uganda.

Background: Major electrocardiographic abnormalities, including prolonged QT interval, have been shown to be independently predictive of adverse cardiovascular events among Western populations. Cardiovascular diseases are on the rise in sub-Saharan Africa with poorly characterized context-specific risk factors. An important question is whether ECG screening might have value in cardiovascular disease risk stratification in SSA.

Methods: We conducted a cross-sectional survey in a sample of adults participating in an ongoing whole-population cohort in Mbarara, Uganda, in 2015. Of 1,814 subjects enrolled in the parent whole-population cohort, 856 (47%) participated in the study. Participants completed 12-lead electrocardiography and cardiovascular disease risk factors assessment. We summarized sex-specific, heart rate variation–adjusted QT (QTa) defining prolonged QTa as >460 ms in women and >450 ms in men. We fit linear and logistic regression models to estimate correlates of (continuous) QTa interval length and (dichotomous) prolonged QTa. Models included inverse probability of sampling weights to generate population-level estimates accounting for study nonparticipation.

Results: We assessed data from 828 participants with electrocardiograms. The weighted population mean age was 38.4 years (95% confidence interval: 36.3–40.4). The weighted population was 50.4% female, 11.5% had elevated blood pressure, and 57.6% had a high-sensitivity C-reactive protein >1 mg/dl. The population mean QTa was 409.1 ms (95% confidence interval: 405.1–413.1), and 10.3% (95% confidence interval: 7.8–13.5) met criteria for prolonged QTa. Women had a higher mean QTa (421.6 ms vs. 396.3 ms; $p < 0.001$), and a higher proportion of women had a prolonged QTa (14.0% vs. 9.3%; $p = 0.122$) than did men. In multivariable-adjusted regression models, female sex and hypertension correlated with higher mean QTa and meeting criteria for prolonged QTa, respectively.

Conclusions: QT interval prolongation is highly prevalent in rural Uganda and may be more common than in high-income settings. Female sex, age, and high blood pressure correlated with QT interval prolongation. Future work should assess whether genetic predisposition or environmental factors in sub-Saharan African populations contribute to prolonged QT and clarify consequences.

Cardiovascular diseases (CVDs) are a growing cause of morbidity and mortality in sub-Saharan Africa (SSA) [1], yet the precise epidemiology of these conditions is not well characterized, in part due to limitations in diagnostic resources in the region [2]. Resting electrocardiography (ECG) is a low-cost, noninvasive technique that has potential for assessing prevalence and risk of CVD in low-income settings [3]. In the United States and Europe, major ECG abnormalities are independently predictive of major cardiovascular adverse events (MACE) [4]. For example, a prolonged QT interval has comparable predictive value for cardiovascular and all-cause mortality as that of many traditional risk factors [5].

However, epidemiological data on ECG abnormalities, including QT prolongation, and their correlates are based predominantly on studies performed in Western populations [6,7]. Notably, ethnicity is an effect modifier of the relationship between many ECG abnormalities and CVD

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outcomes. For example, the association between QT prolongation and MACE is considerably stronger in African Americans than in Caucasians in the United States [8]. Other determinants of QT interval prolongation include human immunodeficiency virus (HIV) infection, drug exposure, diabetes, hypertension, and genetics [9], also differ by region. Thus, establishing regional data on QT intervals to standardize norms and assess for correlations with CVD events in SSA is an important priority. Here, we leverage data from a community-based ECG screening within a population cohort to estimate the population distribution of prolonged QT intervals in a rural population in Uganda and describe its relationship with CVD risk factors. In the absence of local data, we use QT interval length norms defined in Western populations.

METHODS

Study design and setting

We conducted a cross-sectional survey of adults, 18 years and older, who attended a community health fair held over a 5-day period in Nyakabare Parish, Mbarara District, Uganda, in June 2015. The community health fair was advertised to individuals in the community by means of local radio advertisements and through community structures (e.g., church and social gatherings). There were no fees for participation in the health fairs. Nyakabare is a predominantly subsistence pastoral-agrarian community, with significant water and food insecurity [10]. Between May 2014 and June 2015, and preceding the health fairs, a parish-wide census was conducted with demographic and health data collection on 98% (1,814 of 1,851) of all eligible individuals, namely: adults 18 years of age and older (and emancipated minors ages 16–18 years) who considered Nyakabare their primary place of residence. Although pregnant women were not excluded from participation in the health fair, data were not collected on self-reported or biologic-tested pregnancy.

Data collection

Participants in the health fair had their height and weight measured. Blood pressure was measured in a seated position using automated sphygmomanometers (Omron HEM 705 LP, Omron Healthcare, Inc., Bannockburn, IL). Venous blood was collected to assess serum lipids, creatinine, C-reactive protein (CRP), and glycosylated hemoglobin (HbA1c) (Siemens DCA Vantage, Munich, Germany). HIV infection status was determined by rapid antibody testing according to Ugandan National HIV Testing Guidelines (2010) [11]. We defined diabetes mellitus and prediabetes mellitus as HbA1c $\geq$6.5% and 5.7% to 6.4%, respectively [12]. A questionnaire based on the International Physical Activity Questionnaire [13] and the WHO STEPS (STEPwise Approach to Surveillance) survey [14] was administered to collect individual participant data on tobacco use and physical activity. Physical activity was measured as metabolic equivalent of task in minutes per week and categorized as active, minimally active, and inactive following International Physical Activity Questionnaire standard classifications [13]. Lastly, previous medical and family histories of CVD were assessed by self-report. We also documented the use of any medication indicated for common noncommunicable diseases, including hypertension, asthma, heart failure, dyslipidemia, and diabetes mellitus.

Electrocardiogram collection and measurement

A 10-s, 12-lead ECG was recorded for each participant in the seated position [15] using a portable ECG machine (CardioCard Digital ECG Box with CardioCard software, Nasiff Associates, New York, NY). ECGs were collected as PDFs and converted to JPEG image format. Those that were visually assessed as being of adequate quality were digitized by conversion into US Food and Drug Administration standard extensible markup language (aECG FDA HL7 XML) file format using ECG Scan version 3.3.0 (Analyzing Medical Parameters for Solutions, New York, NY). Each digitized XML ECG tracing was then automatically annotated by on-screen digital calipers for QT and RR interval measurement using CalECG version 3.7.0 (Analyzing Medical Parameters for Solutions) [16]. Fully automatic measurements of QT and RR intervals were annotated on limb lead II using the tangent method [17]. The CalECG on-screen calipers automatically specify the onset of the QT interval as the first deflection of the QRS complex. The end of the T wave is estimated at the point at which a tangent line drawn from the steepest portion of the T wave intersects the isoelectric baseline. All CalECG measurements were visually verified by a study clinician (I.M.).

We averaged each of the 3 QT and RR intervals to obtain the final QT and RR intervals for analysis. We compared agreement between CalECG and manually derived intervals in a subset of participants for quality assurance purposes. Two reviewers (I.M. and R.M.) measured QT and RR intervals from 41 randomly selected ECGs using manual calipers. All measurements were made from limb lead II using the tangent method for QT interval measurement. Calculation of the correlation coefficient and the limits of agreement demonstrated that the CalECG and manual caliper-based methods were similar for the QT interval (Pearson correlation coefficient: $r = +0.96$, mean difference $\pm$ 2 SD = 12 $\pm$ 14.76 ms) and RR interval ($r = +0.96$, mean difference $\pm$ 2 SD = 25.0 $\pm$ 32.05 ms) [18].

Because of recent recommendations that discourage the use of Bazett formula for correction of heart rate–associated variation of the QT interval [19], we used the method described by Sagie et al. to adjusted for heart rate variability [20]. To do so, we fitted a linear model of QT interval regressed on RR interval and sex, estimating a β-coefficient of the RR interval of 0.187. We then calculated heart rate–adjusted QT (QTa) using the formula: $QTa = QT + 0.187*(1 - RR)$. The application of this formula in our study sample was intended to make the QT

TABLE 1. Estimated weighted baseline population characteristics

Characteristics	Weighted Estimate			
	Male	Female	p Value	Total Population
Sex, %	49.5	50.4	0.656	—
Age, yrs	36.1 (33.1–39.2)	39.8 (37.8–41.9)	0.027	38.4 (36.3–40.4)
≤30	46.4	35.2		40.7
30–50	33.0	38.0		35.5
>50	20.6	27.0	0.105	23.8
BMI, kg/m^2	22.4 (22.1–22.7)	26.2 (25.6–26.8)	<0.001	24.3 (23.8–24.7)
≤18.5	80.0	44.9		62.2
18.5–24.9	5.3	3.1		4.2
25–29.9	13.2	33.1		23.2
≥30	1.7	18.9	<0.001	10.3
History of stroke, %	4.6 (1.7–11.5)	1.6 (1.0–2.9)	0.065	3.1 (1.5–6.3)
History of heart disease, %	1.8 (0.6–4.9)	6.0 (0.4–8.4)	0.013	3.9 (2.8–5.6)
Current hypertension,* %	10.2 (6.9–14.9)	12.8 (9.8–16.5)	0.345	11.5 (9.2–14.4)
Systolic BP, mm Hg	125.2 (122.0–128.0)	121.6 (119.0–124.2)	0.339	123.2 (121.3–125.0)
Diastolic BP, mm Hg	77.5 (74.8–80.2)	79.6 (78.0–81.2)	0.037	78.4 (77.0–80.0)
HbA1c				
Prediabetes	3.1	10.3		6.8
Diabetes mellitus	1.6	2.3	0.001	2.0
HDL cholesterol, mg/dl				
≥50	28.7	22.7		25.6
40–49	22.0	32.3		27.2
<40	49.3	45.1	0.187	47.2
CRP, mg/dl				
≤1	53.1	31.9		42.4
1–3	35.7	47.0		41.4
>3	11.2	21.1	0.006	16.2
eGFR,* ml/min/1.73 m^2	150.60 (142.0–158.2)	133.5 (129.8–137.1)	<0.001	142.0 (137.2–146.6)
HIV seropositive, %	3.5 (1.9–6.2)	6.7 (4.3–10.4)	0.059	5.0 (3.5–7.1)
Physical activity category				
Inactive	9.0	12.1		10.5
Minimal	16.8	11.1		14.0
Active	74.3	76.7	0.286	75.5
Cigarette smoking				
Current	17.9	4.5		10.6
Former	14.7	14.9		14.5
Never	67.4	80.6	<0.001	74.1
Use of chronic medication, %	3.4 (1.9–5.9)	5.6 (3.9–7.9)	0.127	4.5 (3.3–6.1)

Values are mean (95% confidence interval) or %.

BMI, body mass index; BP, blood pressure; CRP, C-reactive protein; eGFR, estimated glomerular filtration; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; MDRD, Modification of Diet in Renal Disease.

*eGFR according to MDRD study equation.

interval heart rate–invariant (residual slope of regression: <0.001; 95% confidence interval [CI]: −2.88 to 2.88; p = 0.999).

Statistical analysis

We sought to estimate population-level QTa characteristics and correlates, using inverse probability of sampling weights to account for health fair nonattendance. To do so, we used a propensity score–based technique to correct the likelihood of nonresponse based on participants' features from the community census. First, we fit logistic regression models among all census respondents (N = 1,814) with health fair attendance as the outcome of interest and included covariates predicted to correlate with health fair attendance (N = 1,814): food and water insecurity; alcohol use; household asset ownership; sex; age; marital status; village of residence; distance from the health fair; difference between

TABLE 2. Weighted population estimates of ECG characteristics

	Weighted Estimates			
ECG Features	Male	Female	p Value	Population
QTa, ms	396.3 (390.2—402.5)	421.6 (417.6—425.5)	<0.001	409.1 (405.1—413.1)
QTcB, ms	403.5 (396.2—410.8)	434.2 (429.5—438.8)	<0.001	419.0 (414.3—423.7)
Prolonged QTa, %	9.3 (5.7—14.6)	14.0 (10.8—18.0)	0.122	11.7 (9.1—15.0)
Prolonged QTcB, %	9.5 (5.9—15.1)	11.1 (8.2—15.0)	0.586	10.3 (7.8—13.5)
Extreme QTa, %	0.8 (0.4—1.9)	3.3 (2.1—5.3)	0.002	2.1 (1.4—3.2)
Extreme QTcB, %	2.6 (1.0—6.8)	5.3 (3.6—7.7)	0.171	4.0 (2.6—5.9)
Normal ECG, %	70.7 (61.0—78.8)	69.7 (64.4—74.4)	0.848	70.1 (64.8—75.0)
IVCD	1.3 (0.04—0.4)	0.4 (0.0—1.6)	0.173	0.8 (0.0—2.1)
LV hypertrophy	1.3 (0.6—2.9)	0.9 (0.4—2.0)	0.444	0.1 (0.6—1.9)
LBBB	0.3 (0.0—2.3)	0.1 (0.3—1.8)	0.281	0.7 (0.0—1.8)
RBBB	1.3 (0.5—3.9)	0.7 (0.3—1.6)	0.298	1.0 (0.5—2.2)
Q-wave MI	0.8 (0.3—1.9)	0.8 (0.3—2.1)	0.976	0.8 (0.4—1.5)

Values are mean (95% confidence interval).
ECG, electrocardiography; IVCD, interventricular conduction delay; LBBB, left bundle branch block; LV, left ventricular; QTa, heart rate variation—adjusted QT; QTcB, Bazett-corrected QT; Q-wave MI, pathological Q wave myocardial infarction; RBBB, right bundle branch block.

the altitude of the household residence and the altitude of the health fair; educational attainment; self-reported HIV status; self-reported overall health; social network size; and index of social participation (see Online Methods). From this, we predicted the propensity to attend a health fair and then produced sampling weights as stabilized inverse probability of treatment weights (IPTW) using methods described previously [21]. Regression models with these weights were then used to make population-representative estimates. We assessed the validity of this method to correlate with population characteristics using variables that were not included in the IPT model, but for which we had values for the whole population from the census (Online Table 1).

We next estimated summary statistics, applying the IPTW to generate population-representative estimates. We created a graph of mean QTa stratified by age to evaluate their relationship; noting a nonlinear relationship between QTa and age, we categorized age as <30 years, 30 to 50 years, and >50 years for the remainder of our analyses. We next estimated the overall and sex-specific population prevalence of prolonged QTa, defined by a QTa ≥460 ms in women and ≥450 ms in men [19]. We repeated our estimates using extreme QTa as the outcome of interest, defined as QTa ≥500 ms for both men and women [19], and using sex-based Bazett-corrected QT (QTcB) (prolonged QTcB ≥470 ms in women and ≥450 ms in men; extreme QTcB ≥500 ms in both women and men), to allow for comparison with prior studies. We then fit multivariable log binomial regression models reporting relative prevalence as suggested by Reichenheim et al. [22] to estimate correlates of prolonged QTa, including sex, age strata (<30, 30—50, and >50 years), elevated Hb1Ac (≤5.7, 5.7%—6.5%, and ≥6.5%), hypertension (systolic <140 and diastolic <90 vs. systolic ≥140 or diastolic ≥90 mm Hg), estimated glomerular filtration rate (60—89, and ≥90 mL/min/1.73 m^2), body mass index (<18.5, 18.5—24.9, 25.0—29.9, and ≥ 30 kg/m^2), CRP (≤1, 1—3, and ≥3 mg/dl), smoking status (current, former, and never), serum high-density lipoprotein cholesterol (<40, 40—60 and >60 mg/dl), level of physical activity (inactive, minimal, and active), and HIV infection serostatus. We did not include current use of medication as few individuals in the dataset reported use of active medications (<5%). Adjusted models included all factors that achieved a significance level of $p < 0.25$ on univariate analysis. We repeated all analyses considering QTa as a continuous variable and fitting linear models to estimate correlates. Models were re-estimated with trimmed IPTW (i.e., removing probability weights >95% and <5%) to assess for robustness to outliers (Online Table 4). All statistical analyses were performed using Stata version 14.0 (StataCorp, College Station, TX) with a 2-sided p value of < 0.05 considered statistically significant.

Ethical considerations

All study procedures were reviewed and approved by the institutional review boards of Mbarara University of Science and Technology and Partners Healthcare as conforming to the ethical guidelines of the 1975 Declaration of Helsinki. Consistent with national guidelines, we also obtained clearance for the study from the Uganda National Council of Science and Technology and from the Research Secretariat in the Office of the President of Uganda. All study participants gave written informed consent for participation. Participants who could not write were permitted to indicate consent with a thumbprint.

RESULTS

Of 1,851 eligible adults in the parish, 856 (46.2%) participated in the health fair undergoing electrocardiography, and 828 (44.7%) had ECGs deemed of sufficient

quality to be included in the final study sample. Health fair attendees were more likely to be female ($p < 0.001$), older ($p < 0.001$), and have less formal educational attainment ($p < 0.001$) than nonattendees. Notably, attendees were twice as likely as nonattendees were to report very bad or bad health (1.4% vs. 0.7%, and 26.5% vs. 13.1%, respectively; $p < 0.001$) (Online Table 2). Of those who did attend the health fair, 28 (3.3%) participants had no ECG data. However, those missing ECG data were similar to the rest of the sample in terms of CVD risk factors (Online Table 3).

The weighted mean age for the population was 38.4 years (95% CI: 36.3–40.4) (Table 1). The population was 50.4% female, 11.5% had hypertension, 2.0% had diabetes, and 57.6% had a high-sensitivity CRP >1 mg/dl. The majority of the population had never smoked (74.1%) and maintained high levels of physical activity (75.5%). Compared with men, women were older (39.8 vs. 36.1 years; $p = 0.027$), had higher rates of systemic inflammation (CRP >1 mg/dl) (69.1 vs. 46.9%; $p = 0.003$), and were more likely to be obese (mean body mass index: 26.2 vs. 22.4 kg/m^2; $p < 0.001$).

Population-weighted characteristics were as follows: mean QTa: 409.1 ms (95% CI: 405.1–413.1); prolonged QTa: 11.7% (95% CI: 9.1–15.0); extreme QTa prevalence: 2.1% (95% CI: 1.4–3.2); prolonged QTcB prevalence: 10.3% (95% CI: 7.8–13.5); extreme QTcB prevalence 4.0% (95% CI: 2.6–5.9) (Table 2). Compared with men, women had higher mean QTa (421.6 ms vs. 396.3 ms; $p < 0.001$) and increased prevalence of extreme QTa (3.3% vs. 0.8%; $p = 0.002$) (Figure 1). Women also had increased prevalence of prolonged QTa, though the difference was not statistically significant (14.0% vs. 9.3%; $p = 0.122$). The mean QTcB was 403.5 ms in men and 434.2 ms in women ($p < 0.001$). QTa increased with age such that those aged 51 years and older had higher mean QTa than their younger counterparts (16–30 years old) did; however, this association was statistically significant only among women: 433.2 ms (95% CI: 426.1–440.4) versus 403.2 ms among men (95% CI: 392.3–414.2; $p < 0.001$).

In univariable models, female sex, obesity (body mass index ≥30 kg/mm^2), hypertension, CRP, estimated glomerular filtration rate, HbA1c, and physical activity were correlated with prolonged QTa. However, in multivariable-adjusted logistic regression models, only hypertension (adjusted relative prevalence: 1.4; 95% CI: 1.0–3.2; $p = 0.037$) and age (31–50 years: adjusted relative prevalence: 3.1; 95% CI: 1.4–6.8; and >50 years: adjusted relative prevalence: 3.3; 95% CI: 1.3–7.9) had a statistically significant association with prolonged QTa (Table 3). In multivariable-adjusted linear regression models, QTa specified as a continuous variable had a statistically significant association with female sex ($\beta = 21.2$; 95% CI: 14.0–28.3; $p < 0.001$) and age >50 years ($\beta = 14.0$; 95% CI: 4.6–23.3; $p = 0.004$) (Table 4).

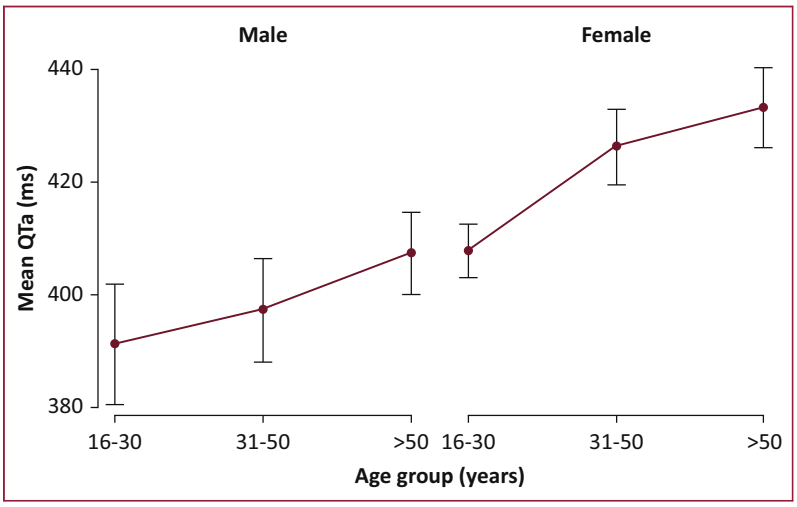

FIGURE 1. QTa according to age group and sex. QTa, heart rate variation–adjusted QT.

DISCUSSION

Our study is among the first population-based investigations of QT interval length and its correlates in SSA. Population prevalence of prolonged QTa was estimated to be 11.7%, and population prevalence of extreme QTa was estimated to be 2.1%. Both were more prevalent in women versus men. Our findings indicate an unexpectedly high prevalence of QT interval lengthening, which is particularly notable given the relatively young population age (<40 years) and the low burden of recognized QT prolongation risk factors.

In combination with prior data, our findings suggest that QT intervals might be more prolonged in SSA than elsewhere. In the only other population-based study from SSA, Dewhurst et al. (2014) [23] reported a mean QTcB of 418 ms ± 24 in men and 429 ms ± 24 in women, among a community of adults at least 70 years of age in rural Tanzania. Three population-based studies conducted in the United States estimated comparatively lower QT intervals. In the MESA (Multi-Ethnic Study of Atherosclerosis), which had a mean age of 62 years, and defined regression-corrected prolonged QTa as ≥460 ms in women and ≥450 ms in men [24], prolonged QTa was observed in only 3.5% of individuals, compared with 11.8% in our population. In the REGARDS (Reasons for Geographic and Racial Differences in Stroke) study [25], mean QTa was estimated to be 409 ms ± 1.1 among African American men and 417 ms ± 0.6 among African American women. Interestingly, we found longer QTa among women (421.6 ms) in our population, but shorter QTa in men (396.3 ms) compared with the African American sample in that study. Lastly, the JHS (Jackson Heart Study) [26], which enrolled an African American population in Mississippi, reported a prevalence of extreme QTcB (≥500 ms) in 0.5% of men and 0.4% of women, compared with 2.6% and 5.3% in our Ugandan population. Moreover, our increased estimates of extreme

TABLE 3. Weighted population univariate and multivariate correlates of prolonged QTa interval

	Univariate			Multivariate		
Characteristic	Relative Prevalence	95% CI	p Value	Adjusted Relative Prevalence	95% CI	p Value
Sex						
Male	Ref.	Ref.		Ref.	Ref.	
Female	1.5	0.9 to 2.6	0.136	1.2	0.7 to 2.0	0.450
Age, yrs						
≤29	Ref.	Ref.		Ref.	Ref.	
30–50	3.6	1.5 to 8.6	0.003	3.1	1.4 to 6.8	0.007
>50	4.4	1.8 to 10.6	0.001	3.3	1.3 to 7.9	0.009
BMI, mean, kg/m^2						
≤18.5	1.2	0.5 to 3.1	0.716	1.7	0.6 to 4.9	0.361
>18.5–24.9	Ref.	Ref.		Ref.	Ref.	
25.0–29.9	1.3	−0.5 to 3.4	0.625	1.4	0.4 to 4.5	0.607
≥30	2.0	0.7 to 5.8	0.183	1.3	0.3 to 4.7	0.715
HDL cholesterol, mg/dl						
<40	Ref.	Ref.				
40–59	0.9	0.4 to 1.8	0.706			
≥60	0.8	0.4 to 1.5	0.495			
Current hypertension						
<140/90 mm Hg	Ref.	Ref.		Ref.	Ref.	
≥140/90 mm Hg	2.5	1.4 to 4.4	0.002	1.4	1.0 to 3.2	0.037
eGFR, ml/min/1.73 mm^2						
≥90	Ref.	Ref.		Ref.	Ref.	
60–89	2.1	1.0 to 4.6	0.056	0.8	0.4 to 1.7	0.622
CRP, mg/dl						
≤1	Ref.	Ref.		Ref.	Ref.	
1–3	2.1	1.1 to 3.9	0.026	1.7	0.9 to 3.1	0.081
>3	1.8	0.9 to 3.9	0.118	1.2	0.5 to 2.5	0.707
HbA1c						
Normal	Ref.	Ref.		Ref.	Ref.	
Prediabetes	2.2	1.1 to 4.4	0.019	1.0	0.5 to 1.9	0.952
Diabetes	1.7	0.6 to 4.5	0.321	2.0	0.7 to 5.5	0.184
Physical activity category						
Inactive	Ref.	Ref.		Ref.	Ref.	
Minimal	0.8	0.3 to 2.3	0.738	0.7	0.3 to 2.1	0.560
Active	0.6	0.3 to 1.2	0.143	0.7	0.4 to 1.4	0.360
Cigarette smoking						
Never	Ref.	Ref.				
Former	1.2	0.7 to 2.0	0.438			
Current	1.5	0.6 to 3.4	0.330			

CI, confidence interval; Ref, reference; other abbreviations as in Tables 1 and 2.

QT prevalence are especially notable given the comparatively younger age and lower prevalence of traditional risk factors (i.e., hypertension 11.5%; current smoking 10.6%; mean age 38.4 years) in our Ugandan cohort (Table 1) compared with the Mississippi cohort (hypertension 57.6%; current smoking 18.0%; mean age 53.2 years) [26].

Our study identified female sex as a correlate of longer QTa and hypertension as a correlate of prolonged QTa. These findings are consistent with a recent systematic review of QT prolongation risk factors in high-income settings [9] and including 89,532 adults. That review also identified age, female sex, smoking, hypertension, hypokalemia, use of diuretic agents and arrhythmogenic drugs, and history of myocardial disease as predictive of prolonged QT. The association of QT prolongation with body mass index in our study was moderate, although we did not estimate a statistically significant correlation with diabetes, dyslipidemia, or renal failure. Although we observed associations between dichotomized and continuous QTa and body mass index, CRP, smoking, and HbA1c on univariate analysis, these associations did not persist in multivariable-adjusted regression models. Notably, the relationship between CRP and QTa has

TABLE 4. Weighted population univariate and multivariate correlates of (continuous) QTa interval

	Univariate			Multivariate		
Characteristic	Coefficient	95% CI	p Value	Coefficient	95% CI	p Value
Sex						
Male	Ref.	Ref.		Ref.	Ref.	
Female	25.6	18.0 to 33.3	<0.001	21.2	14.0 to 28.3	<0.001
Age, yrs						
≤29	Ref.	Ref.		Ref.	Ref.	
30–50	14.3	5.4 to 23.2	0.002	8.2	−0.4 to 17.9	0.062
>50	24.2	15.5 to 32.9	<0.001	14.0	4.6 to 23.3	0.004
BMI, mean, kg/m^2						
≤18.5	0.9	−11.0 to 12.7	0.886	9.6	−4.3 to 23.6	0.177
>18.5–24.9	Ref.	Ref.		Ref.	Ref.	
25.0–29.9	9.0	−3.9 to 21.8	0.171	10.2	−4.0 to 24.3	0.159
≥30	17.8	4.3 to 31.4	0.010	11.3	−4.1 to 26.7	0.151
HDL, mg/dl						
<40	Ref.	Ref.		Ref.	Ref.	
40–59	6.3	−1.6 to 14.2	0.116	1.6	−7.4 to 10.7	0.716
≥60	−1.5	−9.1 to 6.0	0.690	−4.5	−14.3 to 5.3	0.368
Current hypertension						
<140/90 mm Hg	Ref.	Ref.		Ref.	Ref.	
≥140/90 mm Hg	11.9	2.8 to 20.9	0.010	8.7	−4.7 to 22.1	0.202
eGFR, ml/min/1.73 mm^2						
≥90	Ref.	Ref.		Ref.	Ref.	
60 to 89	19.3	4.7 to 34.0	0.010	−1.7	−12.2 to 8.8	0.879
CRP, mg/dl						
≤1	Ref.	Ref.		Ref.	Ref.	
1–3	8.2	1.2 to 15.1	0.022	0.7	−7.8 to 9.1	0.878
>3	12.1	4.1 to 20.0	0.003	0.7	−7.9 to 9.2	0.879
HbA1c						
Normal	Ref.	Ref.		Ref.	Ref.	
Prediabetes	16.3	1.8 to 30.8	0.028	−4.4	−14.8 to 5.6	0.384
Diabetes mellitus	23.3	1.7 to 44.9	0.034	17.5	−12.9 to 47.8	0.259
Physical activity category						
Inactive	Ref.	Ref.				
Minimal	−3.5	−16.3 to 9.3	0.595			
Active	−4.5	−13.4 to 4.5	0.329			
Cigarette smoking						
Never	Ref.	Ref.		Ref.	Ref.	
Former	6.9	−10.2 to 14.0	0.056	0.3	−8.3 to 8.9	0.950
Current	−4.5	−15.6 to 6.5	0.423	0.3	−13.5 to 14.1	0.965

Abbreviations as in Tables 1 to 3.

been previously demonstrated in the setting of chronic inflammatory diseases in high-income settings [27]. This putative link between systemic inflammation and arrhythmic risk, and our observation of highly prevalent (approximately 60%) systemic inflammation (CRP >1 mg/dl) in an apparently healthy population, warrant further investigation.

The relevance of our findings for the health of individuals in rural SSA is unknown. QT prolongation is associated with functional re-entry, torsade de pointes, sudden cardiac death, and coronary heart disease [9]. In both individuals with multiple comorbidities [28], and in the general population, QT interval prolongation is predictive of cardiovascular and all-cause mortality. Such associations between QT prolongation and MACE are comparable in magnitude to the effect of many traditional CVD risk factors [29]. Furthermore, QTc values >500 ms are strongly linked with risk of torsade de pointes and sudden cardiac death [30]. However, current clinical guidance recommends against routine ECG screening [31]. Indeed, to date no studies have demonstrated benefit of QT interval screening on patient outcomes in Western settings. Thus, an important question for the field is whether ECG

screening might have additional value in SSA where we report significantly higher prevalence of prolonged QTa in a relatively young and healthy population.

Strengths and limitations

The major limitation of our study is its cross-sectional design, which limited our ability to infer causal associations. The cross-sectional design also limited our ability to investigate clinical outcomes (e.g., MACE) over longitudinal follow-up. However, as a population-based study, our results are generalizable to rural Uganda. Moreover, our ability to make population-level inferences is strengthened by the placement of our study within a larger census covering nearly 100% of our study population. Differential participation in the health fairs was accounted for with the use of IPTW-adjusted models to derive population-level estimates. Our study might also be limited by residual confounding from known and unmeasured factors related to QT duration. For example, we did not measure electrolytes such as potassium and magnesium concentrations or current medication use, all of which are known to affect QT intervals. However, we did collect data on chronic medication use, which was rare in this study population (4.4%), so it is unlikely to be a major confounder. In a related study in the same population cohort, no individual reported use of quinolones, macrolides, or neurotropic medications, which are known to affect QT intervals [32].

CONCLUSIONS

In summary, this study is among the first population-based studies of QT interval prolongation in rural SSA. We estimated a high prevalence of prolonged QTa in a relatively young rural SSA population, yet failed to identify typical QTa risk factors. Our findings should trigger additional study of the factors contributing to prolonged QT in this setting and its downstream effects on health. Most importantly, additional data are needed to understand context-specific QT interval norms, their clinical, environmental, and genetic determinants, and whether and how they contribute to MACE or death in this setting.

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APPENDIX

Description of variables used in the inverse probability of treatment weights.

Food and water insecurity

Water insecurity. This is a composite of several variables related to water:

1. In the past 30 days, how often did you worry about whether your household would have enough water for all of its needs?
2. In the past 30 days, how often did you or any household members collect water for drinking from an undesirable or dirty water source because you could not collect water from a preferred or clean source?
3. In the past 30 days, how often did you or any household members drink water that you thought might not be safe for health?
4. In the past 30 days, how often did you or any household members drink less water than you needed because there was not enough water or because it was too difficult to collect more water?
5. In the past 30 days, how often did you or any household members use less water than you needed because there was not enough water or because it was too difficult to collect more water?
6. In the past 30 days, how often was there no water at all in your household because it was too difficult to collect more water?
7. In the past 30 days, how often did you or any household members go to sleep at night thirsty because there was not enough water?
8. In the past 30 days, how often did you feel angry or frustrated about not having enough water for the household?

Each question was answered on a 0 to 3 scale, 0 meaning never, 1 meaning rarely, 2 meaning sometimes, and 3 meaning often. Total score was calculated by summing all questions. This total score was then quintiled.

Food insecurity. This is a composite of several variables related to food:

1. In the past 30 days, how often was there no food at all in your household because you lacked money to purchase more?
2. In the past 30 days, how often did you or any household members go to sleep at night hungry because there was not enough food?
3. In the past 30 days, how often did you or any household members go a whole day without eating anything because there was not enough food?

Each question was answered on a 0 to 3 scale, 0 meaning never, 1 meaning rarely, 2 meaning sometimes, and 3 meaning often. Total score was calculated by summing all questions. This total score was then quintiled.

Alcohol use

This variable measured whether the survey participant was a heavy drinker. The heavy drinker variable was created using 3 measures of alcohol use, including bingeing ("In the past year, did you ever take 6 or more drinks in a single morning, afternoon, or night?"), spending on alcohol ("In the past 30 days, did you yourself spend more than 25,000 USh on any kind of alcohol?"), and time spent intoxicated ("In the past 30 days, did you experience drunkenness or intoxication on 3 or more of those days?"). A "Yes" answer to any of those 3 questions classified the respondent as a heavy drinker.

Household asset ownership

The household asset index was created through principal components analysis, including ownership of land (number of plots), a radio, a lantern, a bike, a television, an electric iron, a *boda-boda* (motorcycle), a refrigerator, a stove, a car, a ventilated improved pit latrine, cement walls, and cement floors. The household asset index did not include variables with many missing observations (number of cows, number of goats, number of chickens, ownership of a mobile phone, number of rooms in house, ownership of a rainwater harvesting tank). The household asset index was then quintiled.

Sex

Self-reported sex of the survey respondent.

Age

Age of the survey respondent categorized as 17, 18 to 25, 26 to 35, 36 to 45, 46 to 55, or 56 years and older.

Marital status

Self-reported marital status of the survey respondent (married/cohabitating, single/never married, or separated/divorced/widowed).

Village of residence

Village of residence of the survey respondent (Buhingo, Bushenyi, Nyamikanja I, Bukuna II, Nyakabare, Bukuna I, Rwembogo, or Nyamikanja II).

Distance from the health fair

This variable measured the distance between the survey respondent's village and the health fair site. There were 3 different health fair sites, and each fair occurred on a different day. Using the registration day of the respondent to determine which health fair site they attended, and the coordinates of the respondent's village, distance between respondent village and health fair site was calculated using Stata's geodist command (Stata Corp, College Station, TX). The latitude and longitude of all 3 health fair sites were averaged to compute average village to health fair distances, and this was used to fill in the missing values for respondents who did not attend the health fair.

Difference between the altitude of the household residence and the altitude of the health fair

This variable measured the altitude between the survey respondent's village and the health fair site. There were 3 different health fair sites, each occurring on a different day. Using the registration day of the respondent to determine which health fair site they attended, and the altitude of the respondent's village, altitude between respondent village and health fair site was calculated. The altitudes of all 3 health fair sites were averaged to compute average village to health fair altitude differences, and this was used to fill in the missing values for respondents who did not attend the health fair.

Educational attainment

Educational attainment category of the survey respondent (none; some primary, P1—P6; completed primary, P7—P8; more than primary, S1—S6, vocation, or university).

Self-reported HIV status

Self-reported human immunodeficiency virus (HIV) status of the survey respondent (positive or negative).

Self-reported overall health

Self-reported overall health of the survey respondent (very good, good, bad, or very bad).

Social network size

This variable measured the survey respondent's social network size. The survey respondent was asked to name up to 6 people (18 years or older) in 5 categories (up to 30 people total) that they share some sort of social relationship with. The categories included people with whom the survey respondent spent time for leisure, enjoyment, or relaxation; people with whom the survey respondent discussed any kind of money matters; people to whom the survey respondent had gone to for emotional support; people with whom the survey respondent discussed any kind of health issue; and people with whom the survey respondent shared, borrowed, received, or exchanged any food. The number of people named by the survey respondent was used as an approximate measure for social network size.

Index of social participation

This variable measured the survey respondent's social participation through counting the number of social groups the respondent is a part of. This included vocational groups, positive living groups (for HIV-positive people), local council committees, water committees, village health team groups, National Agricultural Advisory Services groups, revolving fund/savings and credit cooperative organizations/any other registered savings groups, church or other religious groups, women's groups, and gardening committees.

ONLINE TABLE 1. Comparison of population estimates based on weightings from inverse probability of health fair attendance models vs. true population statistics

Characteristic	Weighted Estimate (95% CI)	True Population Estimate
Lifetime consumption of alcohol, %		
Never	42.3 (36.3—48.5)	40.9
>5 yrs ago	17.2 (13.9—21.0)	17.5
1—5 yrs ago	11.3 (7.7—16.4)	9.8
<1 yr ago	29.2 (24.9—34.0)	31.7
Waist circumference, cm	85.6 (84.1—87.1)	85.3
Self-reported HIV status, %	8.3 (6.1—11.1)	8.7
Self-reported happiness, %		
Not happy	17.0 (13.9—20.7)	17.3
Fairly happy	70.6 (64.3—76.2)	72.4
Very happy	12.4 (7.5—19.8)	10.0

CI, confidence interval; HIV, human immunodeficiency virus.

ONLINE TABLE 2. Characteristics of health fair attendees vs. nonattendees

Characteristic	Attendees (n = 829)	Nonattendees (n = 928)	p Value
Sex			
Female	62.4	48.6	<0.001
Age, yrs	43.6 (42.3—44.8)	34.1 (33.1—35.1)	<0.001
≤30	4.3	16.5	
30—50	65.6	69.5	
>50	30.1	14.0	<0.000
Formal educational attainment			
None	18.5	11.7	
Some primary education	34.2	23.1	
Completed primary education	23.5	20.9	
At least secondary education	23.8	44.4	<0.001
Self-reported health			
Very bad	1.4	0.7	
Bad	26.5	13.1	
Good	59.6	71.1	
Very good	12.6	15.0	<0.001

Values are mean (95% confidence interval) or %.

ONLINE TABLE 3. Comparison of characteristics of participants with and without ECG data

Characteristic	With ECG Data (n = 828)	Missing ECG Data (n = 28)	p Value
Age, yrs	43.9 (42.7 to 45.1)	44.7 (38.0 to 51.30)	0.822
Male sex	37.1 (306)	50.0 (14)	0.2
Body mass index, kg/m^2	24.7 (24.3 to 25.0)	24.1 (22.7 to 25.4)	0.524
Diabetes mellitus	2.8 (1.6 to 3.9)	0 (0)	0.428
Hypertension	15.2 (12.8 to 17.7)	13.8 (1.2 to 26.3)	0.833
Prior AMI or heart failure	5.6 (4.0 to 7.1)	6.9 (−2.3 to 1.6)	0.758
Prior stroke	2.7 (1.6 to 3.8)	3.5 (−3.2 to 11.0)	0.796

Values are mean (95% confidence interval) or % (n).
AMI, acute myocardial infarction; ECG, electrocardiography.

ONLINE TABLE 4. ECG outcomes presented with weights trimmed at the 5th and 95th percentiles

ECG Finding	Study Sample Estimates (n = 828)	Trimmed Weight Population Estimate (95% CI)
Normal ECG, %	68.1	68.8 (65.0—72.3)
IVCD, %	0.7	0.9 (0.3—2.2)
LV hypertrophy, %	1.7	1.3 (0.8—2.3)
LBBB, %	0.7	0.8 (0.3—2.1)
Q-wave MI, %	1.2	0.9 (0.5—1.8)
RBBB, %	1.1	1.2 (0.5—2.6)

IVCD, interventricular conduction delay; LBBB, left bundle branch block; LV, left ventricular; Q-wave MI, pathological Q wave myocardial infarction; RBBB, right bundle branch block; other abbreviations as in Online Tables 1 and 3.