Relation of Marital Status and QT Interval Prolongation (from the Third National Health and Nutrition Examination Survey)

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Although the link between marital status and mortality is well established, the pathophysiological basis is unclear. An investigation of the association of marital status with prolonged QT interval may highlight the underlying mechanism for poor outcomes associated with being unmarried. This analysis included 6,562 participants (mean age 58.6 years, 52% women, 50.1% non-Hispanic whites) without a history of cardiovascular disease from the Third National Health and Nutrition Examination Survey. QT was automatically measured from digital 12-lead electrocardiogram in a central reading center. Marital status was defined by self-report as married and unmarried (never married, divorced/separated or widowed). A multivariable logistic regression model was used to examine cross-sectional association between marital status and prolonged QT interval (≥450 ms in men, ≥460 ms in women). Compared with married, unmarried was associated with 46% higher odds of the prolonged QT interval (odds ratio [OR] 95% confidence interval [95% CI]: 1.46[1.16−1.83]). This association was stronger among men versus women (OR[95% CI]: 1.75[1.27−2.41] vs 1.26[0.92−1.73] respectively; interaction p value = 0.03) and in younger versus older participants (OR [95% CI]: 1.72[1.21−2.42] vs 1.40[1.05−1.88], respectively; interaction p value = 0.002). When the types of unmarried were compared to married, a dose-response relation with prolonged QT was observed with the highest odds in never married followed by divorced/separated, and then widowed. In conclusion, marital status is associated with a prolonged QT interval, especially among men and younger participants. Prolonged QT interval may indicate a biologic substrate through which social isolation defined by unmarried state increases the risk of poor outcomes in the future. **(Am J Cardiol 2019;124:211−215)**

Social isolation increases the risk of premature death, and marriage is a rough proxy for social connectedness.[1] Being unmarried has been associated with increased risk of death including cardiovascular disease (CVD) death.[2−4] The underlying pathophysiological basis for the relation between marital status and poor outcomes is unclear. However, various explanations have been proposed such as modification of health behaviors, widening of social networks, and the possibility of selection bias wherein healthy subjects tend to enter marriage more frequently than unhealthy subjects confer a survival advantage.[5] One approach that may provide insight into the mechanisms by which marital status impacts survival is to explore the association of marital status with well-defined pathophysiological markers that have established prognostic value in prediction of similar outcomes. QT interval, a commonly reported electrocardiographic interval on 12-lead electrocardiogram (ECG), has been consistently associated with increased risk of all-cause death and CVD death.[6] Therefore, we examined the relation between marital status and prolonged QT interval in participants free of clinical CVD at baseline using data from the Third National Health and Nutritional Examination Survey (NHANES-III). We hypothesized that compared with married participants, unmarried (widowed, divorced/separated, and never married) participants will be associated with a higher prevalence of prolonged QT interval.

Methods

NHANES is a periodic survey of the noninstitutionalized civilian population in the United States. Its principal aim is to determine estimates of disease prevalence and health status of children and adults. The structure of the NHANES III (1988 and 1994), its components, and resulting data are published somewhere else.[7] The NHANES III study was approved by the National Center for Health Statistics Research Ethics Review Board, and documented consent was obtained from participants.

For this analysis, we only considered NHANES-III participants who underwent an ECG recording (n = 8,561). We excluded participants with prior CVD (coronary heart disease, heart failure, and stroke), those on antiarrhythmic medications and missing key covariates. After exclusions

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(n = 1,999), 6,562 participants were available for final analysis.

Marital status was self-reported at household interview. Patients listed their marital status as married, divorced, separated, widowed, or never married. Divorced and separated states were combined into 1 group for this analysis and will be referred to as the *divorced/separated* group.

Age, gender, race/ethnicity, smoking status, leisure time physical activity were self-reported. Income was assessed using the poverty income ratio, which is the ratio of the midpoint of observed family income category to the official poverty threshold (scaled to family size). To define low versus high family income, the poverty income ratio was dichotomized into below 1.00 (below the official definition of poverty) and 1.00 or greater (income above the poverty level) respectively. Body mass index was calculated from height and weight measurements. Blood pressure (mm Hg) was measured using a mercury sphygmomanometer according to the American Heart Association recommendations. Blood pressure was taken while seated, using a standard mercury sphygmomanometer and up to 3 measurements were averaged. Blood samples were collected through venipuncture by a phlebotomist. Samples were analyzed for total cholesterol, high-density lipoprotein cholesterol , triglycerides and glucoseand so on, using laboratory procedures as reported by National Center for Health Statistics.[7] Hypertension was defined as systolic blood pressure ≥130 mm Hg, or diastolic blood pressure ≥85, or the use of antihypertensive medications. Diabetes was defined as blood sugar level ≥126 mg/ml or use of antidiabetic medications. Hyperlipidemia was defined as serum total cholesterol ≥200 mg/ml or triglycerides ≥150 mg/ml or use of antihyperlipidemic medications.

Resting 12-lead ECGs were obtained with a Marquette MAC 12 system (Marquette Medical Systems, Milwaukee, WI) during the mobile examination visits by trained technicians. Analysis of ECGs was achieved through a computerized automated process and visual inspection by a trained technician located in a centralized core laboratory. Heart rate-corrected QT was calculated using the NHANES specific QT correction formula.[8] Prolonged QT was defined as QT ≥ 460 ms for women and ≥450 ms for men. We used the QRS correction formula to define prolonged QT in participants with bundle branch block, that is, QRS ≥ 120 ms.[9]

Baseline characteristics were tabulated and compared by married and unmarried status. Student *t* test was used to compare the continuous variables while the chi-square test was used to compare categorical variables.

Multivariable logistic regression analysis was used to examine the cross-sectional association between unmarried status and a prolonged QT interval. Odds ratios (OR) and 95% confidence interval (95% CI) were calculated comparing unmarried (overall and stratified by type; widowed, divorced/separated, and never married) to married participants. Models were adjusted as follows: model 1 was adjusted for age, gender, race, and income below poverty; and model 2 adjusted for model 1 plus smoking, hypertension, diabetes, hyperlipidemia, obesity, physical activity, and psychotherapeutic drugs (antidepressants and antipsychotics).

Using a model adjusted similarly to model 2, we conducted a subgroup analysis stratified by age (using 60 years as a cut-point), gender, and race (whites vs nonwhites). Test for interaction was performed between the main effect variable and subgroups on its outcome,that is, prolonged QT interval.

Lastly, we conducted a sensitivity analysis in which we excluded 364 participants with QRS ≥ 120 ms and then reexamined association of marital status with QT interval.

All statistical analyses were performed using with SAS version 9.4 (SAS Institute Inc, Cary, NC) and 2-sided p values were considered significant if less than 0.05.

Results

Among the 6,562 participants included in the analysis (mean age 58.6 years, 52% women, 50.1% non-Hispanic Whites), 5.91% (n = 388) had a prolonged QT interval. The prevalence of prolonged QT interval was higher (7.8%) among unmarried compared to married (4.9%) participants (p-value <0.0001).

Table 1 shows the baseline characteristics of the study participants across marital status. Unmarried participants were more likely to be old, female, nonwhite and smokers, and with more prevalent cardiovascular risk factors.

In a demographically adjusted multivariable logistic regression analysis, being unmarried was associated with 48% (p = 0.0006) higher odds of the prolonged QT interval. After further adjustment for cardiovascular risk factors and potential confounders, the unmarried state remained strongly associated with 46% (p = 0.001) higher odds of prolonged QT interval compared to those who are married (Table 2).

When the types of unmarried compared to married, a dose-response relation with prolonged QT was observed with the highest odds in never married followed by divorced/separated, and then widowed (Table 3).

The association of unmarried (overall) was stronger among men versus women (OR [95% CI]: 1.75 [1.27−2.41] vs 1.26 [0.92−1.73], respectively; interaction p-value = 0.03) and among younger versus older participants (OR [95% CI]: 1.72 [1.21−2.42] vs 1.40 [1.05−1.88], respectively; interaction p-value = 0.02). However, no interaction by race was observed (Table 4).

Divorced/separated and widowed had a consistent association with prolonged QT across subgroups stratified by age, gender, and race. However, never married had a strong association with prolonged QT interval in men versus women (interaction p-value = 0.04) but consistent across age and race subgroups (Table 4).

In the sensitivity analysis of the association of marital status with QT interval without QRS ≥120 ms, similar results of association of marital status and prolonged QT were observed (Supplementary Tables 1 and 2)

Discussion

In this analysis from a large community-based population, we investigated the cross-sectional association between marital status and prolonged QT. The key findings are: First, compared with married participants, we found a significant association between unmarried status and a prolonged QT interval. Second, this association was stronger among men

Table 1
Baseline Characteristics of the Study Participants

Variable	Married (n = 4,395)	Unmarried (n = 2,167)	p value[†]
Age (Years)	57.0 ± 12.3	61.9 ± 14.4	<0.0001
Men	2440 (55.5%)	691 (31.8%)	<0.0001
Income below poverty	608 (13.8%)	599 (27.6%)	<0.0001
Race			<0.0001
Non-Hispanic Whites	2319 (52.7%)	971 (44.8%)	
Non-Hispanic Blacks	807 (18.3%)	711 (32.8%)	
Mexican Americans	1106 (25.1%)	382 (17.8%)	
Others	163 (3.7%)	103 (4.7%)	
Systolic Blood Pressure (mm Hg)	130.5 ± 18.5	134.6 ± 20.6	<0.0001
Diastolic Blood Pressure (mm Hg)	76.8 ± 9.8	75.4 ± 10.4	<0.0001
Antihypertensive medications	847 (19.2%)	514 (23.7%)	<0.0001
Serum Total Cholesterol (mg/dl)	217.1 ± 42.7	218.1 ± 45.1	0.38
Serum Triglycerides (mg/dl)	163.9 ± 134.8	149.6 ± 114.4	<0.0001
Diabetes Mellitus	502 (11.4%)	266 (12.2%)	0.31
Obesity	1195 (27.2%)	649 (30.0%)	<0.0001
Smoker			
Never	1548 (35.2%)	535 (24.6%)	<0.0001
Current	1905 (43.3%)	1049 (48.4%)	0.0001
Former	942 (21.4%)	583 (26.9%)	<0.0001
Physical activity (***METs per week***)*	10.9 (2.3−33.0)	9.0 (0−29.0)	0.003
Psychotherapeutic Drugs	112 (2.5%)	86 (3.9%)	0.001
QT interval (msec)	420.2 ± 20.5	425.2 ± 21.6	<0.0001
Prolonged QT interval [‡]	218 (4.9%)	170 (7.8%)	<0.0001

METs, metabolic equivalent.
Obesity defined as body mass index ≥30 kg/m^2.
* METs reported as median and IQR.
[†] p.value for calculated by *t* test for continuous and chi-square for categorical variables.
[‡] Prolonged QT ≥460 ms in females and ≥450 ms in males.

and younger participants. Third, in the categories on being unmarried, a dose-response relation with prolonged QT was observed with the strongest association in never married followed by divorced/separated, and then widowed. Fourth, never married participants had a stronger association with prolonged QT interval among men compared with women. These associations suggest that abnormal cardiac repolarization may play a role in the increased risk of poor outcomes related to unmarried status with higher susceptibility for certain groups compared to others.

Marriage generally has an overall beneficial effect on health as it provides social support and married persons are more likely to have healthier life styles,[10,11] adherence to treatments, and medications that promote cardiovascular health.[12] Married couples are also less likely to experience stress which can lead to neuroendocrine stimulation.[13] Stress can lead to worsening of cardiovascular risk factors such as hypertension, reduced heart rate variability, impaired vagal tone, diabetes control, and atherosclerosis.[13,14] Emotional support of spouse reduces the excess neuroendocrine response to acute or chronic stressors which translates into a decrease in the progression of cardiovascular risk factors, thus reducing the development and progression of CVD.[15] Marital loss(es) and instability sever shared resources, cause stress and acute changes in emotional well-being, and bring about unhealthy lifestyles that precipitate chronic disease and mortality.[16] Therefore, a possible mechanism by which unmarried state may lead to prolonged QT interval is likely mediated by an increase in sympathetic activity through stress pathways.[17−20]

Table 2
Association between Marital Status and QT interval

Marital Status	Model 1 OR (95% CI)	p value	Model 2 OR (95% CI)	p value[†]
Married	1.0	–	1.0	–
Unmarried	1.48 (1.18−1.85)	0.0006	1.46 (1.16−1.83)	0.001

Model 1 adjusted for age, gender, race, and income below poverty.
Model 2 adjusted for hypertension, diabetes, hyperlipidemia, smoking, obesity, physical activity and psychotherapeutic drugs (antidepressants and antipsychotics).
[†] Calculated using multivariable logistic regression analysis.

With regard to age and gender differences in the association between marital status and health benefits, previous studies have yielded conflicting results. In general, men are observed to benefit from the advantages of marriage more than women,[21,22] and the positive influence of marital status seems to be weaker among elderly participants than among younger participants.[21,23] There are several explanations for marital benefit in men, mainly unmarried men and men living alone have been shown to exhibit poorer health habits and to more likely to die from alcohol-related and external causes of death.[16,24] Men also more often than women rely on their partner as a primary source of emotional and social support possibly resulting in greater vulnerability to marital dissolution and living alone.[25,26] These findings are further supported by our study in which we observed a strong association of unmarried and never married men with prolonged QT interval compared with women.

Table 3
Association between Unmarried Categories and Prolonged QT interval

Marital Status	n (%)	Model 1 OR (95% CI)	p value	Model 2 OR (95% CI)	p value[†]
Married	4395 (66.9%)	1.0	–	1.0	–
Widowed	960 (14.6%)	1.29 (0.96−1.75)	0.09	1.28 (0.94−1.73)	0.10
Divorced/Separated	839 (12.7%)	1.59 (1.16−2.17)	0.003	1.57 (1.13−2.14)	0.005
Never married	368 (5.6%)	1.75 (1.16−2.63)	0.006	1.74 (1.15−2.62)	0.008

Model 1 adjusted for age, gender, race, and income below poverty.

Model 2 adjusted for hypertension, diabetes, hyperlipidemia, smoking, obesity, physical activity and psychotherapeutic drugs (antidepressants and antipsychotics).

[†] Calculated using multivariable logistic regression analysis.

Prolongation of QT interval on surface ECG has been associated with incident CVD, stroke, SCD, CVD death, and all-cause death and is predictive of poor outcomes in those with CVD.[6,27,28] Aside from its direct association with arrhythmia and SCD, prolonged QT is a marker of subclinical atherosclerosis and viewed as a manifestation of subclinical myocardial ischemia, fibrosis, autonomic dysfunction, and left ventricular hypertrophy.[28] Therefore, finding of a strong association between unmarried state and prolonged QT interval in our study may highlight the underlying mechanisms of poor outcomes associated with social isolation and can, therefore, be used for risk stratification in primary care settings. To the best of our knowledge, no previous studies have examined the association between marital status and prolonged QT interval.

Our study has limitations. This is a cross-sectional analysis, and hence our results should be read in the context of issues like temporal relation and causality. Also, despite adjusting of several variables, residual confounding remains an issue. The NHANES-III survey recorded ECG only at 1 point of time, and hence we could not examine the longitudinal changes of QT over time. Also, NHANES lacks information on cohabitation/living with someone, which is associated with a protective effect,[29] thus can introduce bias, with results in negative association with QT interval in unmarried subgroups. Among married, we also lack data on marriage dissatisfaction, which can negatively affect the health of participants.[30] The strength of our study includes large sample size, community-based multiracial population, and well-ascertained variables including ECG data evaluated at a central reading center.

Table 4
Association between Marital Status and QT interval among Subgroups

Marital Status	Subgroups	Participants	Events	OR (95% CI)	*Interaction p value*[†]
Unmarried	**Men**	691	68 (9.8%)	1.75 (1.27-2.41)	0.03
	Women	1476	102 (6.9%)	1.26 (0.92-1.73)	
	>60 years	1164	64 (6.3%)	1.40 (1.05-1.88)	0.002
	≤60 years	1003	106 (9.1%)	1.72 (1.21-2.42)	
	White	971	69 (7.1%)	1.24 (0.87-1.76)	0.45
	Nonwhite	1196	101 (8.4%)	1.57 (1.16-2.12)	
Widowed	**Men**	208	24 (11.5%)	1.17 (0.72-1.92)	0.43
	Women	752	61 (8.1%)	1.22 (0.84-1.78)	
	>60 years	816	76 (9.3%)	1.37 (1.00-1.88)	0.31
	≤60 years	144	9 (6.2%)	1.24 (0.60-2.55)	
	White	541	46 (8.5%)	1.10 (0.72−1.66)	0.68
	Nonwhite	419	39 (9.3%)	1.15 (0.75−1.74)	
Divorced/Separated	**Men**	302	25 (8.2%)	1.64 (1.04−2.59)	0.42
	Women	537	31 (5.7%)	1.21 (0.80−1.84)	
	>60 years	226	17 (7.5%)	0.98 (0.58−1.65)	0.26
	≤60 years	613	39 (6.3%)	1.54 (1.04−2.28)	
	White	294	15 (5.1%)	1.41 (0.97−2.05)	0.69
	Non-White	545	41 (7.5%)	1.31 (0.75−2.30)	
Never married	**Men**	181	19 (10.5%)	2.23 (1.33−3.75)	0.04
	Women	187	10 (5.3%)	0.96 (0.49−1.86)	
	>60 years	122	13 (10.6%)	1.39 (0.76−2.54)	0.46
	≤60 years	246	16 (6.5%)	1.55 (0.90−2.67)	
	White	136	8 (5.8%)	1.25 (0.59−2.64)	0.43
	Non-White	232	21 (9.0%)	1.63 (1.00−2.65)	

Married = reference

Model adjusted for age, gender, race, income below poverty, hypertension, Diabetes, hyperlipidemia, smoking, obesity, physical activity and psychotherapeutic drugs (antidepressants and antipsychotics).

[†] Calculated using multivariable logistic regression analysis.

Disclosures

The authors have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.04.020.

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