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Original Contribution

Sex-Steroid Hormones and Electrocardiographic QT-Interval Duration: Findings From the Third National Health and Nutrition Examination Survey and the Multi-Ethnic Study of Atherosclerosis

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The association between physiologic levels of sex hormones and QT-interval duration in humans was evaluated using data from 727 men enrolled in the Third National Health and Nutrition Examination Survey and 2,942 men and 1,885 postmenopausal women enrolled in the Multi-Ethnic Study of Atherosclerosis (MESA). Testosterone, estradiol, and sex hormone-binding globulin levels were measured in serum and free testosterone was calculated from those values. QT interval was measured using a standard 12-lead electrocardiogram. In men from the Third National Health and Nutrition Survey, the multivariate adjusted differences in average QT-interval duration comparing the highest quartiles with the lowest quartiles of total testosterone and free testosterone were −8.5 ms (95% confidence interval (CI): −15.5, −1.4) and −8.0 ms (95% CI: −13.2, −2.8), respectively. The corresponding differences were −1.8 ms (95% CI: −3.8, −0.2), and −4.7 ms (95% CI: −6.7, −2.6), respectively, in men from MESA and −0.6 ms (95% CI: −3.0, 1.8) and 0.8 ms (95% CI: −1.6, 3.3), respectively, in postmenopausal women from MESA. Estradiol levels were not associated with QT-interval duration in men, but there was a marginally significant positive association in postmenopausal women. The findings suggest that testosterone levels may explain differences in QT-interval duration between men and women and could be a contributor to population variability in QT-interval duration among men.

electrocardiography; estradiol; gonadal sex hormones; testosterone

Abbreviations: BMI, body mass index; CI, confidence interval; ECG, electrocardiogram; MESA, Multi-Ethnic Study of Atherosclerosis; NHANES III, Third National Health and Nutrition Examination Survey; SHBG, sex hormone-binding globulin.

Editor's note: *An invited commentary on this article appears on page 412.*

On average, women have longer electrocardiographic QT intervals than do men, but this sex difference is only apparent after the onset of puberty. Compared with females, QT-interval duration in males begins to shorten at puberty, although by age 50–60 years, males and females tend to have similar QT intervals (1). In addition, women are at higher risk of developing torsade de pointes arrhythmias induced by QT-prolonging medications, further suggesting that sex hormones may influence cardiac repolarization (2–4).

In experimental models and in animal studies, testosterone has been shown to shorten QT-interval duration (5–9), but clinical evidence of the association between testosterone levels and QT-interval duration is limited, and only 1 study has evaluated the association in the general population (10–12). The relation between estrogen levels and repolarization is also unclear. Results from animal studies (6, 7, 13), studies in women in different phases of the menstrual cycle (14–17), and studies of postmenopausal women using hormone replacement therapy (18–20) either showed no association with or prolongation of QT interval by estrogens. The association of estrogen levels with QT-interval duration in men has not been evaluated.

The purpose of the present analysis was to evaluate the association between both physiologic levels of serum sex-steroid hormones (total and free testosterone and total estradiol) and sex hormone-binding globulin (SHBG) and QT-interval duration among men and postmenopausal women in 2 independent general population studies, the Third National Health and Nutrition Examination Survey (NHANES III) and the Multi-Ethnic Study of Atherosclerosis (MESA).

MATERIALS AND METHODS

Study population

NHANES III was a cross-sectional study conducted between 1988 and 1994 that used a multistage stratified clustered probability design to select a representative sample of the civilian noninstitutionalized US population (21). NHANES III included 2 phases (phase I: 1988–1991; phase II: 1991–1994). Unbiased national estimates of health and nutrition characteristics could be independently obtained from each phase. Within each phase, participants were randomly assigned to either a morning examination session or an afternoon/evening examination session. Sex-hormone assays were performed only in men and were limited to those who participated in the morning sessions of phase I to reduce variability due to diurnal production of hormones (22). The present study was restricted to participants 40 years of age or older, as 12-lead electrocardiograms (ECGs) were only performed in this age group. Of the 1,251 men 40 years of age or older who participated in the morning session of phase I, 899 had serum samples available for hormone assays; 817 of those men also had ECG data available. We further excluded 17 participants with missing information on QT-interval duration or heart rate, 51 participants with a QRS complex of 120 ms or longer, and 22 participants with missing sex hormone, SHBG, or albumin levels. The final NHANES III analysis was based on 727 men.

MESA was a multicenter cohort study of the prevalence and correlates of subclinical cardiovascular disease and the factors that influence its progression (23). Between July 2000 and August 2002, 6,814 men and women 45–84 years of age who were without clinical cardiovascular disease and who identified themselves as white, black, Hispanic, or Chinese were recruited from 6 US communities: Baltimore City and Baltimore County, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; Northern Manhattan and the Bronx, New York; and St. Paul, Minnesota. At baseline, sex-hormone assays were performed in 3,213 men and 2,013 postmenopausal women who were not using hormone replacement therapy. We further excluded 39 participants with missing QT interval or heart rate data, 103 with incomplete measures of sex hormones, and 257 with a QRS complex of 120 ms or longer. Thus, the current MESA analyses were based on 2,942 men and 1,885 postmenopausal women.

Data collection

NHANES III included a standardized questionnaire administered in the home by a trained interviewer and a detailed physical examination at a mobile examination center. Demographic characteristics, educational level, household income, smoking status, alcohol consumption, physical activity level, medical history, and medication use were assessed during the interview. QT-prolonging medications were defined according to the Arizona Center for Education and Research on Therapeutics database (24). Height and weight were measured, and body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Blood pressure was measured 3 times during the in-home interview and 3 additional times during the participant's visit to the mobile examination center. Laboratory tests determined total cholesterol, high density lipoprotein cholesterol, serum albumin, and plasma glucose levels. Type 2 diabetes mellitus (hereafter referred to as diabetes) was defined as a person's having a fasting plasma glucose level of 126 mg/dL or higher or a nonfasting plasma glucose level of 200 mg/dL or higher and/or current use of oral hypoglycemic agents or insulin.

MESA collected self-reported information on sex, age, race/ethnicity, smoking, and alcohol use at baseline (23, 25, 26). A woman was considered postmenopausal if she reported being postmenopausal, had undergone a bilateral oophorectomy, or was older than 55 years of age. Height and weight were measured and BMI was calculated. Resting blood pressure was measured 3 times, and the last 2 measurements were averaged for analysis. Fasting blood samples were drawn and were sent to a central laboratory for measurement of glucose and lipids. Diabetes was defined as a patient's having a fasting glucose level of 126 mg/dL or higher or use of hypoglycemic medication. Physical activity was assessed using the MESA Typical Week Physical Activity Survey (26).

Sex-steroid hormones

In NHANES III, participants in the morning examination session fasted overnight. After venipuncture, blood was centrifuged and serum was aliquoted and stored at −70°C. In 2005, stored serum samples were assayed for sex-steroid hormones at Dr. Nader Rifai's laboratory at the Children's Hospital in Boston, Massachusetts. Testosterone, estradiol, and SHBG concentrations were measured by using competitive electrochemiluminescence immunoassays on a 2010 Elecsys autoanalyzer (Roche Diagnostics, Indianapolis, Indiana). Laboratory technicians were blinded to participant characteristics (22). The limits of detection for the assays were 0.02 ng/mL for testosterone, 5 pg/mL for estradiol, and 3 nmol/L for SHBG. The coefficients of variation for quality control specimens were 5.9% and 5.8% for testosterone at concentrations of 2.5 ng/mL and 5.5 ng/mL, respectively; 2.5%, 6.5%, and 6.7% for estradiol at concentrations of 39.4 pg/mL, 102.7 pg/mL, and 474.1 pg/mL, respectively; and 5.3% and 5.9% for SHBG at concentrations of 5.3 nmol/L and 16.6 nmol/L, respectively. Free testosterone concentrations were calculated from total testosterone, SHBG, and albumin levels (27).

In MESA, participants fasted for 12 hours and avoided smoking and heavy physical activity for 2 hours before each blood draw (23, 25, 28). Serum hormone concentrations were measured in Dr. Christopher Longcope's Sex Hormone

Laboratory at the University of Massachusetts Medical Center in Worcester, Massachusetts. Total testosterone was measured directly using radioimmunoassay kits. SHBG was measured by chemiluminescent enzyme immunometric assay using Immulite kits obtained from Diagnostic Products Corporation (Los Angeles, California). Estradiol was measured using an ultrasensitive radioimmunoassay kit from Diagnostic Systems Laboratories (Webster, Texas). This assay has been shown to have good correlations with indirect assays and to provide values that are within what is considered a biologically plausible range (29). The minimal detectable limit was 0.04 ng/mL for testosterone, 2.5 pg/mL for estradiol, and 0.02 nmol/L for SHBG. The coefficients of variation for reassays of 10% of the samples were 12.3% for testosterone, 9.0% for SHBG, and 10.5% for estradiol. Free testosterone concentrations were calculated using the same method as in NHANES III (27).

QT interval

In NHANES III, standard 12-lead resting ECG recordings were performed using a Marquette MAC 12 electrocardiograph (Marquette Medical Systems, Inc., Milwaukee, Wisconsin) with signals sampled at 250 samples per second per channel. A representative P-QRS-T cycle was then derived by selective averaging using the Dalhousie ECG Analysis Program (30). Resting heart rates and QT intervals were obtained from the ECGs.

In MESA, 10 seconds of 12-lead ECGs were obtained using a Marquette MAC-1200 electrocardiograph (Marquette Medical Systems, Inc.) with signals sampled at 500 samples per second per channel. Resting heart rates and QT-interval durations were obtained from the ECGs, which were read electronically at a Central ECG Reading Center (23).

Statistical analysis

For both NHANES III and MESA data, we used QT-interval duration as the primary metric in models with concomitant adjustment for age, race/ethnicity, and RR-interval duration. We also performed sensitivity analyses using Bazett's equation (31), as well as the linear function of the RR interval (32), to obtain a heart rate-corrected QT interval. The formula for the linear RR-corrected QT interval was $QT_L = QT + 0.161 \times (1{,}000 - RR)$, where QT_L was the linear RR-corrected QT interval, QT_B was the Bazett corrected QT interval, and 0.161 was the b coefficient estimated from the linear regression $QT = b_0 + b_1 \times RR + b_2 \times$ sex, based on the combined data set of the 2 studies (NHANES III men and MESA men and women).

For NHANES III, phase I morning sampling weights were used to account for the complex sampling design (21). We categorized the distributions of each hormone and SHBG into quartiles based on the weighted population distribution. Marginally adjusted means and 95% confidence intervals for QT-interval duration by quartile of sex hormone were calculated from multivariable linear regression models. We used 3 models with progressive degrees of adjustment. Initial models were adjusted for age, race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, and other), and RR interval (restricted quadratic splines with knots at the 5th, 50th, and 95th percentiles of the overall study population to allow for possible nonlinear relations between RR- and QT-interval durations). We then further adjusted for BMI, smoking (current, former, and never), alcohol consumption (<12 vs. ≥12 drinks in the past year), physical activity level (0, 1, 2, or ≥3 times per week), high school education, annual household income (<$20,000 vs. ≥$20,000), and use of QT-prolonging medications. The fully adjusted models further included systolic blood pressure, total and high density lipoprotein cholesterol levels, diabetes, history of myocardial infarction, and history of congestive heart failure. Tests for linear trend across quartiles of sex hormones were computed by including a variable with the median value of each quartile of the hormone in the linear regression models. We conducted additional analyses using hormone levels as continuous variables. Interactions by race/ethnicity were tested by including product terms of race/ethnicity categories with hormone levels as continuous variables in the regression models. All analyses were conducted using SUDAAN, version 10.0 (Research Triangle Institute, Research Triangle Park, North Carolina).

We followed a similar analytic strategy for MESA, with separate analyses for men and women. Initial models were adjusted for age, race/ethnicity (non-Hispanic white, non-Hispanic black, Chinese American, and Hispanic), and RR interval (restricted quadratic splines with knots at the 5th, 50th, and 95th percentiles of the overall study population). We then further adjusted for BMI, smoking (current, former, or never), alcohol consumption (current, former, or never), physical activity level (0–34, 35–69, 70–139, or ≥140 metabolic equivalent hours/week), high school education, and annual household income (<$20,000 vs. ≥$20,000). The fully adjusted models were further adjusted for systolic blood pressure, total and high density lipoprotein cholesterol levels, and diabetes. We also tested interactions by sex and by race/ethnicity in the regression models. All analyses were conducted using SAS, version 9.1.3 (SAS Institute Inc., Cary, North Carolina).

RESULTS

The average age of study participants was 54.4 years in NHANES III, 61.8 years in MESA men, and 65.6 years in MESA women (Table 1). Non-Hispanic whites accounted for 81.2% of the NHANES III population, 38.4% of MESA men, and 29.0% of MESA women. Average total testosterone levels were 4.9 ng/mL, 4.3 ng/mL, and 0.3 ng/mL in NHANES III participants, MESA men, and MESA women, respectively. The corresponding levels of total estradiol were 35.7 pg/mL, 32.1 pg/mL, and 19.4 pg/mL, respectively.

After adjustment for age, race/ethnicity, and RR interval, there were graded inverse associations between both total testosterone and free testosterone levels and QT-interval duration in men in NHANES III (Table 2) and MESA (Table 3). In NHANES III, the average differences in QT-interval duration in the fully adjusted models comparing the highest quartiles with the lowest quartiles of total testosterone and free testosterone were −8.5 ms (95% CI: −15.5, −1.4)

Table 1. Baseline Characteristics of Participants in the Third National Health and Nutrition Examination Survey (1988–1991) and the Multi-Ethnic Study of Atherosclerosis (2002)

Characteristic	NHANES III Men (n = 727)		MESA			
			Men (n = 2,942)		Women (n = 1,885)	
	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%
Age, years	54.4 (11.3)		61.8 (10.1)		65.6 (9.2)	
Race						
Non-Hispanic white		81.2		38.4		29.0
Non-Hispanic black		7.3		25.7		31.1
Other		11.4		35.8		40.0
Systolic blood pressure, mm Hg	128.9 (16.0)		125.7 (19.2)		130.7 (24.1)	
Total cholesterol level, mg/dL	216.8 (40.4)		188.6 (34.8)		203.1 (37.0)	
High density lipoprotein level, mg/dL	46.5 (15.2)		45.1 (11.7)		54.5 (14.4)	
Body mass index[a]	26.8 (4.7)		27.8 (4.5)		28.9 (6.1)	
Diabetes		9.8		13.4		14.3
Myocardial infarction		7.0		0.0		0.0
Congestive heart failure		3.0		0.0		0.0
Smoking						
Current smoker		29.3		14.3		10.9
Former smoker		45.3		44.7		25.9
Consumer of alcohol		61.6		89.3		63.7
High school education		68.2		83.6		73.6
Household income <$20,000/year		25.9		18.3		36.0
Sex hormone levels						
Total testosterone, ng/mL	4.9 (1.8)		4.3 (1.6)		0.3 (0.3)	
Free testosterone, ng/mL	0.11 (0.04)		0.083 (0.031)		0.005 (0.005)	
Total estradiol, pg/mL	35.7 (11.5)		32.1 (13.6)		19.4 (18.6)	
Sex hormone-binding globulin, nmol/L	42.5 (19.9)		44.3 (19.3)		56.5 (29.4)	
Heart rate, beats/minute	66.0 (11.7)		61.8 (9.8)		64.3 (9.6)	
QT interval, ms	402.7 (31.6)		408.3 (31.3)		413.2 (30.1)	
Bazett corrected QT interval, ms	418.3 (21.6)		411.3 (19.7)		424.6 (19.8)	
Linear RR-corrected QT interval, ms	412.7 (18.7)		409.2 (18.4)		420.5 (18.0)	

Abbreviations: MESA, Multi-Ethnic Study of Atherosclerosis; NHANES III, Third National Health and Nutrition Examination Survey; SD, standard deviation.

[a] Weight (kg)/height (m)^2.

and −8.0 ms (95% CI: −13.2, −2.8), respectively. The corresponding differences in MESA men were −1.8 ms (95% CI: −3.8, −0.2) and −4.7 ms (95% CI: −6.7, −2.6), respectively. The change in average QT-interval duration associated with an increase of 0.1 ng/mL, which is approximately the difference between the 90th and the 10th percentile in the NHANES III distribution, for free testosterone as a continuous variable in fully adjusted models was −5.6 ms (95% CI: −10.7, −0.5) in NHANES III men and −5.7 ms (95% CI: −8.0, −3.4) in MESA men.

In contrast to the findings in men, in MESA women, testosterone levels were not associated with QT-interval duration (Table 4). The average differences in QT-interval duration in fully adjusted models comparing the highest quartiles with the lowest quartiles of total testosterone and free testosterone in MESA women were −0.6 ms (95% CI: −3.0, 1.8) and 0.8 ms (95% CI: −1.6, 3.3), respectively. The change in average QT-interval duration associated with an increase of 0.1 ng/mL in free testosterone in MESA women was −4.0 ms (95% CI: −20.2, 12.2).

SHBG was positively associated with QT-interval duration in MESA men but not in men in NHANES III or in MESA women (Tables 2–4). Estradiol levels were not associated with QT-interval duration in men, but there was a marginally significant positive association in postmenopausal women (Table 4). Interaction terms for the effects of hormone levels and race/ethnicity on QT-interval duration were not statistically significant ($P > 0.05$) (data not shown). Finally, sensitivity analyses using the Bazett corrected QT interval and linear RR-corrected QT interval showed very similar findings (Web Tables 1–6, available at http://aje.oxfordjournals.org/).

Table 2. Adjusted Mean QT Interval (ms), by Quartile of Hormone Level, Among Men, Third National Health and Nutrition Examination Survey, 1988–1991

	No. of Men in Quartile	Unadjusted Model		Model 1[a]		Model 2[b]		Model 3[c]	
		Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI
Total testosterone, ng/mL									
<3.7	203	408.9	402.7, 415.2	407.6	403.5, 411.7	409.2	404.7, 413.7	408.9	403.4, 414.4
3.7–4.7	170	395.1	390.0, 400.3	401.0	398.1, 403.9	401.6	397.9, 405.2	401.5	397.3, 405.7
4.8–5.9	171	401.6	394.3, 408.8	400.7	397.0, 404.4	400.6	395.7, 405.5	400.3	395.4, 405.1
≥6.0	183	405.0	400.1, 410.0	401.5	399.0, 404.0	401.2	398.3, 404.1	400.4	397.0, 403.9
P for trend			0.85		0.03		0.02		0.05
Free testosterone, ng/mL									
<0.084	236	410.3	405.4, 415.1	408.2	403.9, 412.5	409.3	405.0, 413.6	408.7	404.0, 413.4
0.084–0.102	161	398.4	394.4, 402.3	400.4	397.3, 403.5	400.9	397.3, 404.5	400.6	396.7, 404.4
0.103–0.127	173	401.0	397.5, 404.5	400.5	397.2, 403.7	401.3	396.9, 405.6	401.2	396.7, 405.6
≥0.128	157	401.1	395.9, 406.2	401.6	398.4, 404.8	401.2	397.8, 404.6	400.7	397.2, 404.2
P for trend			0.05		0.01		0.003		0.01
Total estradiol, pg/mL									
<29.3	190	409.1	403.5, 414.6	406.9	403.4, 410.3	408.3	404.1, 412.5	408.3	404.0, 412.7
29.3–34.0	156	399.6	392.7, 406.6	399.6	395.2, 404.1	399.8	394.4, 405.1	399.2	393.9, 404.6
34.1–40.9	185	402.2	395.1, 409.3	401.3	398.3, 404.2	402.0	398.8, 405.2	401.6	397.9, 405.3
≥41.0	195	399.9	394.4, 405.3	402.9	399.2, 406.7	402.9	398.7, 407.2	402.4	397.7, 407.0
P for trend			0.15		0.42		0.35		0.30
Sex hormone-binding globulin, nmol/L									
<27.5	145	397.9	391.0, 404.8	403.6	400.2, 407.0	403.6	399.9, 407.4	403.2	398.5, 407.8
27.5–38.7	170	401.2	395.8, 406.6	403.4	399.2, 407.5	404.7	400.2, 409.1	405.0	400.2, 409.7
38.8–52.7	192	403.3	398.7, 408.0	400.6	397.9, 403.4	401.3	397.4, 405.2	400.7	396.7, 404.8
≥52.8	220	408.1	401.9, 414.2	403.0	400.5, 405.6	403.3	400.0, 406.5	402.4	398.7, 406.0
P for trend			0.05		0.58		0.62		0.55

Abbreviation: CI, confidence interval.

[a] Model 1 was adjusted for age (continuous), race (non-Hispanic white, non-Hispanic black, Mexican American, or other), and RR interval (restricted quadratic splines with knots at the 5th, 50th, and 95th percentiles).

[b] Model 2 was adjusted for the variables in model 1 and body mass index (continuous), smoking (current, former, or never), alcohol consumption (<12 vs. ≥12 drinks in the past year), physical activity level (0, 1–2, or ≥3 times per week), high school education, annual household income (<$20,000 vs. ≥$20,000), and potential QT-prolonging medications.

[c] Model 3 was adjusted for the variables in models 1 and 2 and systolic blood pressure (continuous), total cholesterol level (continuous), high density lipoprotein cholesterol level (continuous), diabetes, history of myocardial infarction, and history of congestive heart failure.

DISCUSSION

Independent analyses of data from NHANES III and MESA showed that higher levels of free testosterone were associated with shorter QT intervals in men. The association was moderately strong, with average adjusted differences in QT-interval duration of −8.0 ms to −4.7 ms for the highest quartile versus the lowest quartiles of free testosterone in NHANES III and MESA, respectively. No association was found between testosterone level and QT interval in postmenopausal women. At the population level, the association of testosterone with QT-interval duration is substantial and comparable in magnitude to that of common genetic variants that affect QT-interval duration (33). Differences in testosterone levels could explain differences in QT-interval duration between men and women. Among men, the level of endogenous testosterone could be a key contributor to population variability in QT-interval duration.

Testosterone may shorten QT-interval duration by affecting several repolarizing currents (5, 7–9, 34). In guinea pig myocytes, testosterone at physiologic concentrations induced a dose-dependent shortening of action potential duration through enhancing the slowly activating delayed rectifier current and suppressing the L-type calcium current (5). Dihydrotestosterone, a metabolite of testosterone, attenuated quinidine-induced QT prolongation in orchiectomized male rabbits, an effect attributed to an increase in the repolorizing inward rectifier current and rapidly activating delayed rectifier current (8). Finally, in one study, testosterone-treated castrated female dogs and unaltered male dogs had higher

Table 3. Adjusted Mean QT Interval (ms), by Quartile of Hormone Levels, Among Men, Multi-Ethnic Study of Atherosclerosis, 2002

	No. of Men in Quartile	Unadjusted		Model 1[a]		Model 2[b]		Model 3[c]	
		Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI
Total testosterone, ng/mL									
<3.3	735	406.0	403.8, 408.3	409.4	408.1, 410.8	409.0	407.3, 410.7	408.9	407.1, 410.7
3.3–4.1	728	408.0	405.7, 410.2	407.7	406.4, 409.1	407.7	406.1, 409.4	407.5	405.8, 409.3
4.2–5.0	740	409.1	406.9, 411.4	407.1	405.7, 408.4	407.4	405.8, 409.1	407.2	405.4, 408.9
≥5.1	739	410.1	407.8, 412.4	406.8	405.4, 408.1	407.4	405.7, 409.0	407.1	405.3, 408.9
P for trend			0.01		0.01		0.12		0.09
Free testosterone, ng/mL									
<0.065	735	410.0	407.7, 412.2	410.7	409.3, 412.1	410.3	408.6, 412.0	410.2	408.4, 411.9
0.065–0.079	736	411.1	408.9, 413.4	409.0	407.7, 410.4	409.2	407.5, 410.8	408.8	407.1, 410.6
0.080–0.098	736	405.9	403.6, 408.2	406.1	404.8, 407.4	406.2	404.5, 407.8	406.0	404.2, 407.8
≥0.099	735	406.3	404.0, 408.5	405.3	403.9, 406.7	405.7	404.0, 407.3	405.5	403.7, 407.3
P for trend			0.002		<0.001		<0.001		<0.001
Total estradiol, pg/mL									
<24.0	795	410.4	408.2, 412.6	407.0	405.7, 408.3	407.3	405.7, 408.9	407.2	405.5, 409.0
24.0–30.9	765	408.6	406.4, 410.8	407.7	406.4, 409.0	407.8	406.2, 409.5	407.8	406.1, 409.5
31.0–37.9	598	408.3	405.8, 410.8	407.2	405.8, 408.7	407.2	405.5, 409.0	406.9	405.1, 408.8
≥38.0	784	405.9	403.7, 408.1	409.1	407.7, 410.4	409.0	407.4, 410.6	408.8	407.0, 410.5
P for trend			0.005		0.04		0.10		0.15
Sex hormone-binding globulin, nmol/L									
<31.2	729	402.8	400.5, 405.0	407.7	406.3, 409.0	407.4	405.7, 409.1	407.4	405.6, 409.2
31.2–40.6	735	407.6	405.4, 409.9	407.5	406.1, 408.8	407.2	405.6, 408.9	407.1	405.3, 408.9
40.7–52.5	739	409.2	406.9, 411.4	406.7	405.4, 408.1	406.8	405.1, 408.4	406.6	404.8, 408.3
≥52.6	739	413.6	411.3, 415.8	409.2	407.8, 410.5	410.0	408.3, 411.6	409.9	408.1, 411.8
P for trend			<0.0001		0.12		0.01		0.01

Abbreviation: CI, confidence interval.

[a] Model 1 was adjusted for age (continuous), race (white, Chinese American, black, or Hispanic), and RR interval (restricted quadratic splines with knots at the 5th, 50th, and 95th percentiles).

[b] Model 2 was adjusted for the variables in model 1 and body mass index (continuous), smoking (never, former, or current), alcohol consumption (never, former, or current), physical activity level (low, medium, or high intensity), educational level (less than high school vs. high school graduate or higher), and household income (<$20,000 vs. ≥$20,000).

[c] Model 3 was adjusted for variables in models 1 and 2 and systolic blood pressure (continuous), total cholesterol level (continuous), high density lipoprotein level (continuous), and diabetes.

expressions of ion channel proteins that underlie inward rectifier current and transient outward current than did estrogen-treated castrated male dogs and unaltered female dogs (7).

Few clinical studies have been conducted to evaluate the influence of testosterone on QT-interval duration. A study of 106 patients (27 castrated men, 26 women with virilization, and 53 controls) found that ventricular repolarization was prolonged in castrated men compared with noncastrated men and that women with hyperandrogenism had shorter QT-interval durations than did other women (10). In another study of 11 hypogonadic men, therapeutic testosterone administration was associated with significant QT-interval shortening (11). Both studies were relatively small, and their results cannot be extrapolated to the general population. Our findings also confirmed previous findings of 2 smaller cross-sectional analyses from the Rotterdam Study ($n = 445$) and the Study of Health in Pomerania ($n = 1{,}428$), in which van Noord et al. (12) reported an inverse association between total testosterone and the Bazett corrected QT interval. In addition, we showed that free testosterone had a stronger association with the QT interval.

Furthermore, in our analyses, the association between testosterone and QT interval was more prominent in NHANES III men than in the MESA men. This could be due to differences in population characteristics, as NHANES III men were 8 years younger on average and had higher testosterone levels.

Our study found a marginally significant association between estradiol levels and QT-interval duration in postmenopausal women. Experimental data in animals have suggested that estradiol may regulate cardiac repolarization through genomic and nongenomic pathways (6, 13, 35). In

Table 4. Adjusted Mean QT Interval (ms), by Quartile of Hormone Level, Among Postmenopausal Women, Multi-Ethnic Study of Atherosclerosis, 2002

	No. of Women in Quartile	Unadjusted		Model 1[a]		Model 2[b]		Model 3[c]	
		Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI
Total testosterone, ng/mL									
<0.18	440	414.4	411.6, 417.2	413.0	411.4, 414.7	415.8	413.8, 417.8	415.2	413.0, 417.4
0.18–0.27	501	412.2	409.6, 414.9	414.5	412.9, 416.1	416.4	414.5, 418.3	415.8	413.7, 417.8
0.28–0.39	465	414.5	411.8, 417.2	414.3	412.6, 415.9	416.4	414.5, 418.3	415.6	413.5, 417.7
≥0.40	479	411.8	409.1, 414.5	413.7	412.0, 415.3	415.5	413.6, 417.4	414.6	412.5, 416.7
P for trend			0.37		0.85		0.67		0.47
Free testosterone, ng/mL									
<0.002	470	414.4	411.7, 417.2	412.7	411.1, 414.3	415.6	413.6, 417.5	415.1	412.9, 417.3
0.002–0.003	472	413.1	410.4, 415.8	412.9	411.3, 414.6	415.5	413.5, 417.4	415.0	412.8, 417.1
0.004–0.005	472	413.3	410.6, 416.0	414.5	412.9, 416.1	416.0	414.2, 417.9	415.2	413.1, 417.2
≥0.006	471	411.9	409.2, 414.7	415.4	413.8, 417.1	416.9	415.0, 418.9	415.9	413.8, 418.1
P for trend			0.24		0.01		0.19		0.43
Total estradiol, pg/mL									
<11.0	424	413.5	410.6, 416.3	411.7	410.0, 413.4	414.7	412.7, 416.7	414.2	411.9, 416.4
11.0–15.9	582	414.7	412.2, 417.1	412.8	411.4, 414.3	415.1	413.3, 416.9	414.5	412.5, 416.4
16.0–21.9	418	413.7	410.8, 416.6	415.8	414.0, 417.5	417.7	415.7, 419.7	416.7	414.5, 418.9
≥22.0	461	410.6	407.8, 413.3	415.6	414.0, 417.3	416.8	414.8, 418.8	416.1	413.9, 418.2
P for trend			0.07		<0.001		0.05		0.07
Sex hormone-binding globulin, nmol/L									
<36.5	471	410.7	408.0, 413.4	415.4	413.7, 417.0	416.7	414.8, 418.7	415.7	413.5, 417.8
36.5–50.0	470	412.8	410.1, 415.5	413.9	412.3, 415.6	415.6	413.7, 417.5	414.7	412.6, 416.8
50.1–68.7	471	414.9	412.2, 417.6	414.3	412.6, 415.9	416.5	414.6, 418.4	415.8	413.7, 417.9
≥68.8	473	414.3	411.6, 417.0	411.9	410.2, 413.6	415.2	413.3, 417.2	414.9	412.7, 417.1
P for trend			0.06		0.01		0.33		0.75

Abbreviation: CI, confidence interval.

[a] Model 1 was adjusted for age (continuous), race (white, Chinese American, black, or Hispanic), and RR interval (restricted quadratic splines with knots at the 5th, 50th, and 95th percentiles).

[b] Model 2 was adjusted for the variables in model 1 and body mass index (continuous), smoking (never, former, or current), alcohol consumption (never, former, or current), physical activity level (low, medium, or high intensity), educational level (less than high school vs. high school graduate or higher), and household income (<$20,000 vs. ≥$20,000).

[c] Model 3 was adjusted for variables in models 1 and 2 and systolic blood pressure (continuous), total cholesterol level (continuous), high density lipoprotein level (continuous), and diabetes.

rabbit hearts, estradiol prolonged the duration of the action potential by down-regulating the expression of potassium currents, such as the slowly activating delayed rectifier current (6). In guinea pig ventricles, estradiol had concentration-dependent effects on cardiac ion channels through non-genomic pathways: At physiologic concentrations, estradiol prolonged QT-interval duration by inhibiting the rapidly activating delayed rectifier current, whereas higher concentrations shortened the QT interval by inhibiting the rapidly activating delayed rectifier current and the L-type calcium current and enhancing the slowly activating delayed rectifier current (13).

Studies of estrogen levels and QT intervals in premenopausal women have been inconclusive. During the menstrual cycle, the circulating level of estradiol is lowest at the beginning of the menses, increases in the follicular phase, peaks at ovulation, and then decreases in the luteal phase. Two studies of healthy women (sample sizes of 23 and 21 women) showed no significant differences in QT-interval duration throughout the menstrual cycle (14, 15), whereas another study of 11 Japanese women showed significantly longer QT intervals in the follicular phase compared with the luteal phase (16). With respect to hormone replacement therapy in postmenopausal women in a large cross-sectional study from the Women's Health Initiative, Kadish et al. (18) reported that estrogen-only hormone replacement therapy was associated with a slight but significant prolongation of the QT interval but the combination of estrogen and progestin was associated with a shortening of this interval. In addition, results from the Atherosclerosis Risk in Communities

Study showed that estrogen replacement therapy but not progestin plus estrogen replacement therapy was associated with QT-interval prolongation (36).

A major strength of our study was the independent replication of the association between testosterone levels and QT-interval duration in men in 2 large general population studies, NHANES III and MESA. Both studies had careful standardization and detailed quality-control procedures that added to the strength of the findings. Because there were methodological differences in sampling procedures, ECG recording, and sex-hormone measurement, we decided not to combine the data; instead, we conducted independent analyses of data from the 2 cohorts separately. The consistency of the findings in both studies supports the validity of the observed inverse association between testosterone levels and QT-interval duration in men.

Several limitations of the present study also need to be considered. QT-interval duration and hormone levels were measured at a single time, which could have resulted in nondifferential measurement error, as there was substantial within-person variability in both exposure and outcome. Our findings suggested that more detailed assessments of both hormone levels and ECG characteristics could further contribute to our understanding of the role of testosterone in QT-interval duration. Another concern is the observational cross-sectional design, which limited our ability to make statements about the causality of the relation between testosterone and QT-interval duration because of potential uncontrolled confounding or selection biases. However, in vitro and experimental animal models have provided a firm experimental basis for the concept of QT shortening by testosterone and support the biologic plausibility of our findings.

In conclusion, data from 2 large general population cohorts showed an inverse association between QT-interval duration and testosterone levels in men but not in women. Testosterone may be a primary determinant of QT-interval duration in men, which could have important implications for understanding sex differences, as well as age-related changes in arrhythmia susceptibility in men. Additional studies in other populations, as well as randomized trials, should be conducted to confirm these findings and to elucidate the clinical impact of sex hormones in modifying the risk of sudden cardiac death and other arrhythmias.

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