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Endogenous Testosterone and Mortality Due to All Causes, Cardiovascular Disease, and Cancer in Men: European Prospective Investigation Into Cancer in Norfolk (EPIC-Norfolk) Prospective Population Study

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Endogenous Testosterone and Mortality Due to All Causes, Cardiovascular Disease, and Cancer in Men

European Prospective Investigation Into Cancer in Norfolk (EPIC-Norfolk) Prospective Population Study

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Background—The relation between endogenous testosterone concentrations and health in men is controversial.

Methods and Results—We examined the prospective relationship between endogenous testosterone concentrations and mortality due to all causes, cardiovascular disease, and cancer in a nested case-control study based on 11 606 men aged 40 to 79 years surveyed in 1993 to 1997 and followed up to 2003. Among those without prevalent cancer or cardiovascular disease, 825 men who subsequently died were compared with a control group of 1489 men still alive, matched for age and date of baseline visit. Endogenous testosterone concentrations at baseline were inversely related to mortality due to all causes (825 deaths), cardiovascular disease (369 deaths), and cancer (304 deaths). Odds ratios (95% confidence intervals) for mortality for increasing quartiles of endogenous testosterone compared with the lowest quartile were 0.75 (0.55 to 1.00), 0.62 (0.45 to 0.84), and 0.59 (0.42 to 0.85), respectively ($P<0.001$ for trend after adjustment for age, date of visit, body mass index, systolic blood pressure, blood cholesterol, cigarette smoking, diabetes mellitus, alcohol intake, physical activity, social class, education, dehydroepiandrosterone sulfate, androstanediol glucuronide, and sex hormone binding globulin). An increase of 6 nmol/L serum testosterone ($\approx$1 SD) was associated with a 0.81 (95% confidence interval 0.71 to 0.92, $P<0.01$) multivariable-adjusted odds ratio for mortality. Inverse relationships were also observed for deaths due to cardiovascular causes and cancer and after the exclusion of deaths that occurred in the first 2 years.

Conclusions—In men, endogenous testosterone concentrations are inversely related to mortality due to cardiovascular disease and all causes. Low testosterone may be a predictive marker for those at high risk of cardiovascular disease. **(*Circulation*. 2007;116:2694-2701.)**

Key Words: testosterone ■ hormones ■ epidemiology ■ men ■ mortality

The role of testosterone in men's health is still controversial. High doses of exogenous testosterone or other anabolic steroids have been associated with adverse health effects, including sudden cardiac death and liver disease.[1–4] Nevertheless, hypogonadism in men is also adversely associated with health, and the use of lower doses of exogenous testosterone is increasingly widespread because of the belief that supplementation has benefits for well-being.[5,6] Although a recent trial in 87 elderly men reported no significant effect of low-dose testosterone replacement on body composition, physical performance, or quality of life, that study did not address the relationship with clinical event end points, and the authors concluded that additional long-term studies of testosterone were warranted.[7,8]

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Surprisingly, the relationship between endogenous testosterone concentrations within the physiological range and overall health in men is still not well established. High endogenous testosterone concentrations in men are associated with a more favorable cardiovascular disease risk factor profile, including higher high-density lipoprotein (HDL) cholesterol concentrations and lower blood pressure, blood triglyceride, and glucose concentrations.[9–17] However, prospective studies to date have not found significant relationships between endogenous testosterone concentrations and cardiovascular disease events.[18–24] Conversely, high endogenous testosterone concentrations

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Table 1. Description of Baseline Variables in Men 42 to 78 Years of Age Who Died Subsequently Because of All Causes, Cardiovascular Diseases, and Cancer Compared With Age-Matched Controls in EPIC-Norfolk 1993 to 2003

	Controls (n=1489)†	All-Cause Mortality (n=825)†	P*	Cardiovascular Mortality (n=369)†	P*	Cancer Mortality (n=304)†	P*
Testosterone, nmol/L, mean (SD)	16.7 (5.7)	15.8 (5.7)	<0.001	15.7 (6.1)	<0.01	15.6 (6.5)	<0.01
SHBG, nmol/L, mean (SD)	45.0 (16.2)	45.4 (18.3)	0.57	45.2 (18.2)	0.85	43.7 (17.4)	0.23
Testosterone/SHBG ratio, mean (SD)	0.39 (0.14)	0.37 (0.15)	<0.001	0.37 (0.13)	<0.001	0.38 (0.17)	0.07
DHEAS, μmol/L, mean (SD)	2.87 (1.81)	2.82 (1.96)	0.55	2.66 (1.79)	0.05	3.09 (2.15)	0.02
Androstanediol glucuronide, nmol/L, mean (SD)	14.0 (8.0)	14.7 (9.1)	0.07	15.2 (9.5)	0.02	14.2 (8.4)	0.71
Age, y, mean (SD)	67.0 (6.6)	67.8 (6.7)	0.01	68.3 (6.4)	<0.01	67.0 (6.6)	0.98
Body mass index, kg/m^2, mean (SD)	26.6 (3.1)	26.8 (3.6)_	0.09	27.1(3.7)	<0.01	26.8 (3.3)	0.27
Waist-hip ratio, mean (SD)	0.94 (0.06)	0.95 (0.06)	<0.001	0.95 (0.06)	<0.01	0.95 (0.06)	<0.01
Systolic blood pressure, mm Hg, mean (SD)	141.9 (18.3)	143.8 (20.0)	0.02	145.5 (19.0)	<0.001	143.9 (19.5)	0.08
Diastolic blood pressure, mm Hg, mean (SD)	84.9 (11.6)	85.4 (12.4)	0.33	86.2 (12.3)	0.05	85.3 (11.7)	0.59
Cholesterol, mmol/L, mean (SD)	6.09 (1.04)	6.07 (1.19)	0.65	6.25 (1.15)	0.01	5.97 (1.18)	0.07
LDL cholesterol, mmol/L, mean (SD)	3.99 (0.93)	3.93 (1.03)	0.15	4.09 (1.02)	0.09	3.82(1.00	0.01
HDL cholesterol, mmol/L, mean (SD)	1.24 (0.32)	1.22 (0.37)	0.44	1.20 (0.33)	0.08	1.22 (3.72)	0.44
LDL/HDL ratio, mean (SD)	3.43 (1.16)	3.46 (1.27)	0.62	3.63 (2.38)	<0.01	3.38 (1.22)	0.46
Triglycerides, mmol/L, mean (SD)	1.98 (1.07)	2.08 (1.20)	0.04	2.23(1.37)	<0.001	2.04 (1.08)	0.37
Alcohol intake, U/wk, mean (SD)	8.7 (10.0)	9.4 (13.2)	0.12	7.8 (10.7)	0.13	11.0 (14.6)	<0.01
History of diabetes, % (n)	2.9 (43)	8.0 (66)	<0.001	9.5 (35)	<0.001	6.9 (64)	<0.001
History of hypertension, % (n)	16.9 (251)	25.7 (212)	<0.001	31.5 (116)	<0.001	22.4 (68)	0.01
History of high cholesterol, % (n)	8.6 (128)	10.4 (86)	0.09	14.1 (52)	<0.001	8.2 (25)	0.47
Aspirin use, % (n)	18.9 (240)	26.2 (174)	<0.001	35.9 (107)	<0.001	18.0 (44)	0.40
Cigarette smokers, % (n)			<0.001		<0.001		0.01
Current	9.1 (134)	13.5 (110)		15.8 (58)		11.4 (34)	
Former	61.4 (902)	65.5 (535)		64.2 (235)		66.2 (198)	
Never	29.6 (435)	21.1 (172)		19.9 (73)		22.4 (67)	
Physical activity: inactive, % (n)	33.5 (499)	49.8 (386)	<0.001	48.5 (179)	<0.001	38.8 (118)	0.13
Social class, % (n)			0.04		0.25		0.11
Nonmanual	59.0 (860)	54.4 (434)		55.5 (197)		53.9 (159)	
Manual	41.0 (598)	45.6 (364)		44.5 (158)		46.1 (136)	
Education level, % (n)			<0.001		0.01		0.02
No qualification	36.2 (538)	45.7 (377)		44.4 (164)		44.1 (134)	
Completed school	51.5 (765)	44.8 (369)		45.3 (171)		46.8 (142)	
Completed university	12.4 (185)	9.6 (79)		9.2 (34)		9.2 (28)	

SHBG indicates sex hormone binding globulin; DHEAS, dehydroepiandrosterone sulfate.

*Probability value of cases vs controls, with *t* test used to compare continuous variables and χ^2 test used for categorical variables.

†Exact numbers may vary slightly because of missing data for some variables. n=2314 for testosterone, n=2287 with cholesterol; n=2172 with LDL and HDL cholesterol.

have been postulated to be a risk factor for prostate cancer, although again, prospective studies have found no consistent relationships.[25] Most of these studies had limited power for disease events. We present data from a prospective population study examining the relationship between endogenous testosterone concentrations and subsequent mortality due to all causes, cardiovascular disease, and cancer in middle-aged and older men.

Methods

The men were participants in the European Prospective Investigation into Cancer in Norfolk (EPIC-Norfolk), a prospective population study of 11 606 men and 14 033 women 40 to 79 years of age, 99% white, recruited from age-sex registers of general practices in Norfolk, United Kingdom, who answered a baseline questionnaire and attended a clinic visit. They were comparable to national population samples with respect to many characteristics.[26]

At the baseline survey in 1993 to 1997, participants completed detailed questionnaires. They were asked about medical history,

Table 2. Description of Baseline Variables in 2314 Men* 42 to 78 Years of Age by Quartile Group of Serum Testosterone in EPIC-Norfolk 1993 to 1997

	Quartile Groups of Testosterone				
	1 <12.5 nmol/L (n=569)	2 12.5–15.6 nmol/L (n=595)	3 15.7–19.6 nmol/L (n=568)	4 >19.6 nmol/L (n=582)	*P* for Trend
Testosterone, nmol/L, mean (SD)	9.5 (2.5)	14.1 (0.96)	17.5 (1.09)	24.2 (4.40)	
SHBG, nmol/L, mean (SD)	35.2 (13.3)	41.7 (13.9)	46.6 (12.9)	56.9 (19.0)	<0.001
Testosterone/SHBG ratio, mean (SD)	0.31 (0.13)	0.37 (0.12)	0.40 (0.11)	0.46 (0.15)	<0.001
DHEAS, μmol/L, mean (SD)	2.44 (1.65)	2.92 (1.83)	2.86 (1.82)	3.19 (2.04)	0.01
Androstanediol glucuronide, nmol/L, mean (SD)	12.1 (7.9)	14.2 (7.8)	14.3 (7.8)	16.4 (8.3)	0.04
Age, y, mean (SD)	67.7 (6.6)	67.2 (6.7)	67.3 (6.7)	66.9 (6.6)	0.06
Body mass index, kg/m^2, mean (SD)	27.7 (3.5)	26.7 (3.1)	26.5 (3.2)	25.7 (3.1)	<0.001
Waist-hip ratio, mean (SD)	0.96 (0.06)	0.96 (0.06)	0.94 (0.06)	0.93 (0.06)	<0.001
Systolic blood pressure, mm Hg, mean (SD)	143.0 (19.6)	142.4 (18.3)	144.0 (19.5)	141.0 (18.5)	0.22
Diastolic blood pressure, mm Hg, mean (SD)	85.2 (12.4)	84.9 (11.8)	85.6 (11.7)	84.7 (11.6)	0.63
Cholesterol, mmol/L, mean (SD)	5.94 (1.15)	6.10 (1.09)	6.08 (1.03)	6.19 (1.08)	<0.001
LDL cholesterol, mmol/L, mean (SD)	3.78 (0.96)	3.95 (0.94)	3.99 (0.54)	4.13 (0.56)	<0.001
HDL cholesterol, mmol/L, mean (SD)	1.18 (0.33)	1.24 (0.34)	1.24 (0.34)	1.28 (0.34)	<0.001
LDL/HDL ratio, mean (SD)	3.41 (1.15)	3.41 (1.17)	3.44 (1.20)	3.51 (1.27)	0.13
Triglycerides, mmol/L, mean (SD)	2.25 (1.27)	2.20 (1.16)	1.92 (1.03)	1.81 (0.96)	<0.001
Alcohol intake, U/wk, mean (SD)	8.1 (9.7)	9.2 (11.7)	9.5 (12.1)	8.9 (11.2)	0.21
History of diabetes, % (n)	7.9 (45)	4.4 (26)	4.8 (27)	1.9 (11)	<0.001
History of hypertension, % (n)	22.5 (128)	23.4 (139)	16.9 (96)	17.2 (100)	<0.01
History of high cholesterol, % (n)	8.3 (47)	9.7 (58)	9.2 (52)	9.8 (57)	0.79
Aspirin use, % (n)	24.0 (357)	21.1 (103)	23.0 (111)	17.7 (87)	0.08
Cigarette smokers, % (n)					<0.01
Current	9.1 (51)	8.5 (50)	11.3 (64)	13.8 (79)	
Former	65.3 (367)	67.7 (398)	59.6 (337)	58.5 (335)	
Never	25.6 (144)	23.8 (140)	29.0 (164)	27.7 (159)	
Physical activity: inactive, % (n)	43.6 (248)	36.0 (170)	27.1 (154)	24.1 (140)	0.03
Social class, % (n)					0.20
Nonmanual	58.4 (330)	56.6 (328)	59.5 (331)	54.1 (305)	
Manual	40.6 (226)	43.4 (252)	40.5 (225)	45.9 (259)	
Education level, % (n)					0.90
No qualification	39.7 (226)	40.8 (243)	39.4 (224)	38.2 (222)	
Completed school	49.5 (281)	47.7 (284)	48.1 (273)	50.9 (296)	
Completed university	10.9 (62)	11.4 (68)	12.5 (71)	10.8 (63)	

SHBG indicates sex hormone binding globulin; DHEAS, dehydroepiandrosterone sulfate.

Values are mean (SD). Continuous variables were compared by ANOVA and categorical values with the χ^2 test.

*Exact numbers may vary slightly because of missing data for some variables. n=2314 for testosterone, n=2287 with cholesterol; n=2172 with LDL and HDL cholesterol.

occupational and educational status, smoking history, alcohol consumption, and physical activity, as described in detail elsewhere.[26–28]

A health examination was performed by trained nurses using a standardized protocol at a clinic visit. This included anthropometry measures and blood pressure measured with an Accutorr monitor after the participant had been seated for 5 minutes. The mean of 2 readings was used for analysis. Nonfasting blood samples taken at the visit were stored in a refrigerator at 4°C overnight, then processed for assays or for frozen storage. Clinic visits were between 9 AM and 4 PM. Fresh samples for lipid measurements were assayed at the Department of Clinical Biochemistry, Cambridge University. Serum total cholesterol, HDL cholesterol, and triglyceride were measured with the RA 1000 (Bayer Diagnostics, Basingstoke, United Kingdom), and low-density lipoprotein (LDL) cholesterol values were calculated with the Friedewald formula. Blood samples for storage were stored as separate 500-μL aliquots of serum and plasma in sealed straws in liquid nitrogen at −120°C.

All participants were flagged for death certification at the Office of National Statistics United Kingdom, with vital status ascertained on the entire cohort. Death certificates were coded by trained nosologists according to the International Classification of Diseases, 9th or 10th revision (ICD9 or ICD10, respectively). A death due to cardiovascular causes was defined as ICD9 400 to 448 or ICD10 I10 to I79 listed as the underlying cause of death; coronary heart disease

Table 3. Distribution of Cases and Controls Among Men 42 to 78 Years of Age and OR* of Mortality Due to All Causes, Cardiovascular Disease, and Cancer by Quartile Group of Serum Testosterone in EPIC-Norfolk 1993 to 2003

	Quartile Groups of Testosterone				
	1 <12.5 nmol/L	2 12.5–15.6 nmol/L	3 15.7–19.6 nmol/L	4 >19.6 nmol/L	*P* for Trend
All-cause mortality: cases/controls, n	234/335	216/379	184/384	191/391	<0.001
Age-adjusted OR (95% CI)*	1	0.82 (0.65–1.04)	0.69 (0.54–0.88)	0.71 (0.56–0.90)	
Age- and hormone-adjusted OR (95% CI)†	1	0.81 (0.63–1.04)	0.65 (0.50–0.84)	0.61 (0.45–0.82)	
Age-, covariate-, and hormone-adjusted OR‡	1	0.75 (0.55–1.00)	0.62 (0.45–0.84)	0.59 (0.42–0.85)	
Cardiovascular mortality: cases/controls, n	105/335	108/379	81/384	75/391	<0.01
Age-adjusted OR (95% CI)*	1	0.93 (0.69–1.27)	0.68 (0.49–0.94)	0.62 (0.45–0.87)	
Age- and hormone-adjusted OR (95% CI)†	1	0.88 (0.64–1.21)	0.63 (0.44–0.89)	0.52 (0.35–0.77)	
Age-, covariate-, and hormone-adjusted OR‡	1	0.89 (0.60–1.32)	0.60 (0.39–0.92)	0.53 (0.32–0.86)	
CHD mortality: cases/controls, n	62/335	64/379	53/384	45/391	
Age-adjusted OR (95% CI)*	1	0.92 (0.62–1.35)	0.74 (0.5–1.10)	0.63 (0.42–0.95)	
Age- and hormone-adjusted OR (95% CI)†	1	0.86 (0.57–1.28)	0.72 (0.47–1.10)	0.57 (0.35–0.95)	
Age-, covariate-, and hormone-adjusted OR‡	1	0.71 (0.43–1.17)	0.59 (0.39–1.00)	0.52 (0.28–0.97)	
Cancer mortality: cases/controls, n	88/335	73/379	71/384	71/391	0.04
Age-adjusted OR (95% CI)*	1	0.73 (0.52–1.04)	0.71 (0.50–0.99)	0.70 (0.50–0.98)	
Age- and hormone-adjusted OR (95% CI)†	1	0.82 (0.57–1.18)	0.74 (0.50–1.08)	0.73 (0.49–1.11)	
Age-, covariate-, and hormone-adjusted OR‡	1	0.74 (0.48–1.15)	0.77 (0.49–1.20)	0.71 (0.43–1.20)	

CHD indicates coronary heart disease.

*ORs were estimated with logistic regression. All estimates are adjusted for age and date of visit. The *P* values for trend are based on χ^2 test.

†Variables included are age, date of visit, sex hormone binding globulin, dehydroepiandrosterone sulfate, and androstanediol glucuronide.

‡Covariates are age, date of visit, body mass index, waist-hip ratio, systolic blood pressure, cholesterol, history of diabetes, history of hypertension, history of high cholesterol, aspirin use, alcohol intake, cigarette smoking status, physical activity, social class, education level, sex hormone binding globulin, dehydroepiandrosterone sulfate, and androstanediol glucuronide.

was ICD9 410 to 414 or ICD10 I20 to I25; and cancer was ICD9 140 to 208 or ICD10 C00 to C97.

In 2003, after the exclusion of 1183 men who reported having cardiovascular disease or cancer at the baseline visit in 1993 to 1997, which left 10 423 men, we identified men who had died because of any cause and up to 2 sex-matched, age-matched (±3 years), and date-of-visit–matched (±3 months) control subjects from the cohort who were still alive. The average follow-up time in the present analysis was 7 years (range 1 to 125 months). Frozen serum samples identified from case and control subjects taken at the baseline visit in 1993 to 1997 were retrieved from the liquid nitrogen stores. Total testosterone, dehydroepiandrosterone sulfate, and sex hormone binding globulin were assayed in a research laboratory with an Immulite Chemiluminescent Immunoassay System (DPC, Gwynedd, United Kingdom) and androstanediol glucuronide with a radioimmunoassay (DSL-6000, Diagnostic Systems Laboratories Inc, Webster, Tex). The intra-assay precision, interassay precision, and sensitivity for testosterone were 7.5%, 6.6%, and 0.3 nmol/L, respectively, and for sex hormone binding globulin, they were 6.1%, 7.5%, and 0.2 nmol/L, respectively.

The study was approved by the Norwich District Health Authority Ethics Committee, and all participants gave signed informed consent. The present analysis was based on 825 men without prevalent cardiovascular disease and cancer in 1993 to 1997 who had since died and 1489 control subjects who were alive in 2003.

We compared risk factor distributions by mortality status and by quartile groups of endogenous testosterone. Although some variables were slightly skewed, results were similar when log transformed, so the untransformed data are shown for ease of interpretation. Although we matched total mortality cases and controls individually for age and date of visit, to enable us to conduct the analyses on subgroups by cause of death and after exclusion of deaths in the first 2 years, we used unconditional logistic regression to determine the odds ratios (ORs) of mortality by testosterone quartile group, incorporating for matching in the analysis by including age and visit date as covariates in all analyses. In these circumstances, unconditional logistic regression that is adjusted for matching will be essentially the same as conditional logistic regression. We used logistic regression to determine the ORs of mortality by testosterone quartile group, then used testosterone as a continuous variable after adjusting for age and date of visit, and then for age, date of visit, and other covariates. Analyses were also run with a Cox regression model, and results were similar. Results are presented for the logistic regression modeling as the generally accepted method for case-control analyses. Nevertheless, we also examined time-dependent survival curves by testosterone quartile using the Cox model. Statistical analyses were conducted with SPSS 11.5 (SPSS Inc, Chicago, Ill).

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Table 1 shows baseline measurements in men who subsequently died from all causes, cardiovascular disease, and cancer, as well as control subjects who were still alive. Mean testosterone concentrations were lower in men who died of any cause, cardiovascular disease, or cancer than in control subjects. Mean waist-hip ratio, prevalence of cigarette smoking, and prevalence of diabetes mellitus were also higher in men who died of any cause, cardiovascular disease, or cancer than in control subjects. Men who died of any cause or of cardiovascular causes had significantly higher mean systolic blood pressure and blood triglycerides. Men who died of cardiovascular causes also had significantly higher mean body mass index, serum cholesterol, and LDL:HDL cholesterol ratios. Of the 304 cancer deaths identified, there were 55

Table 4. ORs* of Mortality Due to All Causes, Cardiovascular Disease, and Cancer Associated With Serum Testosterone Increase of 6 nmol/L in Men 42 to 78 Years of Age in EPIC-Norfolk 1993 to 2003, Adjusted for Age and Covariates

		Age Adjusted		Age and Covariate† Adjusted	
	Cases/Controls, n	OR (95% CI)	*P*	OR (95% CI)	*P*
All men					
All-cause mortality	825/1489	0.86 (0.79–0.94)	<0.001	0.81 (0.71–0.92)	<0.01
Cardiovascular mortality	369/1489	0.83 (0.74–0.94)	<0.01	0.76 (0.63–0.93)	<0.01
CHD mortality	224/1489	0.86 (0.74–1.00)	0.07	0.82 (0.64–1.05)	0.11
Cancer mortality	304/1489	0.82 (0.72–0.94)	<0.01	0.84 (0.68–1.03)	0.08
Excluding deaths within 2 y					
All-cause mortality	677/1489	0.86 (0.78–0.94)	<0.01	0.79 (0.69–0.91)	<0.01
Cardiovascular mortality	293/1489	0.85 (0.74–0.97)	0.02	0.79 (0.64–0.97)	0.02
CHD mortality	170/1489	0.86 (0.65–1.12)	0.27	0.89 (0.75–1.06)	0.12
Cancer mortality	249/1489	0.81 (0.69–0.94)	<0.01	0.81 (0.65–1.01)	0.06

*ORs are shown per 6-nmol/L increase in serum testosterone (≈1 SD) with logistic regression. All ORs are adjusted for age and date of visit.

†Covariates are age, date of visit, body mass index, waist-hip ratio, systolic blood pressure, cholesterol, history of diabetes, history of hypertension, history of high cholesterol, aspirin use, alcohol intake, cigarette smoking status, physical activity, social class, education level, dehydroepiandrosterone sulfate, androstanediol glucuronide, and sex hormone binding globulin.

lung, 50 prostate, 37 colorectal, 15 esophageal, and 11 stomach cancer deaths.

Table 2 shows the distribution of variables by quartile group of serum testosterone level. Testosterone concentrations were significantly inversely related to body mass index, waist-hip ratio, triglycerides, and prevalence of diabetes mellitus and were positively related to total cholesterol, LDL cholesterol, and HDL cholesterol concentrations and to cigarette smoking habit.

Table 3 shows the distribution of men who died and control subjects by quartile group of serum testosterone. Age-adjusted OR for mortality due to all causes, cardiovascular disease, coronary heart disease, and cancer decreased significantly with increasing quartile group of testosterone and strengthened slightly after multivariable adjustment for other hormones and for covariates. For total mortality, the ORs (95% confidence intervals [CIs]) for increasing quartiles of endogenous total testosterone compared with the lowest quartile were 0.75 (0.55 to 1.00), 0.62 (0.45 to 0.84), and 0.59 (0.42 to 0.85), respectively, after adjustment for age, date of visit, body mass index, systolic blood pressure, blood cholesterol, cigarette smoking, physical activity, alcohol intake, diabetes mellitus, history of hypertension, history of high blood cholesterol, social class, education level, dehydroepiandrosterone sulfate, androstanediol glucuronide, and sex hormone binding globulin.

Table 4 shows the multivariable relationship of testosterone modeled as a continuous variable with mortality due to all causes, cardiovascular disease, coronary heart disease, and cancer and after the exclusion of those who died within 2 years. For every 6-nmol/L increase in serum testosterone (≈1 SD), there was a 14% lower risk of mortality (OR 0.86, 95% CI 0.79 to 0.94, $P<0.001$). The magnitude of effect was similar for deaths due to cardiovascular causes and those due to cancer and was little changed after adjustment for cardiovascular risk factors and sex hormone binding globulin or after the exclusion of deaths within 2 years. Inclusion of LDL and HDL cholesterol or triglycerides in the model in place of total cholesterol did not substantially alter the findings, and these associations were also consistent in subgroups that were stratified by body mass index and by smoking (not shown). In analyses stratified by age <65 years and ≥65 years, the multivariable-adjusted ORs for total mortality for every 6-nmol/L increase in serum testosterone were 0.95 (95% CI 0.85 to 1.20, $P=0.63$) in men <65 years old (206 case subjects and 427 control subjects) and 0.79 (0.68 to 0.92, $P=0.002$) in men ≥65 years old (619 case subjects and 1062 control subjects). The age-testosterone interaction term was not significant ($P=0.10$). The findings were similar when testosterone–sex hormone binding globulin ratio was used instead of total testosterone in analyses (data not shown).

The Figure shows survival curves by quartile of testosterone with the Cox regression model. These curves must be interpreted with caution, because they were based on a nested case-control rather than cohort analysis. Nevertheless, the results are consistent with ORs estimated on the basis of logistic regression.

Discussion

In the present study population of men, increasing endogenous testosterone concentrations appeared to be inversely related to mortality due to all causes, cardiovascular causes, and cancer, with ≈25% to 30% lower risk of total mortality in the highest compared with the lowest quartile of testosterone level. A 1-SD increase in testosterone level was associated with an ≈14% lower risk of total mortality. Testosterone concentrations were significantly associated with several cardiovascular risk factors, including HDL cholesterol, triglyceride, body mass index, and diabetes prevalence, in an apparently beneficial direction and with total cholesterol and LDL cholesterol in an unfavorable direction. However, the relationship with mortality due to all causes, cardiovascular

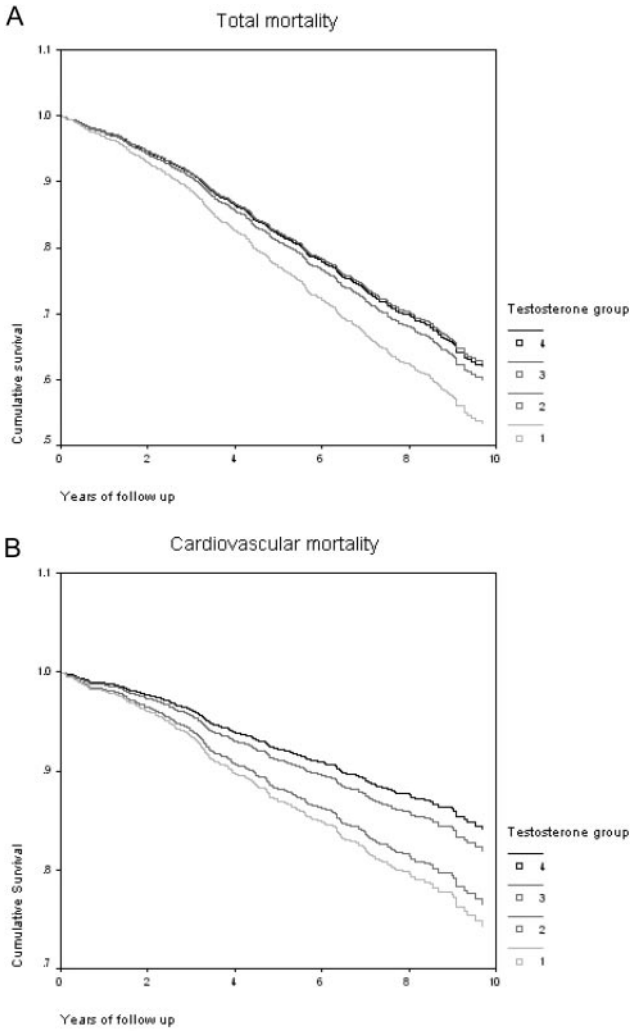

Figure. Multivariate-adjusted survival by quartile group of endogenous testosterone concentrations (1 is lowest, 4 is highest) in 2314 men 42 to 78 years old in EPIC-Norfolk 1993 to 2003.

disease, and cancer was still present after adjustment for other hormones, sex hormone binding globulin, and cardiovascular risk factors that included age, body mass index or waist-hip ratio, systolic blood pressure, lipid profile, diabetes status, history of hypertension, history of high blood cholesterol, social class, education status, alcohol intake, physical activity, and cigarette smoking habit.

The relationship between endogenous testosterone and cardiovascular disease has been reviewed extensively elsewhere.[16,29,30] In general, most cross-sectional studies have reported higher endogenous testosterone concentrations associated with more favorable cardiovascular disease risk factor profiles, including higher HDL cholesterol and lower triglyceride concentrations, blood glucose, blood pressure, and body mass index. Nevertheless, several cross-sectional and prospective studies have found no significant relationships between endogenous testosterone concentrations and cardiovascular disease events, although the trend has been generally in an inverse association. Cauley et al,[18] in a 6- to 8-year follow-up of men in the Multiple Risk Factor Intervention Study, reported that testosterone concentrations in 163 men who had a coronary event were not significantly different from those in 163 age-matched control subjects. The Honolulu Heart Study reported no difference in testosterone concentrations in 96 men who had heart disease after 20 years' follow-up compared with 96 control subjects.[19] The Rancho Bernardo Study reported 114 cardiovascular and 82 coronary heart disease deaths in 872 men who were 40 to 79 years of age without baseline cardiovascular disease who were followed up for 12 years; mean testosterone concentrations did not differ in those who subsequently did or did not experience an event.[20] Contoreggi et al[21] reported no difference in 46 men who developed coronary artery disease compared with 124 men who did not after 9.5 years of follow-up. The Caerphilly Study followed up 2512 men 45 to 59 years old for 5 years; 153 men who experienced an ischemic heart disease event had concentrations of plasma testosterone at baseline similar to those of the rest of the cohort.[22] In a twin study of 566 participants, there were no significant differences between hormone concentrations in participants with and without prevalent (n=78) or incident (n=154) coronary heart disease.[23] More recently, a study from Framingham reported serum testosterone was not significantly associated with incident cardiovascular disease in a 10-year follow-up of 2084 men who experienced 386 events.[24]

The lack of significant associations of testosterone with cardiovascular events in prospective studies has been variously attributed to measurement error in the characterization of testosterone concentrations in individuals with only 1 blood sample and methodological issues that surround the assay of testosterone or the stability of frozen samples.[31] These measurement issues, together with the limited size of the studies to date, mean that these studies were limited in statistical power either to detect or to exclude a moderate relationship with cardiovascular events.

Nevertheless, there is supportive evidence from studies examining the relationship between endogenous testosterone and atherosclerosis that suggests a mechanism through which testosterone may relate to cardiovascular end points. Phillips et al[32] reported the first study of a strong inverse correlation between free testosterone and degree of coronary artery disease in 55 men undergoing angiography without a history of myocardial infarction. Subsequent studies reported a similar inverse relationship cross-sectionally with carotid atherosclerosis[33] and also with progression of atherosclerosis in the aorta[34] and carotid artery.[35]

Although testosterone supplementation studies have been conducted, their relevance to interpretation of the data on endogenous hormone concentrations and cardiovascular disease in the general population are limited, because many were not properly randomized or blinded, were conducted in highly selected patient groups, or used pharmacological doses of testosterone, and none had cardiovascular disease end points. Some supplementation studies have reported beneficial effects of oral testosterone undecanoate therapy or intravenous administration on symptomatic angina pectoris, ECG patterns, and cardiovascular function,[36,37]

In the present cohort, we found both potentially beneficial and adverse relationships of endogenous testosterone concentrations with these classic risk factors, but the relationship with cardiovascular disease was unchanged after adjustment for these factors, which indicates that if a protective cardiovascular effect

exists, it does not appear to be mediated through them.[38] Higher testosterone has been associated with lower concentrations of inflammatory markers, insulin, and hemostatic factors,[39–42] measures that were not available in the present cohort, and it is possible that any protective cardiovascular effect may act through these mechanisms or through improved endothelial function and coronary vasodilatation.[43,44]

Suppression of testosterone concentrations leads to regression of prostate cancer,[45] which leads to the concern that high testosterone concentrations might be a risk factor for prostate and other male reproductive cancers; however, prospective studies or supplementation studies, reviewed elsewhere,[5,25] have not reported significant relationships of endogenous testosterone concentrations or of testosterone supplementation with prostate cancer. Although in the present analysis, there was insufficient power to examine the relationships with prostate or other specific cancers, we observed an inverse relationship of endogenous testosterone concentrations with cancer mortality.

The present study had limitations. Only a single, nonfasting blood sample was used to characterize individuals with respect to testosterone status. This may have resulted in considerable random measurement error because of high intraindividual variation in testosterone with seasonal, diurnal, and episodic variation. Nevertheless, a single measure is reported to be adequate for population studies[25,31]; in any case, random variation is likely to attenuate rather than produce spurious relationships.

It is possible that testosterone concentrations may be low in men who are already ill and more likely to die during follow-up. Men with known serious chronic disease, namely, cancer, heart disease, and stroke, were excluded from the present analyses. This was based on self-report, and it is possible that there were still men with subclinical disease included. Nevertheless, the relationships were also consistent after the exclusion of all those who died within 2 years of the baseline, who may have had had preclinical illness. Although we cannot exclude residual confounding from other factors not measured here, these findings are consistent with existing evidence from epidemiological and clinical studies indicating that endogenous testosterone concentrations may be an indicator of good health. Of course, generalizability of results from the present study is limited to men; furthermore, the generalizability of these findings to other ethnic groups is unknown.

The present study suggests that high endogenous testosterone concentrations appear to be beneficially associated with mortality due to all causes, cardiovascular disease, and cancer. These findings require replication in other population studies. The Women's Health Initiative[46] and the Hormone and Estrogen Replacement Study,[47] which found adverse effects of estrogen and progestin replacement therapy in women, emphasize the necessity for end-point trials. Paradoxically, although many men are already using testosterone supplementation, concern about increased cancer risk has been one reason trials have not been conducted in this area. We concur with the conclusions from recent reviews that although the data appear reassuring, definitive assessment of the long-term effects of testosterone replacement therapy on health will require large-scale controlled trials.[3,5,48] Data from the present study may encourage consideration of further research into the role of testosterone in health in men.

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Disclosures

None.

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CLINICAL PERSPECTIVE

The role of testosterone in men's health is still controversial. High doses of exogenous testosterone or other anabolic steroids have been associated with adverse health effects, including sudden cardiac death and liver disease, but hypogonadism in men is also adversely associated with health. Surprisingly, the relationship between endogenous testosterone concentrations within the physiological range and overall health in men is still not well established. A 10-year prospective study in men aged 40 to 79 years now reports that higher endogenous testosterone is associated with lower subsequent mortality from all causes, cardiovascular causes, and cancer. Men in the top quartile for endogenous testosterone concentrations had ≈40% lower risk of death due to any cause than men in the bottom quartile, and this relationship appeared independent of age, body mass index, smoking and other lifestyle factors, cardiovascular risk factors, and other hormone levels. These findings require replication in other population studies, and the lessons from postmenopausal hormone therapy in women emphasize the necessity for end-point trials. Paradoxically, although many men are already using testosterone supplementation, concern about increased cancer risk has been one reason trials have not been conducted. Although data appear reassuring, definitive assessment of the long-term effects of testosterone replacement therapy on health will require large-scale controlled trials. In the interim, endogenous testosterone appears to be a predictor of health in men, and these findings highlight the need for further research into the role of testosterone in health in men.