Title

Supplement to "Serum testosterone is inversely, and sex hormone-binding globulin directly, associated with all-cause mortality in men".

Authors

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Supplementary material

Methods

Alcohol consumption was categorised as abstainers <1, low 1-<7, moderate 7-<14, medium 14-<21, high ≥21 units/week (1 unit=8 g pure alcohol).[1] Diet categories were high red meat (beef, lamb and pork >3 times/week), low red meat (≤3/week), poultry (no red meat), fish (no red meat or poultry), vegetarians (no red meat, poultry or fish), vegan (no red meat, poultry, fish, eggs or diary).[2] Vigorous and moderate physical activity undertaken per week was categorised to World Health Organization recommendations as sufficient: ≥75 minutes vigorous or ≥150 minutes moderate, or equivalent combination; insufficient: less than this; additional: ≥150 minutes vigorous- or ≥300 minutes moderate-level or equivalent combination (for "additional" health benefits).[3]

Diabetes was determined as blood glucose ≥11.1 mmol/L unfasted or ≥7.0 mmol/L fasting, or glycated haemoglobin ≥48 mmol/mol (6.5%), or previous hospital admission diagnosis, or insulin use, or self-report condition. Dementia was determined as use of anti-dementia

medication(s), or previous hospital admission diagnosis, or self-report condition. Renal impairment was determined as creatinine >150 umol/L, or previous hospital admission diagnosis or self-report of renal/kidney failure, dialysis, nephropathy or nephritis. Hypertension was determined as systolic blood pressure ≥140 or diastolic ≥90 mmHg or taking blood pressure medication, prior hospital admission diagnosis, or self-report condition. Hyperlipidemia was categorised according to the use of lipid-lowering medications.[4] The number of medications was further recoded into categories of 0, 1-2, 3-4, 5+ medications taken, consistent with NHS reporting.[5]

Statistical analysis

Median follow-up time was calculated using the reverse Kaplan-Meier method.[6] Cox proportional hazards models were fitted using the rms package in R version 4.0.2.[7] Site was modelled as a stratified factor to account for the relatedness of observations taken for individuals recruited to different UK Biobank assessment centres at baseline. Accordingly, the site term represents geographic variation among the sites for the population of male UK Biobank participants. Continuous explanatory variables were modelled using pre-specified restricted cubic splines to account for the prospect of non-linearities in modelled associations. Restricted cubic splines were used to model non-linear associations with continuous covariates, with 3 internal knots at the 27.5th, 50th, 72.5th percentiles and linear constraints outside of the outer knots at the 5th and 95th percentiles of the marginal distribution of these covariates.

Complete-case analyses were done in the first instance. Analyses were repeated for multiply-imputed datasets, as well as for data excluding deaths occurring in the first two years of follow-up, for inferring the potential effects of missing data and reverse causation on results.

Multiple Imputation using Chained Equations (MICE)[8,9] was used to impute the missing values. Ten imputed datasets were each created from 20 MICE iterations including the following variables: log(*Y*), δ, hormone variables (testosterone, SHBG), participants' age, ethnicity, living with partner, qualifications, alcohol consumption, dietary patterns, total cholesterol, physical activity, smoking status, BMI, waist circumference, assessment centre (site), medication variables (anticonvulsants, lipid, glucocorticoids, opioids, total number of medications), and prevalent health condition variables (angina, atrial fibrillation, COPD, dementia, diabetes, HIV, hypertension, liver disease, renal impairment, thyroid disease). Prevalent CVD and region (i.e., instead of site: UK, Scotland, Wales) were included in multiple imputations for analyses of CVD deaths. Prevalent cancer was included in multiple imputations for analyses of cancer deaths. The *Y* and δ variables are the minimum of the event and censoring times, and the censoring variable, respectively, and so are commensurate with, and represent, a separate set of imputations for each of the analysis outcomes. Logistic regression was used for δ and factors with two levels, polytomous regression used for factors with more than two levels, and predictive mean matching used for continuous covariates. The estimated minimum number of imputed datasets was determined using the formula of von Hippel[10] applied to the log hazard ratio estimates from the first five imputed datasets. The highest estimate of the minimum number of imputations across all analyses was 8.2. Multiply imputed estimates were pooled using Rubin's rules,[11] and, for tests of association, likelihood ratio statistics were pooled using the method of Meng and Rubin.[12]

Prior to fitting models, the number of events per variable[13] for complete-case analyses for the most complex Multivariable 2 model was 159.6 for all-cause deaths, 30.1 for CVD deaths, and 77.0 for cancer deaths. The validity of the proportional hazards assumption was assessed using per-variable and global tests.[14] Plots of the Schoenfeld residuals, with estimated

coefficients and 95% confidence intervals plotted against follow-up times, were inspected for statistically significant results. Test results were ignored when the detected temporal variation for proportional hazard estimates was shown to be negligible.[15] The prevalent cancer status variable was modelled as a stratification factor in analyses of cancer deaths to account for a violation of the proportional hazards assumption when it had been included as a model predictor in that analysis.

No CVD deaths were recorded for one of the sites (Wrexham) and so for that analysis site was recoded to broader geographic categories of region (UK, Scotland, Wales).[4] Correlations of estimated coefficients with coefficients for the exposure variable were assessed for all model fits and did not exceed |0.2| in any analysis.

References

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Table S1. Hospital diagnosis and cancer registry codes used to identify health conditions of interest or for covariate adjustment terms or determining exclusions.*

Health condition	**ICD-9**	**ICD-10**
CVD deaths	ICD-10 only for incident outcomes	I20, I21, I22, I23, I24, I25, I42.0, I46, I50, I60, I61, I63, I64, I70, I71
Cancer deaths	ICD-10 only for incident outcomes	C00-C97
Androgenital / testicular disorders	255.2, 257	E25, E29
Pituitary disease	253.0-253.4, 253.7	E22.0, E22.1, E22.8, E22.9, E23.0, E22.1, E23.3, E24
Angina	413.0, 413.1, 413.9	I20.0, I20.1, I20.8, I20.9
Atrial Fibrillation	427.3	I48, and, where the 4th digit was provided**, I48.0, I48.1, I48.2, I48.9
Cancer	140-172, 174-209	C00-C43, C45-C97
COPD	490, 491, 492, 494, 496	J43.1, J43.2, J43.8, J43.9, J44.0, J44.1, J44.8, J44.9
CVD	410, 428, 430-437	I21, I22, I50, I60-I64, I69.0-I69.4
Diabetes	250.0 - 250.9	E10 - E14
Dementia	290.0, 290.1, 290.2, 290.3, 290.4, 290.8, 290.9, 294.1, 294.8, 331.0, 331.1, 331.2, 331.4, 331.82	F00, F01, F02.0, F02.2, F02.3, F02.8, F03, F05.1, G10, G30, G31.0, G31.1, G31.8, G31.9
HIV	042	B20-B24
Hypertension	401	I10
Liver disease	570-573	K70-K76
Renal Impairment	582, 583, 585, 586	N03, N04, N05, N08.1-NO8.3, NO8.5, N11.1, N11.8, N11.9, N14, N18.2, N18.3, N18.4, N18.5, N18.6, N18.9, N19
Thyroid disease	240-245	E00-E06

* = Additional data sources were also used for identifying prevalent conditions (e.g., from self-report medical conditions, self-report medication usage, physical examination and blood chemistry measurements).

** = In many cases only "I48" was provided but in others the full 4 digit code was provided.

Table S2. Hazard ratios of all-cause mortality, deaths due to CVD, and deaths due to cancer by quintiles of testosterone (T): Pooled estimates from analysis of multiply-imputed data.

Model	Q5 (highest T) (n = 41,676) [§]	Q4 (n = 41,673)	Q3 (n = 41,686)	Q2 (n = 41,704)	Q1 (lowest T) (n = 41,686)	*P* Value
All-cause deaths: 15,914 events						
	3,209 events	***2,853 events***	***2,865 events***	***3,133 events***	***3,854 events***	
Univariable	ref.	0.95 (0.92-0.97)	0.96 (0.92-1.02)	0.96 (0.92-1.00)	1.21 (1.16-1.26)	< 0.001**
Multivariable 1*	ref.	0.92 (0.90-0.95)	0.89 (0.84-0.93)	0.84 (0.80-0.88)	0.90 (0.87-0.95)	< 0.001**
Multivariable 2	ref.	1.00 (0.97-1.03)	1.02 (0.97-1.08)	1.04 (0.99-1.10)	1.18 (1.11-1.24)	< 0.001**
CVD deaths: 3,128 events						
	590 events	***530 events***	***573 events***	***640 events***	***795 events***	
Univariable	ref.	0.98 (0.92-1.05)	1.01 (0.89-1.13)	1.07 (0.97-1.18)	1.35 (1.23-1.49)	< 0.001**
Multivariable 1	ref.	0.92 (0.86-0.98)	0.85 (0.76-0.96)	0.83 (0.74-0.92)	0.83 (0.75-0.92)	0.003**
Multivariable 2	ref.	0.96 (0.90-1.03)	0.94 (0.82-1.07)	0.95 (0.84-1.07)	1.01 (0.89-1.14)	0.328
Cancer deaths: 7,468 events						
	1,411 events	***1,339 events***	***1,383 events***	***1,493 events***	***1,842 events***	
Univariable	ref.	1.01 (0.97-1.05)	1.05 (0.97-1.13)	1.01 (0.94-1.07)	1.28 (1.21-1.36)	< 0.001**
Multivariable 1	ref.	0.96 (0.92-1.00)	0.96 (0.89-1.03)	0.92 (0.86-0.99)	1.03 (0.96-1.10)	< 0.001**
Multivariable 2	ref.	1.01 (0.97-1.06)	1.05 (0.97-1.14)	1.06 (0.98-1.14)	1.20 (1.11-1.30)	< 0.001**

[§] = Quintile boundaries Q1/2 8.9 nmol/L (256 ng/dL), Q2/3 10.8 nmol/L (311 ng/dL), Q3/4 12.5 nmol/L (360 ng/dL) and Q4/5 14.8 nmol/L (427 ng/dL). 2.5th percentile = 5.9 nmol/L (170 ng/dL), 97.5th = 20.1 nmol/L (579 ng/dL); Presented numbers are for imputed data, after exclusions.

* = Multivariable 1 models included age, ethnicity, living with partner, qualifications, alcohol consumption, smoking status, diet, physical activity, BMI, waist circumference, cholesterol, prevalent diabetes, hypertension, angina, atrial fibrillation, COPD, dementia, renal impairment, liver disease, thyroid disease, HIV, and use of lipid medications (a proxy for hyperlipidemia), glucocorticoids, opioids, and anticonvulsants, with the number of medications included as a proxy for overall comorbidity status and assessment centre as a stratification factor. Prevalent CVD and Cancer status were included as additional terms in analyses of CVD deaths and Cancer deaths, respectively. Multivariable 2 models for testosterone included SHBG as an additional covariate.

** = Result interpreted as significant.

Table S3. Hazard ratios of all-cause mortality, deaths due to CVD, and deaths due to cancer by quintiles of testosterone (T): Analysis of data excluding participants who died within the first two years of follow-up.

Model	Q5 (highest T) (n = 30,289) §	Q4 (n = 30,383)	Q3 (n = 30,093)	Q2 (n = 29,634)	Q1 (lowest T) (n = 28,245)	*P* Value
All-cause deaths: 9,261 events						
	1,869 events	*1,781 events*	*1,701 events*	*1,829 events*	*2,081 events*	
Univariable	ref.	0.97 (0.93-1.00)	1.00 (0.93-1.07)	0.97 (0.91-1.02)	1.21 (1.15-1.28)	< 0.001**
Multivariable 1*	ref.	0.93 (0.89-0.96)	0.89 (0.83-0.96)	0.82 (0.78-0.87)	0.89 (0.84-0.95)	< 0.001**
Multivariable 2	ref.	0.99 (0.95-1.03)	1.01 (0.94-1.09)	0.99 (0.92-1.06)	1.12 (1.04-1.20)	< 0.001**
CVD deaths: 1,734 events						
	328 events	*328 events*	*315 events*	*354 events*	*409 events*	
Univariable	ref.	0.98 (0.90-1.07)	1.01 (0.86-1.18)	1.07 (0.94-1.22)	1.33 (1.17-1.51)	< 0.001**
Multivariable 1	ref.	0.91 (0.83-0.99)	0.83 (0.71-0.98)	0.82 (0.71-0.94)	0.83 (0.73-0.96)	0.060
Multivariable 2	ref.	0.94 (0.86-1.04)	0.90 (0.76-1.07)	0.92 (0.79-1.08)	1.00 (0.84-1.18)	0.346
Cancer deaths: 4,534 events						
	854 events	*847 events*	*851 events*	*917 events*	*1,065 events*	
Univariable	ref.	1.02 (0.97-1.08)	1.06 (0.97-1.17)	1.02 (0.94-1.11)	1.32 (1.22-1.43)	< 0.001**
Multivariable 1	ref.	0.97 (0.92-1.02)	0.96 (0.87-1.06)	0.91 (0.84-1.00)	1.05 (0.97-1.15)	< 0.001**
Multivariable 2	ref.	1.00 (0.94-1.06)	1.02 (0.92-1.14)	1.01 (0.92-1.12)	1.19 (1.07-1.32)	< 0.001**

§ = Quintile boundaries Q1/2 8.9 nmol/L (256 ng/dL), Q2/3 10.8 nmol/L (311 ng/dL), Q3/4 12.5 nmol/L (360 ng/dL) and Q4/5 14.8 nmol/L (427 ng/dL). 2.5th percentile = 5.9 nmol/L (170 ng/dL), 97.5th = 20.1 nmol/L (579 ng/dL); Presented numbers are for complete cases, after exclusions, and after excluding participants who died in the first two years of follow-up.

* = Multivariable 1 models included age, ethnicity, living with partner, qualifications, alcohol consumption, smoking status, diet, physical activity, BMI, waist circumference, cholesterol, prevalent diabetes, hypertension, angina, atrial fibrillation, COPD, dementia, renal impairment, liver disease, thyroid disease, HIV, and use of lipid medications (a proxy for hyperlipidemia), glucocorticoids, opioids, and anticonvulsants, with the number of medications included as a proxy for overall comorbidity status and assessment centre as a stratification factor. Prevalent CVD and Cancer status were included as additional terms in analyses of CVD deaths and Cancer deaths, respectively. Multivariable 2 models for testosterone included SHBG as an additional covariate.

** = Result interpreted as significant.

Table S4. Hazard ratios of all-cause mortality, deaths due to CVD, and deaths due to cancer by quintiles of SHBG: Pooled estimates from analysis of multiply-imputed data.

Model	Q5 (highest) (n = 30,576) [§]	Q4 (n = 38,559)	Q3 (n = 38,532)	Q2 (n = 38,610)	Q1 (lowest) (n = 38,600)	*P* Value
All-cause deaths: 14,757 events						
	4,398 events	*3,125 events*	*2,704 events*	*2,470 events*	*2,060 events*	
Univariable	ref.	0.77 (0.75-0.80)	0.66 (0.63-0.70)	0.58 (0.56-0.61)	0.51 (0.49-0.53)	< 0.001**
Multivariable 1*	ref.	0.87 (0.84-0.89)	0.80 (0.76-0.84)	0.76 (0.73-0.80)	0.74 (0.70-0.78)	< 0.001**
Multivariable 2	ref.	0.85 (0.83-0.88)	0.77 (0.73-0.81)	0.72 (0.68-0.76)	0.65 (0.62-0.70)	< 0.001**
CVD deaths: 2,896 events						
	766 events	*591 events*	*547 events*	*557 events*	*435 events*	
Univariable	ref.	0.84 (0.79-0.90)	0.77 (0.69-0.87)	0.72 (0.65-0.80)	0.62 (0.56-0.69)	< 0.001**
Multivariable 1	ref.	0.88 (0.82-0.95)	0.82 (0.73-0.93)	0.81 (0.73-0.90)	0.72 (0.64-0.81)	< 0.001**
Multivariable 2	ref.	0.89 (0.83-0.96)	0.83 (0.73-0.94)	0.81 (0.72-0.92)	0.71 (0.62-0.81)	< 0.001**
Cancer deaths: 6,936 events						
	1,924 events	*1,491 events*	*1,325 events*	*1,176 events*	*1,020 events*	
Univariable	ref.	0.82 (0.78-0.85)	0.71 (0.66-0.77)	0.62 (0.58-0.67)	0.55 (0.52-0.59)	< 0.001**
Multivariable 1	ref.	0.92 (0.88-0.96)	0.87 (0.81-0.94)	0.85 (0.79-0.91)	0.88 (0.82-0.95)	< 0.001**
Multivariable 2	ref.	0.90 (0.86-0.95)	0.84 (0.77-0.91)	0.79 (0.73-0.85)	0.77 (0.70-0.84)	< 0.001**

[§] = Quintile boundaries Q1/2 26.0 nmol/L, Q2/3 33.3 nmol/L, Q3/4 40.9 nmol/L and Q4/5 51.4 nmol/L. 2.5th percentile = 15.2 nmol/L, 97.5th = 79.1 nmol/L; Presented numbers are for imputed data, after exclusions.

* = Multivariable 1 models included included age, ethnicity, living with partner, qualifications, alcohol consumption, smoking status, diet, physical activity, BMI, waist circumference, cholesterol, prevalent diabetes, hypertension, angina, atrial fibrillation, COPD, dementia, renal impairment, liver disease, thyroid disease, HIV, and use of lipid medications (a proxy for hyperlipidemia), glucocorticoids, opioids, and anticonvulsants, with the total number of medications used included as a proxy for overall comorbidity status and assessment centre as a stratification factor. Prevalent CVD and Cancer status were included as additional terms in analyses of CVD deaths and Cancer deaths, respectively. Multivariable 2 models for SHBG included testosterone as an additional covariate.

** = Result interpreted as significant.

Table S5. Hazard ratios of all-cause mortality, deaths due to CVD, and deaths due to cancer by quintiles of SHBG: Analysis of data excluding participants who died within the first two years of follow-up.

Model	Q5 (highest) (n = 29,987) [§]	Q4 (n = 30,193)	Q3 (n = 29,982)	Q2 (n = 29,708)	Q1 (lowest) (n = 28,774)	*P* Value
All-cause deaths: 9,261 events						
	2,727 events	***2,014 events***	***1,722 events***	***1,573 events***	***1,225 events***	
Univariable	ref.	0.78 (0.75-0.81)	0.68 (0.63-0.72)	0.60 (0.57-0.63)	0.51 (0.48-0.54)	< 0.001**
Multivariable 1*	ref.	0.87 (0.84-0.91)	0.81 (0.76-0.87)	0.79 (0.74-0.84)	0.76 (0.71-0.81)	< 0.001**
Multivariable 2	ref.	0.87 (0.83-0.91)	0.80 (0.75-0.86)	0.76 (0.71-0.81)	0.69 (0.63-0.74)	< 0.001**
CVD deaths: 1,734 events						
	463 events	***367 events***	***325 events***	***345 events***	***234 events***	
Univariable	ref.	0.83 (0.76-0.91)	0.77 (0.67-0.89)	0.76 (0.67-0.87)	0.58 (0.50-0.67)	< 0.001**
Multivariable 1	ref.	0.88 (0.81-0.97)	0.84 (0.72-0.98)	0.88 (0.77-1.01)	0.71 (0.61-0.83)	< 0.001**
Multivariable 2	ref.	0.90 (0.81-0.99)	0.86 (0.73-1.01)	0.88 (0.75-1.03)	0.69 (0.58-0.83)	< 0.001**
Cancer deaths: 4,534 events						
	1,209 events	***1,001 events***	***886 events***	***787 events***	***651 events***	
Univariable	ref.	0.84 (0.80-0.89)	0.74 (0.67-0.81)	0.65 (0.60-0.71)	0.58 (0.53-0.63)	< 0.001**
Multivariable 1	ref.	0.94 (0.89-0.99)	0.90 (0.82-0.99)	0.88 (0.81-0.96)	0.94 (0.85-1.03)	0.006**
Multivariable 2	ref.	0.93 (0.88-0.99)	0.87 (0.79-0.97)	0.83 (0.75-0.92)	0.81 (0.73-0.91)	0.002**

[§] = Quintile boundaries Q1/2 26.0 nmol/L, Q2/3 33.3 nmol/L, Q3/4 40.9 nmol/L and Q4/5 51.4 nmol/L. 2.5th percentile = 15.2 nmol/L, 97.5th = 79.1 nmol/L; Presented numbers are for complete cases, after exclusions and after excluding participants who died in the first two years of follow-up.

* = Multivariable 1 models included included age, ethnicity, living with partner, qualifications, alcohol consumption, smoking status, diet, physical activity, BMI, waist circumference, cholesterol, prevalent diabetes, hypertension, angina, atrial fibrillation, COPD, dementia, renal impairment, liver disease, thyroid disease, HIV, and use of lipid medications (a proxy for hyperlipidemia), glucocorticoids, opioids, and anticonvulsants, with the total number of medications used included as a proxy for overall comorbidity status and assessment centre as a stratification factor. Prevalent CVD and Cancer status were included as additional terms in analyses of CVD deaths and Cancer deaths, respectively. Multivariable 2 models for SHBG included testosterone as an additional covariate.

** = Result interpreted as significant.

Figure S1. Derivation of the study cohort.

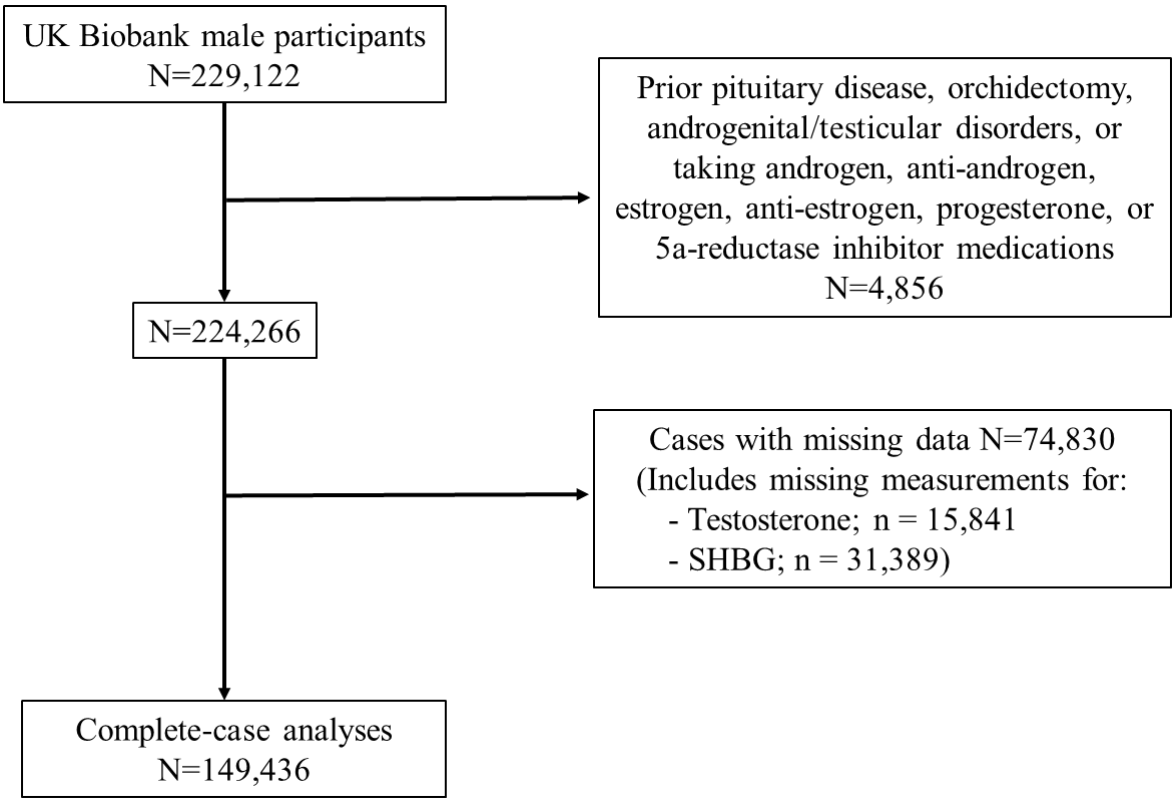

Figure S2. Kaplan-Meier survival plot according to quintiles of testosterone, showing average times to A: death from any cause, B: CVD death, C: cancer death.

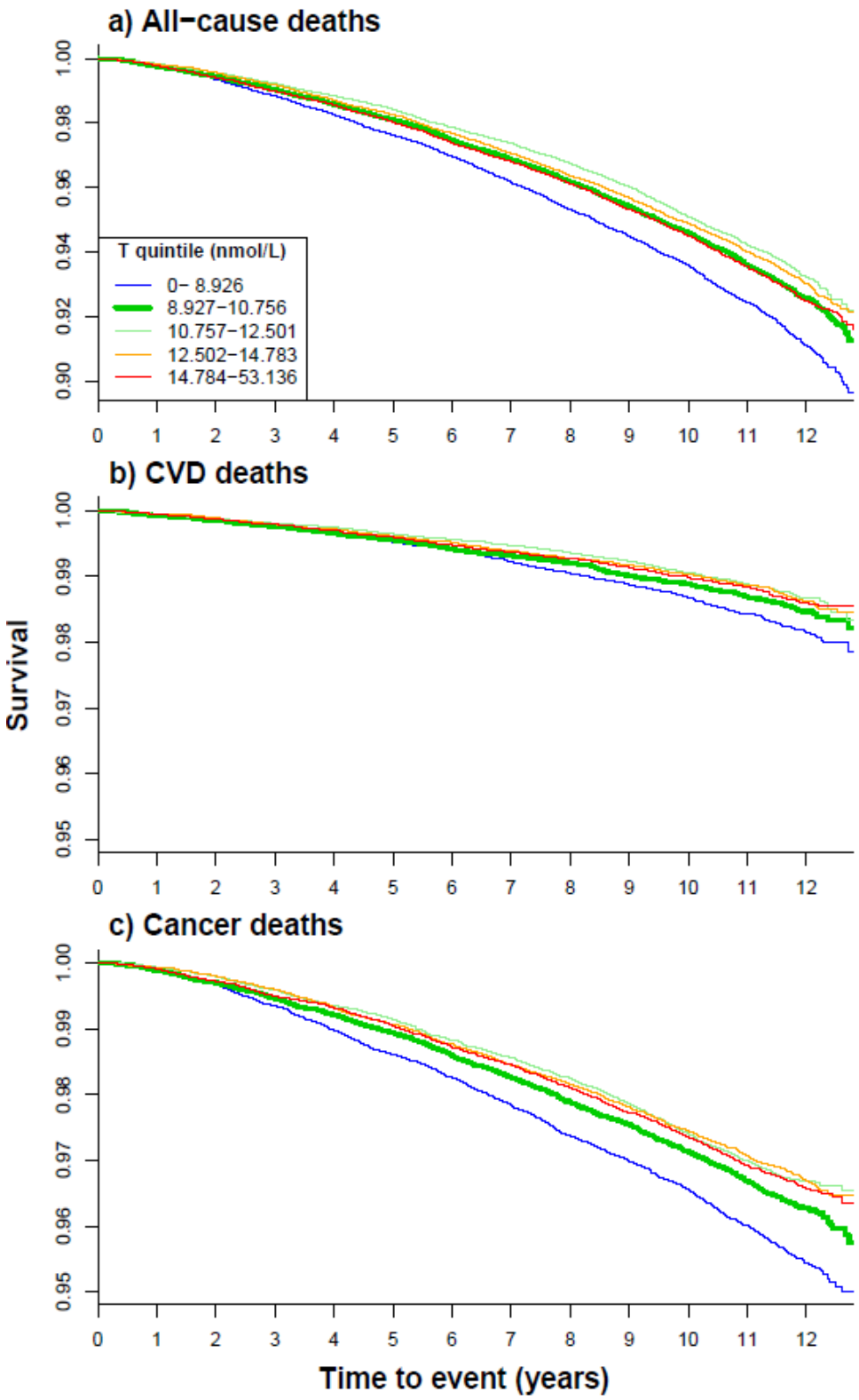

Figure S3. Univariable Cox proportional hazards regression model showing effect of baseline serum testosterone on risk of A: death from any cause, B: CVD death, C: cancer death. The horizontal dashed line is at the reference hazard (median of the fifth quintile). Shaded areas are the 95% confidence intervals. The vertical dashed lines are at medians for quintiles of testosterone.

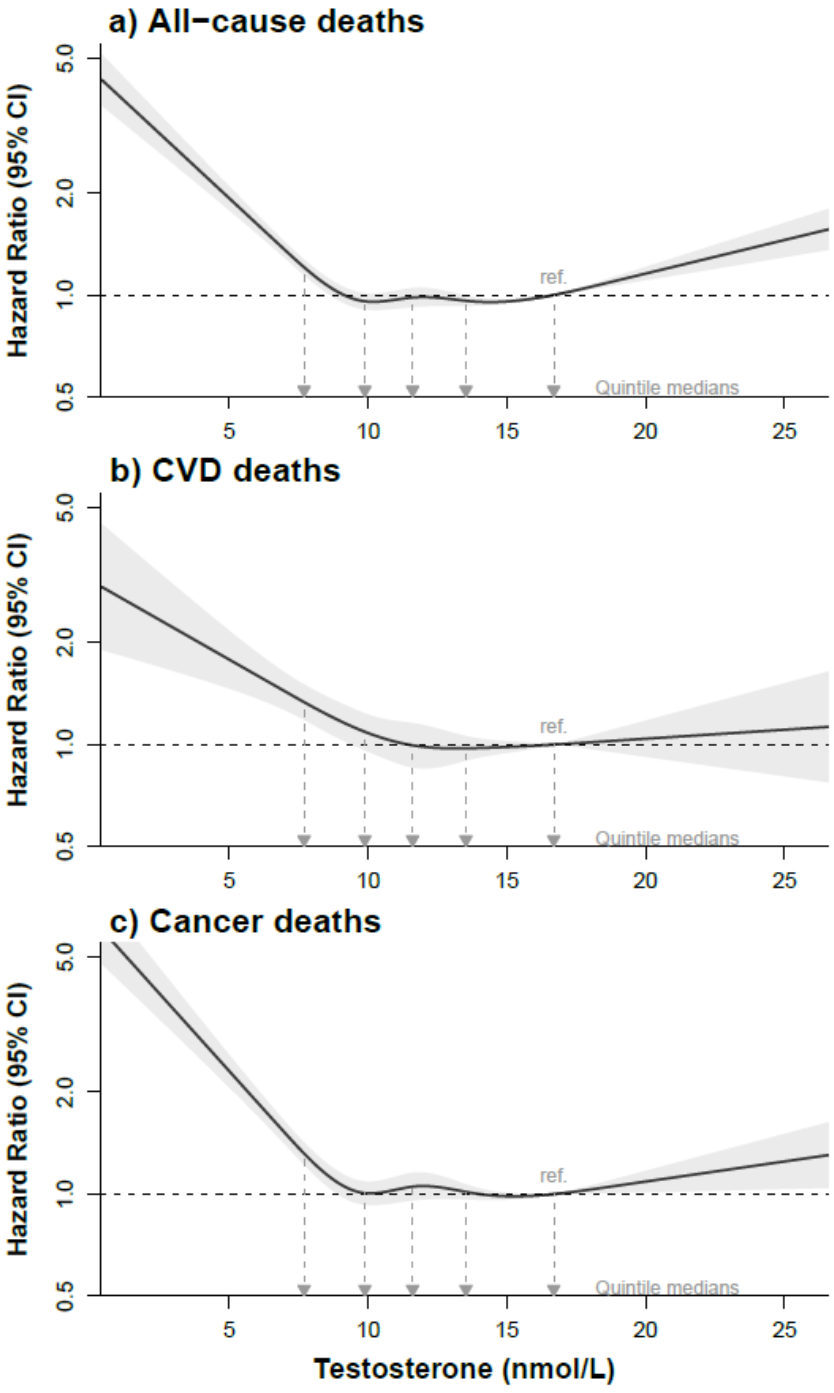

Figure S4. Multivariable Cox proportional hazards regression model showing effect of baseline serum testosterone on risk of A: death from any cause, B: CVD death, C: cancer death, adjusted for risk factors and potential confounders (not including SHBG). The horizontal dashed line is at the reference hazard (median of the fifth quintile). Shaded areas are the 95% confidence intervals. The vertical dashed lines are at medians for quintiles of testosterone.

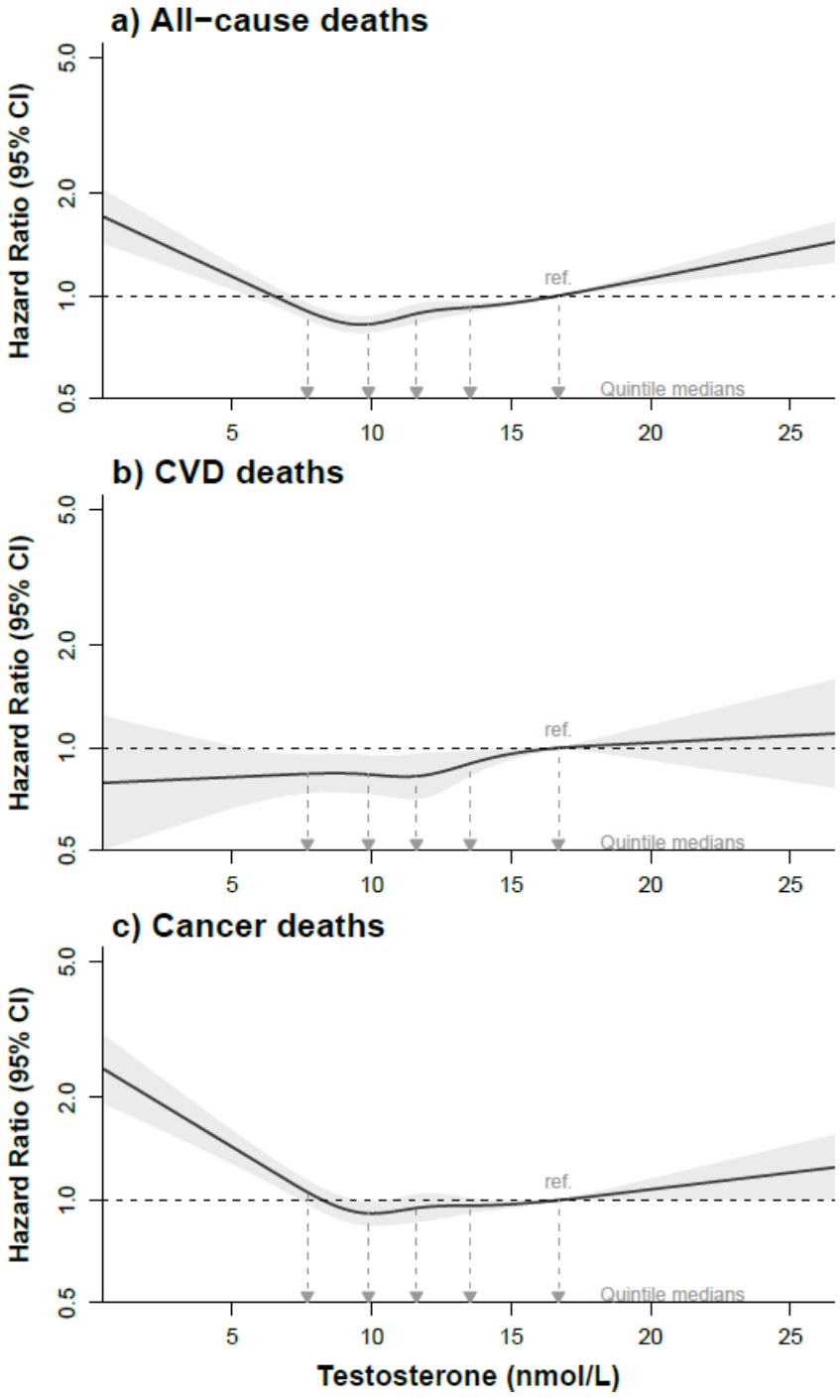

Figure S5. Kaplan-Meier survival plot according to quintiles of SHBG, showing average times to A: death from any cause, B: CVD death, C: cancer death.

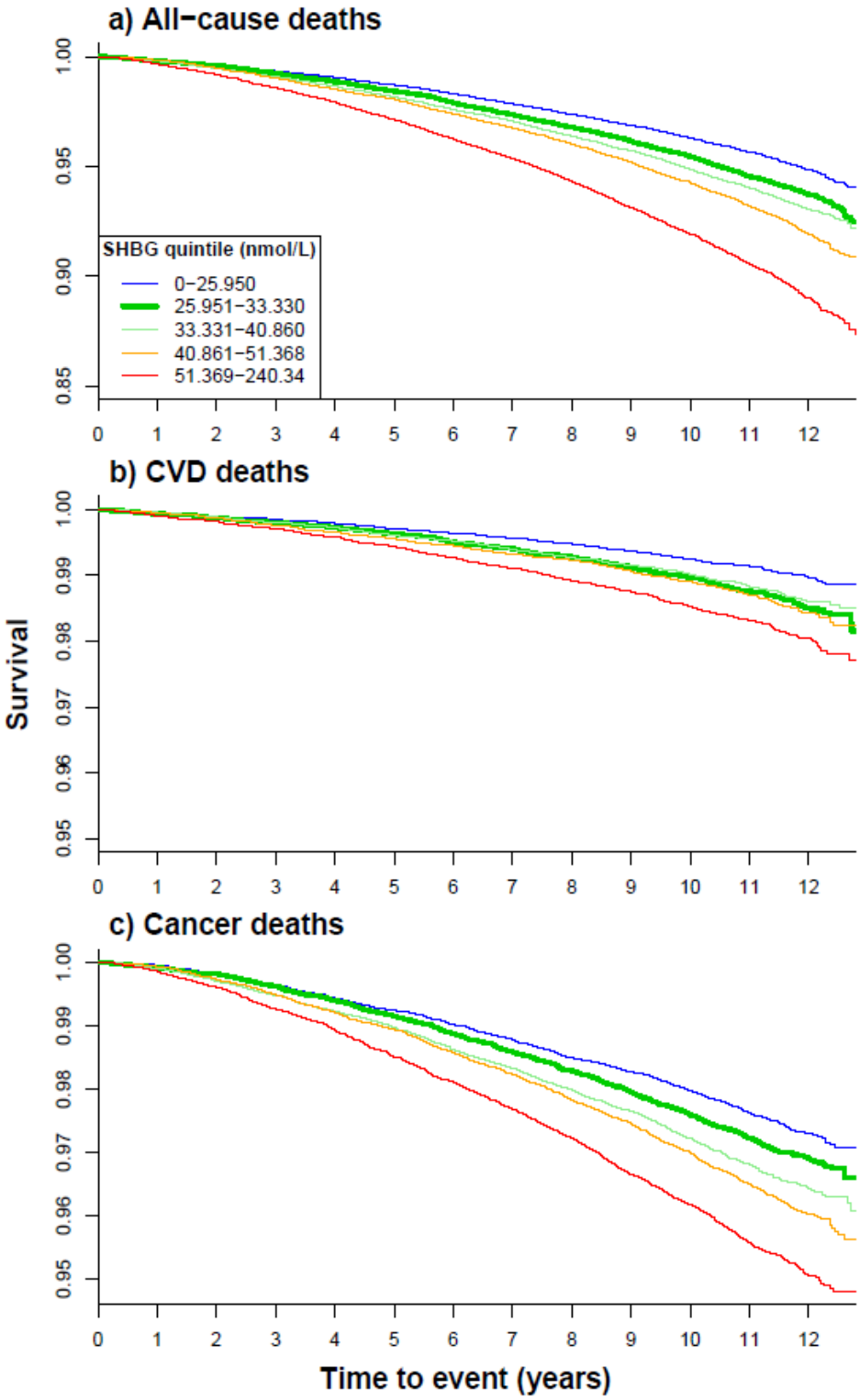

Figure S6. Univariable Cox proportional hazards regression model showing effect of baseline serum SHBG on risk of A: death from any cause, B: CVD death, C: cancer death. The horizontal dashed line is at the reference hazard (median of the fifth quintile). Shaded areas are the 95% confidence intervals. The vertical dashed lines are at medians for quintiles of SHBG.

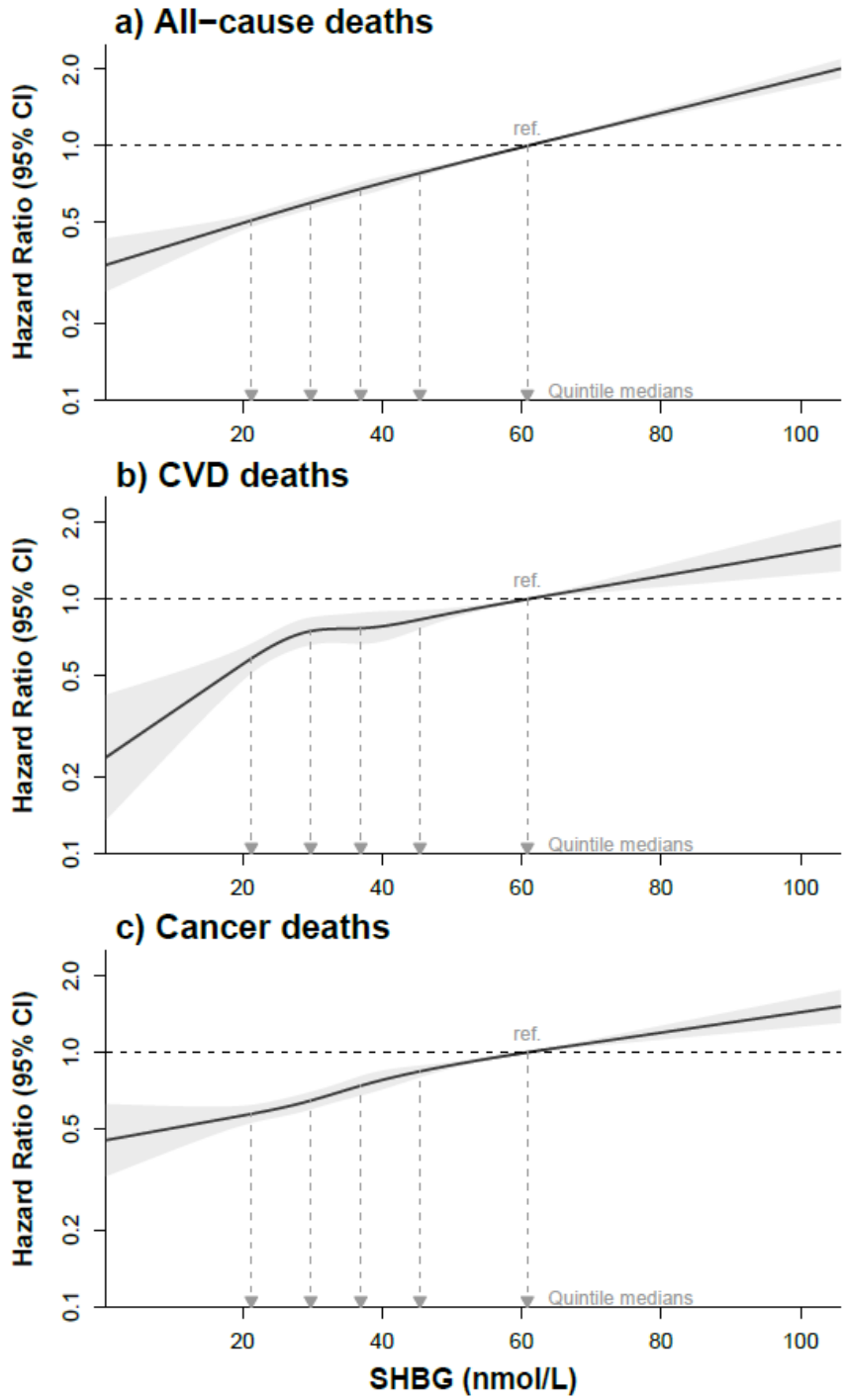

Figure S7. Multivariable Cox proportional hazards regression model showing effect of baseline serum SHBG on risk of A: death from any cause, B: CVD death, C: cancer death, adjusted for risk factors and potential confounders (not including testosterone). The horizontal dashed line is at the reference hazard (median of the fifth quintile). Shaded areas are the 95% confidence intervals. The vertical dashed lines are at medians for quintiles of SHBG.

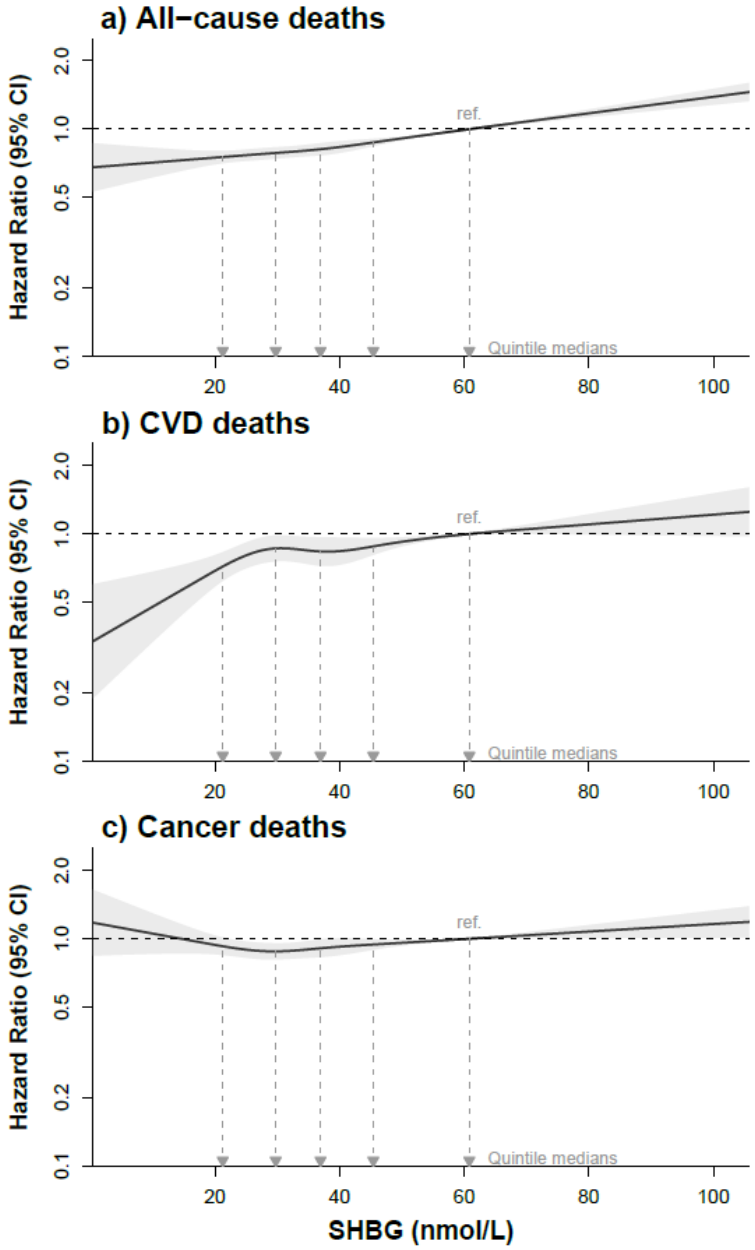

Figure S8. Kaplan-Meier survival plot according to quintiles of calculated free testosterone (cFT), showing average times to A: death from any cause, B: CVD death, C: cancer death.

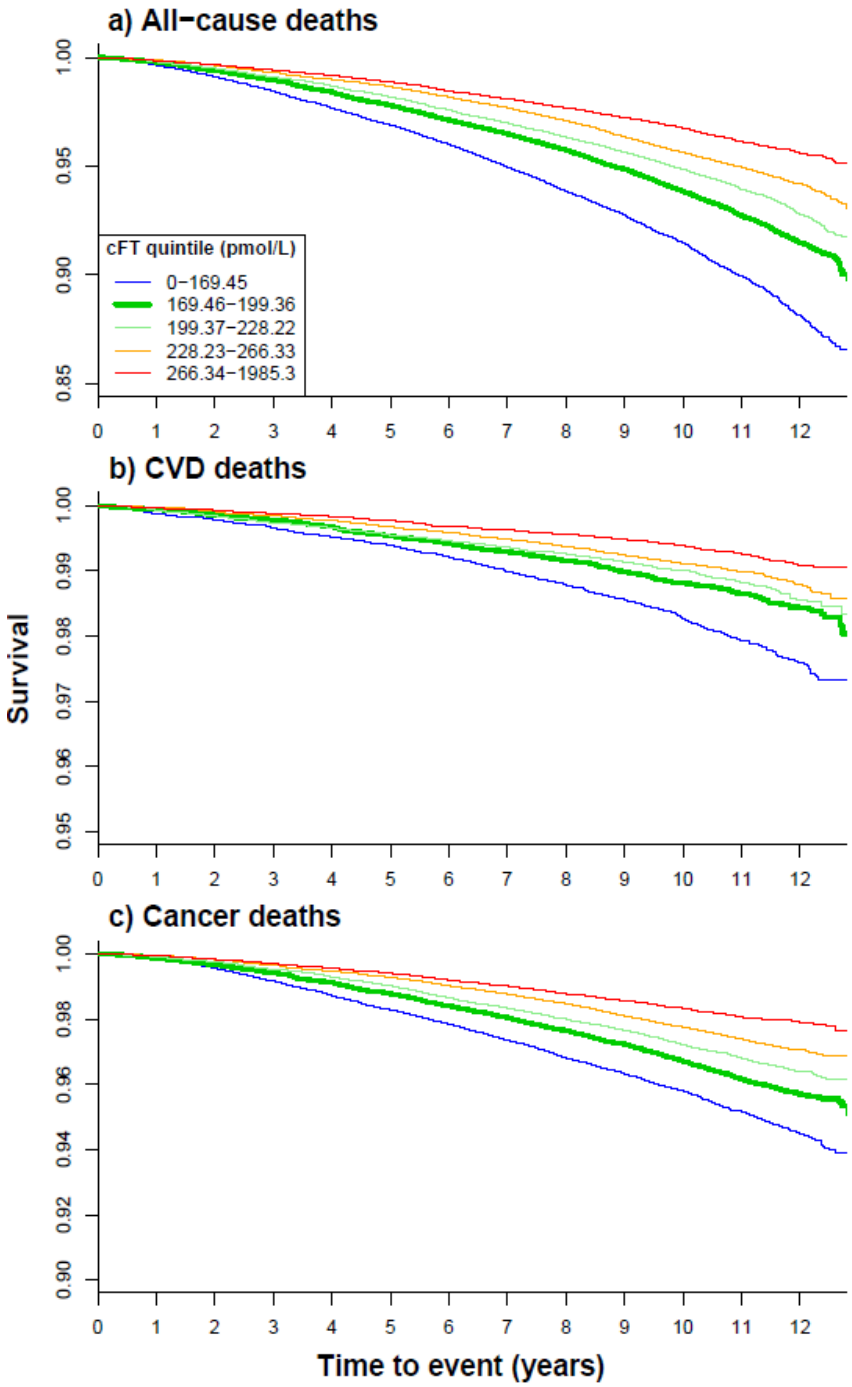

Figure S9. Univariable Cox proportional hazards regression model showing effect of baseline calculated free testosterone (cFT) value on risk of A: death from any cause, B: CVD death, C: cancer death. The horizontal dashed line is at the reference hazard (median of the fifth quintile). Shaded areas are the 95% confidence intervals. The vertical dashed lines are at medians for quintiles of cFT.