

SUPPLEMENTARY TABLE S1

Cox proportional hazards regression with the outcome of incident any fracture (A) and hip fracture (B) according to T modelled as quartiles. Data are shown as hazard ratios (95% confidence intervals) for each quartile with men in the lowest quartile (Q1) as the reference group. Model 1: adjusted for age, smoking, alcohol, hypertension, dyslipidemia, prevalent diabetes, prevalent cardiovascular disease, depression, frailty, body mass index (BMI)/waist, creatinine, and vitamin D. Model 2: adjusted for all variables in Model 1, and also for SHBG. Model 3: adjusted for all variables in Model 1, and also for E2.

A

Variable	Quartile	Range	Incident any fracture, N	Hazard ratio (95% confidence interval) and p-value		
				Model 1	Model 2	Model 3
T (nmol/L)	1	3.61-9.96	105			
T	2	9.99-12.6	76	0.69 (0.51-0.94) 0.020	0.66 (0.48-0.91) 0.010	0.66 (0.48-0.91) 0.012
T	3	12.7-15.9	64	0.59 (0.42-0.83) 0.002	0.56 (0.39-0.79) 0.001	0.56 (0.39-0.80) 0.002
T	4	16.0-27.6	79	0.85 (0.61-1.17) 0.321	0.70 (0.48-1.02) 0.063	0.70 (0.47-1.07) 0.098

B

Variable	Quartile	Range	Incident hip fracture, N	Hazard ratio (95% confidence interval) and p-value		
				Model 1	Model 2	Model 3
T (nmol/L)	1	3.61-9.96	45			
T	2	9.99-12.6	29	0.60 (0.37-0.98) 0.043	0.61 (0.37-1.00) 0.050	0.62 (0.38-1.03) 0.065
T	3	12.6-15.9	25	0.52 (0.31-0.88) 0.015	0.51 (0.29-0.88) 0.015	0.53 (0.30-0.94) 0.029
T	4	16.0-27.6	41	1.04 (0.65-1.67) 0.875	0.92 (0.53-1.60) 0.767	1.00 (0.54-1.84) 0.989

SUPPLEMENTARY TABLE S2

Cox proportional hazards regression with the outcome of incident any fracture (A) and hip fracture (B) according to E2 modelled as quartiles. Data are shown as hazard ratios (95% confidence intervals) for each quartile with men in the lowest quartile (Q1) as the reference group. Model 1: adjusted for age, smoking, alcohol, hypertension, dyslipidemia, prevalent diabetes, prevalent cardiovascular disease, depression, frailty, body mass index (BMI)/waist, creatinine, and vitamin D. Model 2: adjusted for all variables in Model 1, and also for SHBG. Model 3: adjusted for all variables in Model 1, and also for T.

A

Variable	Quartile	Range	Incident any fracture, N	Hazard ratio (95% confidence interval) and p-value		
				Model 1	Model 2	Model 3
E2 (pmol/L)	1	17.4-54.3	89			
E2	2	54.7-71.2	79	0.88 (0.64-1.21) 0.441	0.88 (0.64-1.22) 0.451	0.93 (0.67-1.29) 0.663
E2	3	71.6-90.7	80	1.03 (0.75-1.40) 0.858	1.03 (0.75-1.41) 0.842	1.14 (0.82-1.58) 0.449
E2	4	90.9-157	74	1.02 (0.74-1.41) 0.908	0.98 (0.70-1.37) 0.908	1.14 (0.79-1.65) 0.476

B

Variable	Quartile	Range	Incident hip fracture, N	Hazard ratio (95% confidence interval) and p-value		
				Model 1	Model 2	Model 3
E2 (pmol/L)	1	17.4-54.3	38			
E2	2	54.7-71.2	38	0.96 (0.60-1.54) 0.880	0.98 (0.61-1.58) 0.942	1.01 (0.62-1.63) 0.975
E2	3	71.6-90.7	34	1.00 (0.62-1.61) 0.989	1.00 (0.62-1.63) 0.988	1.05 (0.63-1.75) 0.842
E2	4	90.9-157	29	0.94 (0.57-1.55) 0.809	0.93 (0.55-1.55) 0.771	1.00 (0.57-1.77) 0.995

SUPPLEMENTARY TABLE S3

Cox proportional hazards regression with the outcome of incident hip fracture according to SHBG modelled as quartiles. Data are shown as hazard ratios (95% confidence intervals) for each quartile with men in the lowest quartile (Q1) as the reference group. Model 1: adjusted for age, smoking, alcohol, hypertension, dyslipidemia, prevalent diabetes, prevalent cardiovascular disease, depression, frailty, body mass index (BMI)/waist, creatinine, and vitamin D. Model 2: adjusted for all variables in Model 1, and also for T. Model 3: adjusted for all variables in Model 1, and also for E2.

Variable	Quartile	Range	Incident hip fracture, N	Hazard ratio (95% confidence interval) and p-value		
				Model 1	Model 2	Model 3
SHBG (nmol/L)	1	15.7-31.4	28			
SHBG	2	31.5-39.6	40	1.35 (0.82-2.24) 0.239	1.42 (0.85-2.37) 0.182	1.35 (0.76-2.39) 0.300
SHBG	3	39.7-50.3	24	0.72 (0.40-1.28) 0.262	0.77 (0.42-1.42) 0.403	0.71 (0.33-1.54) 0.392
SHBG	4	50.4-99.5	46	1.76 (1.05-2.97) 0.033	2.05 (1.12-3.77) 0.020	1.78 (0.60-5.24) 0.296

SUPPLEMENTARY TABLE S4

Cox proportional hazards regression with the composite outcome of incident hip, vertebral, humerus or forearm fractures, according to T and E2 modelled as quartiles. Data are shown as hazard ratios (95% confidence intervals) for each quartile with men in the lowest quartile (Q1) as the reference group. Models are shown unadjusted, adjusted for age, and adjusted for age, smoking, alcohol, hypertension, dyslipidemia, prevalent diabetes, prevalent cardiovascular disease, depression, frailty, body mass index (BMI)/waist, creatinine, and vitamin D.

Variable	Quartile	Range	Incident hip, vertebral, humerus and forearm fractures, N	Hazard ratio (95% confidence interval) and p-value		
				Unadjusted	Age-adjusted	Fully adjusted
T (nmol/L)	1	3.61-9.96	56			
T	2	9.99-12.6	54	0.90 (0.62-1.30) 0.566	0.93 (0.64-1.36) 0.725	0.91 (0.62-1.36) 0.658
T	3	12.7-15.9	35	0.58 (0.38-0.88) 0.011	0.59 (0.39-0.91) 0.016	0.58 (0.37-0.92) 0.021
T	4	16.0-27.6	55	1.04 (0.71-1.50) 0.855	1.07 (0.74-1.55) 0.727	1.12 (0.74-1.71) 0.584
E2 (pmol/L)	1	17.4-54.3	50			
E2	2	54.7-71.2	52	1.06 (0.72-1.57) 0.768	1.06 (0.72-1.56) 0.775	1.06 (0.70-1.59) 0.796
E2	3	71.6-90.7	53	1.17 (0.79-1.73) 0.424	1.19 (0.81-1.75) 0.385	1.25 (0.84-1.87) 0.270
E2	4	90.9-157	41	0.93 (0.62-1.42) 0.750	0.98 (0.64-1.48) 0.917	1.02 (0.66-1.58) 0.924

SUPPLEMENTARY TABLE S5

Cox proportional hazards regression with the outcome of incident any fracture (A) and hip fracture (B) according to T modelled as quartiles. Data are shown as hazard ratios (95% confidence intervals) for each quartile with men in the lowest quartile (Q1) as the reference group. Models are adjusted for age, smoking, alcohol, hypertension, dyslipidemia, prevalent diabetes, prevalent cardiovascular disease, depression, frailty, body mass index (BMI)/waist, creatinine, and vitamin D. Model 1: fracture outcome occurring any time after blood sampling. Model 2: fracture outcome occurring within five years of blood sampling. Model 3: fracture outcome occurring >5 years of blood sampling.

A						Hazard ratio (95% confidence interval) and p-value		
Variable	Quartile	Range	Incident any fracture, N	≤5 years	>5 years	Model 1	Model 2	Model 3
T (nmol/L)	1	3.61-9.96	105	26	79			
T	2	9.99-12.6	76	15	61	0.69 (0.51-0.94) 0.020	0.49 (0.25-0.95) 0.035	0.76 (0.53-1.08) 0.125
T	3	12.7-15.9	64	18	46	0.59 (0.42-0.83) 0.002	0.61 (0.32-1.16) 0.129	0.58 (0.39-0.86) 0.007
T	4	16.0-27.6	79	15	64	0.85 (0.61-1.17) 0.321	0.48 (0.24-0.95) 0.036	1.00 (0.69-1.45) 0.991

B						Hazard ratio (95% confidence interval) and p-value		
Variable	Quartile	Range	Incident hip fracture, N	≤5 years	>5 years	Model 1	Model 2	Model 3
T (nmol/L)	1	3.61-9.96	45	11	34			
T	2	9.99-12.6	29	5	24	0.60 (0.37-0.98) 0.043	0.31 (0.10-0.98) 0.046	0.70 (0.41-1.22) 0.212
T	3	12.7-15.9	25	6	19	0.52 (0.31-0.88) 0.015	0.47 (0.17-1.33) 0.157	0.53 (0.29-0.96) 0.038
T	4	16.0-27.6	41	9	32	1.04 (0.65-1.67) 0.875	0.64 (0.24-1.71) 0.379	1.19 (0.69-2.05) 0.537

SUPPLEMENTARY TABLE S6

Cox proportional hazards regression with the outcome of hip fracture according to SHBG modelled as quartiles. Data are shown as hazard ratios (95% confidence intervals) for each quartile with men in the lowest quartile (Q1) as the reference group. Models are adjusted for age, smoking, alcohol, hypertension, dyslipidemia, prevalent diabetes, prevalent cardiovascular disease, depression, frailty, body mass index (BMI)/waist, creatinine, and vitamin D. Model 1: hip fracture outcome occurring any time after blood sampling. Model 2: hip fracture outcome occurring within five years of blood sampling. Model 3: hip fracture outcome occurring >5 years of blood sampling..

Variable	Quartile	Range	Incident hip fracture, N	≤5 years	>5 years	Hazard ratio (95% confidence interval) and p-value		
						Model 1	Model 2	Model 3
SHBG (nmol/L)	1	15.7-31.4	28	5	23			
SHBG	2	31.5-39.6	40	4	36	1.35 (0.82-2.24) 0.239	0.64 (0.15-2.72) 0.545	1.45 (0.84-2.50) 0.180
SHBG	3	39.7-50.3	24	7	17	0.72 (0.40-1.28) 0.262	1.32 (0.40-4.31) 0.648	0.56 (0.28-1.11) 0.098
SHBG	4	50.4-99.5	46	14	32	1.76 (1.05-2.97) 0.033	2.89 (0.94-8.87) 0.064	1.49 (0.83-2.69) 0.184

Supplementary Figure S1: origins of the Health In Men study cohort



