Low Testosterone Concentrations in Men Contribute to the Gender Gap in Cardiovascular Morbidity and Mortality

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ABSTRACT

Background: Across the industrialized world, men experience an earlier onset of cardiovascular disease (CVD) and a life expectancy 5 to 10 years shorter than women. Low total testosterone (TT) concentrations in men have been suggested as a novel CVD risk factor, but its contribution to this gender gap is less well studied.

Methods: We used data of 4152 individuals (2113 women and 2039 men) aged 20 to 79 years from the longitudinal population-based cohort Study of Health in Pomerania, Germany. Multivariable Poisson and Cox proportional hazard regression models were used to investigate the risk of incident cardiovascular morbidity (5-year examination follow-up), as well as all-cause and CVD mortality (10-year follow-up) between men and women. Additionally, the added risk attributable to low TT in men (<10th percentile) was assessed.

Results: Compared with women, men were uniformly at higher risk of incident cardiovascular morbidity, including overweight, hypertension, dyslipidemia, metabolic syndrome, and type 2 diabetes mellitus. Men were also at increased all-cause mortality (hazard ratio = 2.05; 95% CI, 1.61–2.60) and 10-year CVD risk compared with women. In subgroup analyses, men with low TT showed the highest 10-year CVD and mortality risk compared with both men with higher TT and women. TT was also negatively associated with cardiovascular risk as defined by the Framingham risk score ($P < 0.001$), after multivariable adjustment.

Conclusions: Analyzing a large population-based sample, we observed that men have a generally higher risk of incident cardiovascular morbidity and mortality. Furthermore, men with low TT concentrations were identified as high-risk individuals with regard to 10-year CVD and mortality risk. (*Gend Med.* 2012; 9:557–568)

Key words: cardiovascular disease, epidemiology, gender gap, mortality, testosterone.

INTRODUCTION

Across industrialized countries, the divergence of the average life span of men and women is a consistent and well-established observation.[1] Although the gender gap in life expectancy has narrowed since the 1970s, the male disadvantage of currently 5 to 8 years in life expectancy at birth continues.[2] These gender differences are also present with regard to the onset and progression of cardiovascular disease (CVD).[3] It has been shown that men experience incident CVD events up to 10 years earlier compared with women.[4] Despite a vast number of hypotheses, explanations for the male excess morbidity and mortality generally relate to a combination of biologic, social, and behavioral factors.[5]

Low serum total testosterone (TT) concentrations in men have been linked to various cardiovascular risk factors, including incident hypertension,[6] dyslipidemia,[7,8] metabolic syndrome (MetS),[9–11] type 2 diabetes mellitus,[12,13] and increased mortality risk.[14] Thus, we previously suggested low TT concentrations in men as a risk marker beneficial for the identification of high-risk individuals and improved risk stratification.[15,16]

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Although the role of major cardiovascular risk factors in the temporal sequence of incident CVD and subsequent mortality is well established, and cardiovascular risk factor patterns are known to be more favorable among women than among men, the additional influence of low TT concentrations on men's excess cardiovascular risk factor burden and mortality risk is poorly understood.

Therefore, we aimed to evaluate gender differences in the prevalence and incidence of cardiovascular risk factor profiles and mortality risk in a large, population-based cohort and to further investigate the potential of TT assessment for the identification of male high-risk individuals.

METHODS

Study Population

The Study of Health in Pomerania is a population-based cohort study in West Pomerania, a region in northeastern Germany. Details on the Study of Health in Pomerania study design, recruitment, and procedures have been published previously.[17] In brief, from the total population of West Pomerania comprising 213,057 inhabitants in 1996, a 2-stage stratified cluster sample of adults aged 20 to 79 years was drawn. The net sample (without migrated or deceased persons) comprised 6265 eligible participants. Only individuals with German citizenship and main residency in the study area were included. All participants received a maximum of 3 written invitations. In cases of nonresponse, letters were followed by repeated telephone calls or by home visits if contact by telephone was not possible.[18] After written informed consent was obtained, 4308 (2192 women) participants were examined (response proportion 68.8%) between 1997 and 2001. During the 5-year follow-up, 3300 (1711 women) participants were re-examined (response proportion 83.6%) between 2002 and 2006. The study conformed to the principles of the Declaration of Helsinki as reflected in an a priori approval of the Ethics Committee of the University of Greifswald. After the exclusion of individuals with missing covariate or outcome data, we analyzed a final study sample of 4152 (2113 women). For secondary analyses, we further excluded 88 men without testosterone measurements or the use of sexual hormones (anatomic-therapeutical-chemical [ATC] code G03), testosterone 5α reductase inhibitors (ATC code G04CB), or sexual hormone antagonists (ATC code L02B).

Measures

Baseline data included socioeconomic characteristics, behavioral risk factors, medical history, as well as sonographic, laboratory, and somatometric examinations. Behavioral risk factors and socioeconomic characteristics were assessed by a computer-assisted personal interview and included sex, age, education level (<10, =10, or >10 years of schooling), occupational status (paid job vs no paid job), smoking habits (categorized into current, former, and never-smokers), exercise level (<1 h/week physical training during summer or winter), and "equalized" household income (in Euros). Because income is a household-level variable, the equivalence criteria allow for economies of scale at the household level. We used the commonly adopted procedure of the Luxembourg Income Study to divide the household income by the square root of the number of household members, thus assuming an equivalence parameter of 0.5.[19] Alcohol consumption was evaluated as beverage-specific alcohol consumption (beer, wine, and distilled spirits) during the previous weekend and last weekday preceding the examination, and the mean daily alcohol consumption was calculated using beverage-specific pure ethanol volume proportions.[20]

Waist circumference was measured to the nearest 0.1 cm using an inelastic tape midway between the lower rib margin and the iliac crest in the horizontal plane, with the subject standing comfortably with weight distributed evenly on both feet. Height and weight were measured for the calculation of the body mass index (BMI) (weight in kilograms/height in meters^2. Overweight was defined by a BMI >25 kg/m^2. After a resting period of at least 5 minutes, systolic (SBP) and diastolic blood pressure (DBP) were measured 3 times on the right arm of seated participants by use of an oscillometric digital blood pressure monitor (HEM-705CP; Omron Corporation, Tokyo, Japan). The interval between the readings was 3 minutes.

The mean of the second and third measurements was calculated and hypertension was defined as systolic or diastolic blood pressure ≥140 mm Hg or ≥90 mmHg, respectively, or use of antihypertensive medication (ATC codes C02, C03, C04, C07, C08, and C09).[21]

Lifestyle characteristics including BMI (18.5–25.0 vs <18.5 and >25, respectively),[22] smoking status (former and never-smokers vs current smokers), alcohol consumption (<5.0 g/day vs ≥5.0 g/day), a dietary score in the top 2 quintiles[23] (measured from a validated food-frequency score reflecting the food quality), and exercise (>2 h/week vs <2 h/week physical training during summer or winter) were summed with a score of 1 for each, ranging from 0 to 5.[24] Type 2 diabetes mellitus was defined based on self-reported physicians diagnosis, use of antidiabetic medication (ATC code A10) during the past 7 days, or glycosylated hemoglobin concentrations >6.5%. MetS was defined by any 3 or more of the 5 components proposed by the National Cholesterol Education Program Adult Treatment Panel III,[25] as previously described in detail.[9,26]

We also assessed the cardiovascular risk factor burden based on the individual risk factor level: all optimal (total cholesterol [TC] <4.65 mmol/L, blood pressure <120/<80 mm Hg, former or never smoker, and nondiabetic), 1 low risk factor (TC 4.65–5.15 mmol/L, SBP 120–139 mm Hg, DBP 80–89 mm Hg, former or never smoker, and nondiabetic), 1 intermediate risk factor (TC 5.16–6.19 mmol/L, SBP 140–159 mm Hg, DBP 90–99 mm Hg, former or never smoker, and nondiabetic), 1 major risk factor only (TC ≥6.20 mmol/L, SBP ≥160 mm Hg, DBP ≥100 mm Hg, current smoker, or diabetic), or 2 major risk factors.[27] Gender-specific 10-year CVD risk (ranging from <5%–>30%) was calculated based on the Framingham risk score using age, TC, HDL-C, SBP, antihypertensive medication use, current smoker, and type 2 diabetes mellitus as predictors.[28]

Laboratory Measures

Nonfasting blood samples were taken from the cubital vein in the supine position between 8:00 AM to 7:00 PM and prepared for immediate analysis or for storage at −80°C for further analysis. TT was measured during December 2005 and January 2006 from frozen serum aliquots using competitive chemiluminescent enzyme immunoassays on an Immulite 2500 analyzer (Siemens Healthcare Medical Diagnostics, Bad Nauheim, Germany). The inter-assay coefficients of variation were 13.2% with a systematic deviation of +2.3% at the 3.2 nmol/L level, and 8.9% with a systematic deviation of +0.24% at the 22.5 nmol/L level.[29] Based on previously established prevalence and incidence estimates,[30] low TT concentrations were defined according to the 10th percentile in every 10-year age group.[15,16,30]

TC was measured photometrically (Hitachi 704, Roche, Mannheim, Germany), whereas HDL-C and (LDL-C cholesterol was determined after precipitation procedures. Dyslipidemia was defined as TC >6.2 mmol/L, LDL-C >4.1 mmol/L, HDL-C <1.03 mmol/L, or currently taking lipid medication.[8] Triglycerides and glucose concentrations were determined enzymatically using reagents from Roche Diagnostics (Hitachi 717; Roche Diagnostics, Mannheim, Germany). Glycosylated hemoglobin concentrations were determined by high-performance liquid chromatography (Bio-Rad Diamat, Munich, Germany). All assays were performed according to the manufacturers' recommendations by skilled technical personal. In addition, the laboratory takes part in official quarterly German external proficiency testing programs.

Mortality Follow-Up

Information on vital status was collected from population registries at annual intervals from time of enrollment into the study through December 15, 2009. Participants were censored at either death or loss to follow-up, and the number of months between baseline examination and censoring was used as follow-up length. Death certificates were requested from the local health authority at the place of death. Causes of deaths were coded by a certified nosologist according to the *International Classification of Diseases 10th Revision* (ICD-10). Additionally, two internists independently validated the underlying cause of death and performed a joint reading in cases of disagreement.

A third internist finally decided in cases of still existing disagreement. Cardiovascular mortality comprised the ICD-10 codes I10 to I79.

Statistical Analysis

Continuous data are expressed as median (Q1, Q3) and nominal data as percentage, using χ^2 test (nominal data) or Mann-Whitney U test (quantitative data) for intergroup comparisons by gender. We used Poisson regression models with robust standard errors and effects presented as relative risks (RR) and their 95% CIs to analyze the risk of incident cardiovascular morbidity by gender between baseline and the 5-year examination follow-up, including overweight, hypertension, dyslipidemia, MetS, and type 2 diabetes mellitus. For incidence analyses, the sample was limited to individuals without the respective condition at baseline. To analyze the risk of all-cause and cardiovascular mortality by gender over the 10-year mortality follow-up period we used Cox proportional hazards regression models. Kaplan-Meier analyses were graphed and survival curves compared by log-rank test. We graphically explored log–log plots to satisfy the proportional hazards assumption.

Covariables adjusted for in multivariable models included age, BMI, smoking status, exercise, alcohol consumption, and education level. We used an established threshold at age 50 years to repeat the conducted models stratified by age.[27] Sensitivity analyses were performed to evaluate the potential nonresponse bias introduced by missing follow-up data, additionally including inverse probability weights into the multivariable models calculated with respect to baseline variables contained in the multivariable model (see above).[31] In a next step, we used TT concentrations to assess the combined risk profile of male gender and low TT concentrations with regard to 10-year CVD risk and all-cause mortality risk. Furthermore, we used linear regression models to assess the possible association between continuous TT and cardiovascular risk, as defined by the Framingham risk score. Two-sided probability values <0.05 were considered statistically significant. All the statistical analyses were performed using Stata 11.0 (Stata Corporation, College Station, Texas).

RESULTS

Baseline characteristics of the study sample are shown in **Table I**. Compared with women, men showed more disadvantageous cardiovascular risk factors profiles as well as health behaviors, and experienced a higher corresponding cardiovascular risk factor burden and 10-year CVD risk. As shown in **Table II** and **Figure 1**, men were uniformly at higher risk of incident cardiovascular morbidity compared with women, including the development of overweight (RR = 1.45; 95% CI, 1.15–1.83), hypertension (RR = 1.35; 95% CI, 1.08– 1.68), dyslipidemia (RR = 1.78; 95% CI, 1.57–2.03), MetS (RR = 1.66; 95% CI, 1.43– 1.93), and type 2 diabetes mellitus (RR = 1.14; 95% CI, 1.01–1.28). Age-stratified analyses identified young men (aged 20 to 49 years) as particularly responsive to the investigated associations showing highest risk of incident cardiovascular morbidity in this age group (**Table II**).

During 41,603 person-years (median = 10.1 years; 25th percentile = 9.3; 75th percentile = 10.7) of follow-up, 475 (women = 154; men = 321) participants died (11.0%), whereas 157 (33.1%) died from cardiovascular causes, reflecting an overall crude mortality rate of 11.4 deaths per 1000 person-years. Kaplan-Meier survival curves for all-cause mortality show that men experienced significantly shorter survival times compared with women (log-rank test, $P < 0.001$). Multivariable Cox models presented in **Table III** indicate that men were also at higher risk of all-cause mortality (HR = 2.05; 95% CI, 1.61–2.60) and CVD mortality (HR = 2.85; 95% CI, 1.86–4.36) compared with women. Age-stratified analyses identified also younger men (aged 20 to 49 years) at increased mortality risk (**Table III**). Sensitivity analyses with the additional inclusion of inverse probability weights altered the revealed estimates only slightly (data not shown).

Baseline prevalence of low TT concentrations was 10% (n = 199) with a crude incidence rate of 11.0 cases per 1000 person-years. Additional risk stratification based on TT identified men with low TT concentrations as high-risk individuals with regard to 10-year CVD risk (**Figure 2**) and all-cause mortality risk (**Figure 3**). Compared to men with higher TT concentrations, men with low TT con-

Table I. Baseline characteristics of the study population by gender.

Characteristic	Percentage or median (Q1, Q3) Women (N = 2113)	Men (N = 2039)	*P**
Age, y	49.1 (35.5, 62.2)	52.0 (37.4, 65.5)	<0.001
Occupational status (paid job), %	48.3	47.7	0.723
Educational level, %			<0.001
<10 years of schooling	37.6	42.6	
=10 years of schooling	48.9	40.2	
>10 years of schooling	15.6	17.1	
Equalized household income, Euros	920.5 (627.3, 1175.0)	958.7 (677.9, 1254.6)	<0.001
Current smoker, %	27.0	33.8	<0.001
Alcohol consumption, g/d	2.2 (0.0, 6.6)	11.9 (1.5, 28.2)	<0.001
Exercise > 1 h/week, %	43.3	40.9	0.111
Healthy lifestyle characteristics, %			<0.001
0	2.2	9.2	
1-2	44.9	66.8	
3-4	50.0	23.4	
5	2.8	0.5	
Body mass index, kg/m^2	26.9 (22.8, 30.2)	27.7 (24.9, 30.0)	<0.001
≥25 to <30 kg/m^2, %	31.8	48.9	
≥30 kg/m^2, %	26.0	25.1	
Waist circumference, cm	81.5 (73.0, 92.1)	95.3 (87.5, 103.0)	<0.001
Diastolic blood pressure, mm Hg	80.0 (73.0, 87.5)	85.0 (78.0, 93.0)	<0.001
Systolic blood pressure, mm Hg	126.5 (114.0, 143.0)	140.5 (129.5, 153.0)	<0.001
Hypertension, %	37.5	61.6	<0.001
Total cholesterol, mmol/L	5.67 (4.90, 6.50)	5.69 (4.95, 6.44)	0.852
Low-density lipoprotein cholesterol, mmol/L	3.43 (2.69, 4.22)	3.56 (2.84, 4.26)	<0.001
High-density lipoprotein cholesterol, mmol/L	1.54 (1.29, 1.84)	1.24 (1.04, 1.50)	<0.001
Triglyceride, mmol/L	1.31 (0.92, 1.91)	1.69 (1.16, 2.62)	<0.001
Dyslipidemia, %	42.9	54.7	<0.001
Nonfasting glucose, mmol/L	5.19 (4.76, 5.70)	5.42 (5.0, 6.0)	<0.001
Glycosylated hemoglobin, %	5.3 (4.8, 5.7)	5.4 (5.0, 5.9)	<0.001
Type 2 diabetes mellitus, %	9.6	12.4	0.003
Metabolic syndrome, %	22.2	34.4	<0.001
Risk factor burden, %			<0.001
All optimal risk factors	6.9	1.3	
≥1 Not optimal risk factor	9.9	7.7	
≥1 Elevated risk factor	23.0	22.8	
1 Major risk factor	42.7	39.8	
≥2 Major risk factors	18.3	28.4	
10-year cardiovascular disease risk, Framingham score	9 (4, 13)	12 (7, 16)	<0.001

*Calculated using χ^2 test for categorical and Mann-Whitney U test for continuous variables.

centrations had a significantly higher 10-year CVD risk (Fisher's exact test, $P < 0.001$), all-cause mortality risk (HR = 1.82; 95% CI, 1.30 to 2.55), and CVD mortality risk (HR = 2.25; 95% CI, 1.30 to 3.90) (**Table 3**). Furthermore, TT was negatively associated with the Framingham risk score after multivariable adjustment (regression coefficient = −0.75; 95% CI, −1.13 to −0.36; $P < 0.001$).

DISCUSSION

Our population-based cohort study showed that men were at increased risk of incident cardiovas-

Table II. Prevalence and relative risk (95% CI) for incident cardiovascular morbidity, by gender.

	Prevalence, %				
Participant*	Overweight	Hypertension	Dyslipidemia	Metabolic Syndrome	Type 2 Diabetes
Whole sample	65.6	49.4	48.7	27.8	10.5
<50 y					
Men	64.2	44.1	44.5	25.5	3.9
Women	41.9	16.3	23.4	9.1	1.2
≥50 y					
Men	82.1	77.0	63.8	41.2	19.2
Women	74.2	59.6	63.0	35.5	17.1
	Incidence (Relative risk men vs women [95% CI])				
Whole sample	1.45 (1.15; 1.83)†	1.35 (1.08; 1.68)†	1.85 (1.26; 2.70)†	1.66 (1.43; 1.93)†	1.14 (1.01; 1.28)†
<50 y (n = 2031)	1.73 (1.31; 2.29)†	1.61 (1.15; 2.26)†	2.56 (1.07; 6.11)†	1.93 (1.51; 2.47)†	1.08 (0.90; 1.29)
≥50 y (n = 2121)	1.22 (0.79; 1.91)	1.15 (0.86; 1.56)	1.73 (1.14; 2.64)†	1.49 (1.23; 1.80)†	1.06 (0.90; 1.26)

*The multivariable model was adjusted for age, body mass index, smoking status, exercise, alcohol consumption, dietary pattern, and education level. Multivariable models estimating the relative risk of incident overweight were not adjusted for body mass index.
†$P < 0.05$.

cular morbidity, including overweight, hypertension, dyslipidemia, MetS, and type 2 diabetes mellitus, and exposed a higher all-cause and CVD mortality risk. Additionally, risk stratification by low TT concentrations revealed a subgroup of high-risk individuals with regard to cardiovascular risk factor burden, 10-year CVD risk, and mortality.[29]

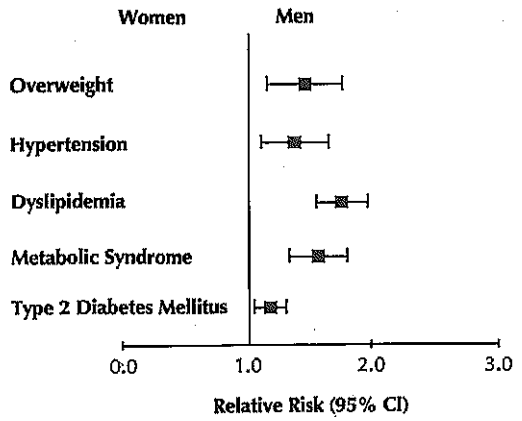


Figure 1. Forrest plot for incident cardiovascular morbidity; men versus women. Relative risk estimates and 95% CIs were derived from multivariable Poisson regression models adjusted for age, body mass index, smoking status, exercise, alcohol consumption, dietary pattern, and education level.

As expected, and in agreement with previous longitudinal studies,[32,33] we found a higher cardiovascular risk factor burden, incident CVD risk, and mortality risk in men compared with women.[34] Although previous analyses in the Framingham Heart Study repeatedly identified male gender as major risk factor of 10-year or 30-year CVD,[35] putting an emphasis solely on biological explanations for the female survival advantage would be misleading. Given identical environmental conditions, an investigation of a Catholic cloistered population showed a clearly lower mortality of monks compared with nuns.[36] Also, genetic analyses showed that individuals older than age 85 years carry the same number of risk alleles for common diseases, including coronary artery disease, cancer, and type 2 diabetes, as young control subjects,[37] further limiting biological explanations for the observed gender gap.

Environmental or nonbiological explanations relate to differences in major cardiovascular risk factors caused by the adverse lifestyles followed by men. In a study among 14,786 Finnish men and women aged 25 to 64 years, these differences have

Table III. Hazard ratio (95% CI) for all-cause and cardiovascular disease (CVD) mortality, by gender and testosterone concentration.

	All-Cause Mortality	CVD Mortality
Men vs women		
Age-adjusted model	2.00 (1.65; 2.43)*	1.95 (1.40; 2.71)*
Multivariable model†	2.05 (1.61; 2.60)*	2.85 (1.86; 4.36)*
<50 y (No. of deaths from all causes/cardiovascular causes: 31/4)	2.83 (1.12; 7.16)*	1.03 (0.07; 15.76)
≥50 y (No. of deaths from all causes/cardiovascular causes: 444/153)	2.00 (1.56; 2.58)*	2.91 (1.89; 4.49)*
Men with low vs higher total testosterone concentrations		
Age-adjusted model	1.64 (1.18; 2.29)*	2.13 (1.24; 3.67)*
Multivariable model†	1.82 (1.30; 2.55)*	2.25 (1.30; 3.90)*

*$P < 0.05$.

†The multivariable model was adjusted for age, body mass index, smoking status, exercise, alcohol consumption, dietary pattern, and education level.

been shown to explain nearly half of the gender gap in CVD risk between men and women.[32] Manifesting mostly after age 60 years, CVD is a process that builds slowly over decades and is therefore widely perceived as a life course disease. Hence, the temporal relationship between risk factor change and improvements in CVD and mortality risk has been traditionally perceived in terms of decades. Even more surprising is the accumulating empirical evidence showing that substantial reductions in CVD and mortality can occur rapidly after individual or population-wide changes in risk factors, including smoking,[38] diet,[39] physical activity, or body weight.[40] Although the suggested changes are often subjectively challenging, it has been shown that individuals adopting a healthy lifestyle in middle-age experience a prompt benefit of lower CVD and mortality rates.[41]

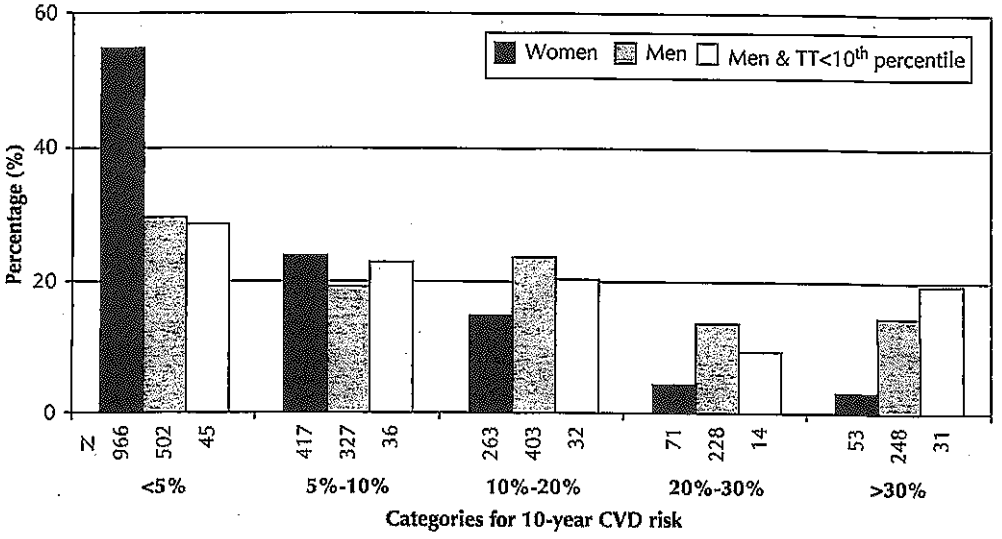
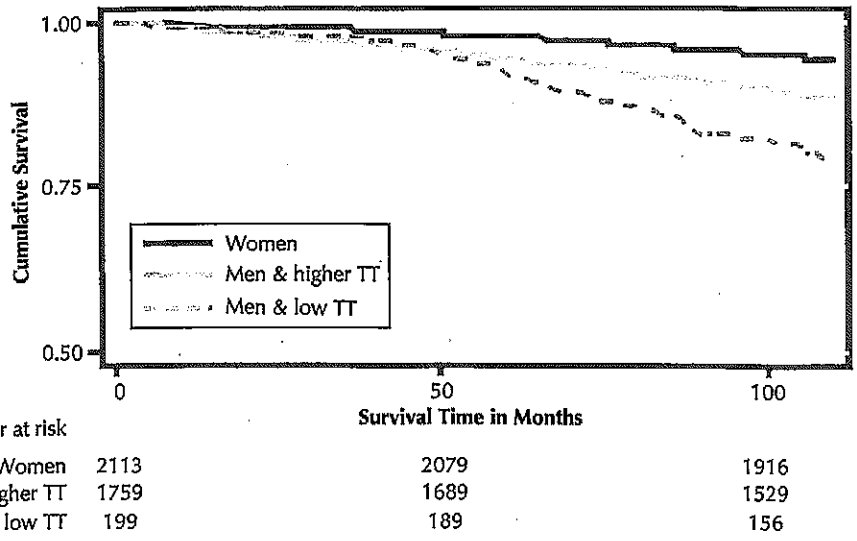


Figure 2. Distribution of 10-year cardiovascular disease (CVD) risk burden separately for women, men, and men with total testosterone (TT) concentrations less than the age-specific 10th percentile. Ten-year CVD risk scores were calculated only for individuals without baseline CVD.



Number at risk			
Women	2113	2079	1916
Men & higher TT	1759	1689	1529
Men & low TT	199	189	156

Figure 3. Kaplan-Meier survival curves for all-cause mortality separately for women, men, and men with total testosterone (TT) concentrations less than the age-specific 10th percentile. Survival times differed significantly between these groups (log-rank test, $P < 0.001$).

However, the fact that excess cardiovascular morbidity and mortality in men is mainly determined by adverse lifestyle habits suggests a considerable potential for CVD reductions among men. There is no doubt that a healthy lifestyle, including regular exercise, not smoking, a favorable diet, and optimal weight is associated with significant reductions in CVD and mortality.[42–44] This association has been proved to be linear in the sense that an increased number of healthy lifestyle characteristics proportionally reduce cardiovascular risk burden.[42] Consequently, low cardiovascular risk factors levels have been shown to be the most important factor associated with reaching age 90 years for men.[45]

Further risk stratification by testosterone status revealed that men with low TT concentrations were at the highest risk of 10-year CVD and mortality compared with both men with higher TT concentrations and women. This result substantiates findings from the 7-year follow-up of our cohort[16] and from other studies[46] suggesting low TT concentrations in men as a general CVD risk marker.[47] However, low TT is considered secondary to increased CVD risk factor burden because healthy lifestyle habits have been shown to predict higher TT concentrations[48] and to even prevent the age-related decline of TT concentrations in men.[30,49]

Collectively, there is little published evidence on how to improve men's uptake and maintenance of preventive health services.[50] Despite the variety of interventions to promote healthy lifestyle changes for cardiovascular risk factor reduction in adults,[51] a gender-specific intervention addressing specific men's needs and topics, as popular as testosterone, are not available to date. Thus, testosterone monitoring may offer a motivational biomarker to encourage improved lifestyle adherence and thereby achieve substantial reductions of CVD risk factor burden among men. But to prove the suggested role of testosterone monitoring as part of an interventional strategy for the adoption and maintenance of cardiovascular risk-reducing lifestyle changes, large-scale interventional studies are required. However, it is important to not understand our results in favor of initiating testosterone therapy. Quite the opposite, caution should be exercised with regard to testosterone therapy because the safety of testosterone supplementation and its adverse cardiovascular effects are still unknown,[52] and therapy should only be considered in the presence of at least 3 sexual symptoms.[53]

Limitations of our investigation may arise from the study sample comprising whites only, therefore limiting the generalizability of our findings to individuals of other ethnicities. Furthermore, measured TT concentrations based on a single serum sample drawn between 8:00 AM and 7:00 PM. Despite the apparent diurnal variation in TT concentrations, a single-point TT concentration is considered to reflect longer-term androgen status in healthy men fairly well.[54] Strengths of our study include its longitudinal population-based sample, extensive covariate assessment, and a comprehensive analytical approach to investigate not only gender differences in cardiovascular risk factor burden and mortality, but also the additional influence of TT assessment for the identification of high-risk male individuals.

CONCLUSIONS

Our investigation confirmed the commonly observed gender gap in cardiovascular morbidity and mortality with substantially higher risks in men compared with women. Furthermore, we identified men with low TT concentrations as high-risk individuals particularly responsive to excess cardiovascular morbidity and mortality. Our study further emphasizes the need for particularly rigorous lifestyle counseling in men, whereas the potential application of additional TT assessment as a motivational biomarker for improved lifestyle adherence merits further investigation.

CONFLICTS OF INTEREST

Novo Nordisk provided partial grant support for the determination of serum samples and data analysis. Furthermore, the funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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Dr. Haring researched data and wrote manuscript. Drs. Völzke, Nauck, and Wallaschofski organized data collection and laboratory measurements. Drs. John, Völzke, Nauck, Dörn, Felix, and Wallaschofski reviewed and edited the manuscript. Drs. Wallaschofski, John, and Völzke contributed to discussion.

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