

Late-Onset Hypogonadism and Mortality in Aging Men

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Context: Late-onset hypogonadism (LOH) has recently been defined as a syndrome in middle-aged and elderly men reporting sexual symptoms in the presence of low T. The natural history of LOH, especially its relationship to mortality, is currently unknown.

Objective: The aim of this study was to clarify the associations between LOH, low T, and sexual symptoms with mortality in men.

Design, Setting, and Participants: Prospective data from the European Male Aging Study (EMAS) on 2599 community-dwelling men aged 40–79 years in eight European countries was used for this study.

Main Outcome Measure(s): All-cause, cardiovascular, and cancer-related mortality was measured.

Results: One hundred forty-seven men died during a median follow-up of 4.3 years. Fifty-five men (2.1%) were identified as having LOH (31 moderate and 24 severe). After adjusting for age, center, body mass index (BMI), current smoking, and poor general health, compared with men without LOH, those with severe LOH had a 5-fold [hazard ratio (HR) 5.5; 95% confidence interval (CI) 2.7, 11.4] higher risk of all-cause mortality. Compared with eugonadal men, the multivariable-adjusted risk of mortality was 2-fold higher in those with T less than 8 nmol/L (irrespective of symptoms; HR 2.3; 95% CI 1.2, 4.2) and 3-fold higher in those with three sexual symptoms (irrespective of serum T; compared with asymptomatic men; HR 3.2; 95% CI 1.8, 5.8). Similar risks were observed for cardiovascular mortality.

Conclusions: Severe LOH is associated with substantially higher risks of all-cause and cardiovascular mortality, to which both the level of T and the presence of sexual symptoms contribute independently. Detecting low T in men presenting with sexual symptoms offers an opportunity to identify a small subgroup of aging men at particularly high risk of dying. (*J Clin Endocrinol Metab* 99: 1357–1366, 2014)

Serum T levels gradually decline with age in men (1, 2). However, the clinical significance of this remains unclear and controversial (3). Recent guidelines have attempted to establish a syndrome of late-onset hypogonadism (LOH) as a clinical and biochemical state with advancing age, characterized by typical symptoms and low T (4). This concept, however, remains contentious (5) because there is uncertainty about the clinical significance of LOH in the absence of objective information on its

natural history and response to T replacement therapy (6). To improve the specificity of the diagnosis, we have recently proposed the minimum criteria for LOH based on the simultaneous occurrence of three sexual symptoms (decreased sexual interest and morning erections and erectile dysfunction) and total T below 11 nmol/L and free T below 220 pmol/L (7). Using these criteria, we have also reported associations between LOH and a variety of end organ deficits suggestive of androgen deficiency (8). How-

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

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Received April 25, 2013. Accepted November 11, 2013.

First Published Online December 11, 2013

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Abbreviations: BDI, Beck's Depression Inventory; BMI, body mass index; CI, confidence interval; CVD, low-density lipoprotein; ED, erectile dysfunction; EMAS, European Male Aging Study; HR, hazard ratio; LDL, low-density lipoprotein; LOH, late-onset hypogonadism.

ever, the clinical significance and the natural history of LOH remain largely undefined.

Several studies have shown association of low T with increased risk of all-cause and cardiovascular-related mortality, although a recent meta-analysis of 12 community-based studies have revealed considerable inconsistency between individual studies (9). Whether low T is a nonspecific risk marker of poor health (9, 10) or the association is mediated by the effects of T deficiency on the cardiovascular system (11) is currently unclear. Erectile dysfunction (ED) is increasingly recognized as an early warning signal of impending cardiovascular disease and a predictor of excessive mortality (12–14). If our proposed criteria of low T and sexual symptoms (including ED) identify a syndrome of symptomatic androgen deficiency (7, 8), it would be important to determine whether LOH is also associated with increased all-cause or cause-specific mortality.

Using longitudinal data from the European Male Aging Study (EMAS), the primary aim of this study was to examine the association between LOH and mortality with the secondary objective of estimating the relative contributions of low T and sexual symptoms.

Materials and Methods

Subjects and study design

Subjects were recruited to participate in the EMAS, the details of which, including study design and methodologies, have been fully described (15). Briefly, an age-stratified probability sample of 3369 men aged 40–79 years (mean \pm SD: 60 \pm 11 y) were recruited from population registers in eight European centers (Florence, Italy; Leuven, Belgium; Malmö, Sweden; Manchester, United Kingdom; Santiago de Compostela, Spain; Łódź, Poland; Szeged, Hungary; Tartu, Estonia). Subjects completed a postal questionnaire and then attended a research clinic for detailed clinical assessments (15). They subsequently completed a further postal questionnaire and attended a follow-up assessment approximately 4 years later (range 3.0–5.7 y). Ethical approval for the study was obtained in accordance with local institutional requirements in each center. All subjects provided written informed consent.

Assessments

The postal questionnaires included questions concerning current smoking and current treatments for 14 medical conditions (heart conditions; hypertension; diabetes; bronchitis; asthma;

peptic ulcer; epilepsy; liver, kidney and prostate conditions; and pituitary, testicular, adrenal and thyroid diseases) or whether they had ever been diagnosed with cancer or stroke. Participants were asked also about their general health (response set: excellent, very good, good, fair, poor) and completed the Beck's Depression Inventory (BDI), a sexual function questionnaire (15) and information on current medications was collected. Height and body weight were measured in a standardized manner for body mass index (BMI) calculation. Waist circumference was measured at the midpoint between supra-iliac crest and lowest rib to the nearest 0.1 cm.

Hormones and biochemistry

A single fasting morning (before 10:00 AM) venous blood sample was obtained from each subject. T was measured by gas chromatography-mass spectrometry as described previously (16). SHBG was measured by the Modular E170 platform electrochemiluminescence immunoassay (Roche Diagnostics). Free T levels were derived from total T, SHBG, and albumin concentrations by the Vermeulen formula (17).

Fasting total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein cholesterol, triglycerides, and glucose were measured by standard methods (18). Insulin was measured using chemiluminescence immunoassay (Siemens Immulite 2000). Insulin resistance was calculated using the homeostatic model (19).

Mortality

Deaths during the follow-up period were initially ascertained either through contact by relatives on receipt of the postal questionnaire or, if this was not returned, by further inquiries to ascertain the subject's vital status. The enquiry procedure varied between centers and included review of the medical records/death registers and telephone follow-up. Deaths were verified from death certificates (25%), death registers (37%), or medical/hospital records (27%). Eleven percent of deaths were unverified and information from the family member/contact person was the only source. Deaths were categorized where possible as being due to C (CVD), cancer, or other causes. Subjects who did not reply to the follow-up postal questionnaire and for whom no further information was available were classified as lost to follow-up.

Statistical analysis

LOH was defined as the presence of three sexual symptoms (decreased frequency of morning erections and sexual thoughts and erectile dysfunction) in combination with total T less than 11 nmol/L and free T less than 220 pmol/L (7). LOH was further divided into two symptomatic subgroups: moderate, with total T less than 11 and 8 nmol/L or greater and free T less than 220 pmol/L, and severe, with total T less than 8 nmol/L and free T less than 220 pmol/L. Smoking status was categorized as current vs

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never and ex-smokers. Cardiovascular disease was defined as subjects who reported having a stroke or were currently being treated for heart conditions or hypertension. Comorbidity was defined as a count of the number of medical conditions for which a subject was currently being treated. Poor general health was defined as poor/fair vs good/very good/excellent.

Kaplan-Meier methods were used to trace survival, and Cox proportional hazard models were used to assess the risk of mortality (all cause, CVD related, and cancer related were examined separately). The following Cox proportional hazard models were tested: 1) T and free T categorized into quintiles, with the highest quintile as the reference group; 2) LOH status, with subjects without LOH as the referent group; 3) low T irrespective of sexual symptoms, with eugonadal as the referent group; 4) number of sexual symptoms (0–3) irrespective of T levels, with 0 as the referent group; and 5) each individual sexual symptom irrespective of T levels. These analyses were performed unadjusted (model I) and then with serial adjustment for age and center (model II), BMI (model III), and finally the remaining confounders found to be associated with both LOH status and mortality (model IV).

A stepwise Cox regression analysis was also performed. Model A included only the confounders, model B added low T with the eugonadal group as the reference category, model C

added the number of sexual symptoms (0–3, with 0 as the reference group) to model A, and finally, model D included low T, number of sexual symptoms, and the confounders. The predictive power of each of the models was compared using Harrell's C concordance statistic. An interaction term between low T and sexual symptoms was fitted to model D to examine interactions.

Subanalyses were conducted excluding deaths in the first 12 months of follow-up, subjects with BMI greater than 30 kg/m², and subjects with diabetes. Results are reported as hazard ratios (HRs) and 95% confidence intervals (CIs). For all models, the assumption of proportional hazards was tested using the Schoenfeld residuals. All statistical tests were performed using STATA version 11.2 (<http://www.stata.com>).

Results

From the initial 3369 participants at baseline, 149 were excluded because of known pituitary, testicular or adrenal diseases, or current use of medications affecting pituitary/testicular functions or clearance of sex steroids. Complete

Table 1. Baseline Characteristics of Subjects by Vital Status at End of the Follow-Up

Variable	Survived (n = 2452) Mean (SD)	Died (n = 147)	P ^{diff} Value
Age, y	58.9 (10.6)	69.3 (8.2)	<.001
Height, cm	174.1 (7.2)	170.0 (6.9)	<.001
Weight, kg	83.9 (13.7)	80 (16.9)	<.001
BMI, kg/m ²	27.6 (4.0)	27.7 (5.1)	NS
Waist circumference, cm	98.3 (10.8)	99.6 (12.6)	NS
T, nmol/L	16.64 (5.9)	16.56 (6.3)	NS
Free T, pmol/L	296.0 (86.3)	252.6 (88.1)	<.001
SHBG, nmol/L	42.0 (18.9)	53.3 (26.0)	<.001
Total cholesterol, mmol/L	5.6 (1.3)	5.4 (1.3)	<.05
HDL cholesterol, mmol/L	1.41 (0.37)	1.42 (0.44)	NS
LDL cholesterol, mmol/L	3.5 (1.2)	3.3 (1.1)	<.05
Fasting glucose, mmol/L	5.6 (1.2)	6.2 (2.7)	<.001
Triglycerides, mmol/L	1.6 (1.2)	1.5 (0.8)	NS
Insulin, pmol/L	11.9 (11.2)	13.1 (11.4)	NS
HOMA-IR	3.2 (4.2)	3.7 (4.0)	.09
BDI total score	6.4 (6.1)	11.2 (8.6)	<.001
	%		
Current smoker, yes vs no	20.1	29.9	<.01
General health, fair or poor	28.4	63.7	<.001
Two or more morbid conditions	47.2	81.7	<.001
CVD, yes vs no	33.6	59.9	<.001
Diabetes, yes vs no	6.2	14.8	<.001
Metabolic syndrome, yes vs no	21.6	27.2	NS
Cancer, yes vs no	4.5	15.0	<.001
Infrequent sexual thoughts, yes vs no	24.1	54.4	<.001
Morning erection, yes vs no	35.0	70.8	<.001
Erectile dysfunction, yes vs no	26.7	66.7	<.001
Number of sexual symptoms			
0	47.6	17.0	
1	28.3	16.3	
2	14.9	24.5	
3	9.3	42.2	<.001

Abbreviation: HDL, high-density lipoprotein; HOMA-IR, homeostatic model for insulin resistance; ND, not determined. P^{diff} used the *t* test, Wilcoxon rank-sum, or χ^2 test as appropriate.

Table 2. Influence of T and Free T (Categorized Into Quintiles) on Risk of All-Cause Mortality

	Hazard Ratio (95% CI) for All-Cause Mortality			
	Model I	Model II	Model III	Model IV
Quintiles of T, range in nmol/L				
5, >21.20	Referent	Referent	Referent	Referent
4, 17.28–21.20	1.1 (0.7, 1.8)	1.1 (0.7, 1.7)	1.1 (0.7, 1.8)	1.2 (0.7, 2.0)
3, 14.61–17.28	0.7 (0.4, 1.2)	0.7 (0.4, 1.2)	0.8 (0.4, 1.3)	0.7 (0.4, 1.3)
2, 11.65–14.61	0.7 (0.4, 1.2)	0.7 (0.4, 1.2)	0.7 (0.4, 1.3)	0.7 (0.4, 1.3)
1, <11.65	1.1 (0.7, 1.7)	1.0 (0.6, 1.6)	1.1 (0.6, 1.8)	1.1 (0.6, 1.8)
Quintiles of free T, range in pmol/L				
5, >362.14	Referent	Referent	Referent	Referent
4, 310.00–362.14	2.0 (1.0, 3.9) ^a	1.4 (0.7, 2.8)	1.3 (0.7, 2.7)	1.5 (0.8, 3.0)
3, 266.18–310.00	1.8 (0.9, 3.6)	1.0 (0.5, 2.0)	1.1 (0.5, 2.1)	1.0 (0.5, 2.1)
2, 224.86–266.18	2.1 (1.1, 4.1) ^a	0.9 (0.4, 1.7)	0.9 (0.5, 1.8)	0.9 (0.4, 1.8)
1, <224.86	4.2 (2.3, 7.7) ^b	1.4 (0.7, 2.7)	1.5 (0.8, 2.9)	1.3 (0.7, 2.6)

Model I is unadjusted; model II is adjusted for age and center; model III is adjusted for age, center, and BMI; and model IV is adjusted for age, center, BMI, current smoking, and poor general health.

^a $P < .05$.

^b $P < .001$.

baseline data on T and sexual symptoms were available from 2966 men, among whom no information about vital status could be obtained in 367 subjects (82 were too frail or institutionalized and 285 lost to follow-up) leaving a total of 2599 in this analysis. During a median of 4.3 years of follow-up (range 3.0–5.7), comprising 11 140 person-years, there were 147 deaths (overall mortality rate 5.7%), of which 56 (38.1%) were due to CVD and 60 (40.8%) to cancer. Six deaths were attributable to both CVD and cancer. Of the remainder, 22 (15.0%) were due to other causes and 15 (10.2%) had an unknown cause. Of the 55 men (2.1% of baseline cohort) classified as having LOH (31 moderate and 24 severe), eight with moderate and nine with severe LOH died. The baseline characteristics of subjects who died by LOH status are presented in Supplemental Table 1, published on The Endocrine Society's Journals On-

line web site at <http://jcem.endojournals.org>. Mortality in men with LOH was higher, 30.9% (17 of 55), than that of the entire cohort (5.7%). The distribution of causes of death in subjects with LOH (64.7% from CVD and 29.4% from cancer) was different from that in the whole cohort.

Table 1 shows the baseline demographic, clinical, and biochemical characteristics of the entire analysis cohort stratified by vital status at the end of the follow-up period. There was no difference in total T levels between the groups. However, those who died were older and had lower free T and total and LDL cholesterol. They also had higher SHBG, fasting glucose, and BDI total score. Among those who died, a greater proportion smoked, were in fair/poor general health, had at least two comorbid conditions, CVD, diabetes, and cancer. Those who died were also more likely to have one or more sexual symptoms.

Table 3. Influence of T and Free T (Categorized Into Quintiles) on Risk of Cardiovascular-Related Mortality

	Hazard Ratio (95% CI) for Cardiovascular-Related Mortality			
	Model I	Model II	Model III	Model IV
Quintiles of T, range in nmol/L				
5, >21.20	Referent	Referent	Referent	Referent
4, 17.28–21.20	0.8 (0.4, 1.8)	0.8 (0.4, 1.8)	0.9 (0.4, 1.9)	1.1 (0.5, 2.4)
3, 14.61–17.28	0.4 (0.1, 1.0)	0.4 (0.2, 1.0)	0.4 (0.2, 1.1)	0.4 (0.2, 1.2)
2, 11.65–14.61	0.5 (0.2, 1.2)	0.5 (0.2, 1.3)	0.5 (0.2, 1.4)	0.5 (0.2, 1.4)
1, <11.65	1.0 (0.5, 2.2)	0.9 (0.4, 2.0)	0.9 (0.4, 2.1)	1.0 (0.4, 2.2)
Quintiles of free T, range in pmol/L	7			
5, >362.14	Referent	Referent	Referent	Referent
4, 310.00–362.14	1.2 (0.4, 4.0)	0.9 (0.3, 2.9)	0.7 (0.2, 2.5)	0.8 (0.2, 3.0)
3, 266.18–310.00	1.8 (0.6, 5.3)	0.9 (0.3, 2.7)	0.9 (0.3, 2.7)	1.0 (0.3, 2.9)
2, 224.86–266.18	2.1 (0.7, 6.1)	0.7 (0.2, 2.1)	0.7 (0.2, 2.1)	0.6 (0.2, 1.9)
1, <224.86	5.2 (2.0, 13.7) ^a	1.5 (0.5, 4.1)	1.4 (0.5, 4.1)	1.2 (0.4, 3.4)

Model I is unadjusted; model II is adjusted for age and center; model III is adjusted for age, center, and BMI; and model IV is adjusted for age, center, BMI, current smoking, and poor general health.

^a $P < .01$.

There was no association between T (categorized into quintiles) and all-cause or CVD-related mortality (Tables 2 and 3). The apparent association between free T and mortality did not persist after adjustment for age and other confounding factors. In contrast, there was a strong association between LOH and all-cause mortality with a progressive decline in the probability of survival over time (Figure 1A). In unadjusted analyses, compared with men without LOH, those with moderate and severe LOH had nearly a 6- and a 10-fold higher risk of all-cause mortality, respectively (Figure 2A, model I). Adjustment for age, but not BMI or other potential confounders, attenuated this relationship, which remained statistically significant only for subjects with severe LOH who had a 5-fold higher risk of mortality (HR 5.5; 95% CI 2.7, 11.4) (Figure 2A, model IV).

In men with low T, irrespective of sexual symptoms, similar although weaker relationships with mortality were observed (Figures 1B and 2B and Table 4). Those with T less than 8 nmol/L had a 2-fold higher risk. Adding low T to a model containing the confounding factors improved the all-cause mortality prediction slightly (C statistic 0.824 compared with 0.817) (Table 4). The occurrence (number) of sexual symptoms, irrespective of T levels, was associated with a higher risk of all-cause mortality (Figures 1C and 2C and Table 4). Those with two or more sexual symptoms were at higher risk of mortality after adjustment for confounders (Figure 2C and Table 4). Adding the number of sexual symptoms to a model containing the confounding factors improved the mortality prediction (C statistic 0.837 compared with 0.817; Table 4). Adding low T to this model improved the prediction very slightly (C statistic 0.842 vs 0.837; Table 4). There was no statistically significant interaction between low T and the number of sexual symptoms with respect to all-cause mortality.

When the sexual symptoms were examined individually, irrespective of T levels, all three were associated with a higher risk of mortality: erectile dysfunction (HR 2.0, 95% CI 1.3, 2.9), poor morning erection (HR 2.1, 95% CI 1.4, 3.1), and infrequent sexual thoughts (HR 1.6, 95% CI 1.1, 2.3) (Figure 2D).

Similar associations were observed between LOH status and CVD-related mortality (Figure 3A). Compared with men without LOH, those with moderate and severe LOH had a 3-fold (HR 2.9, 95% CI 1.2, 7.1) and 8-fold (HR 8.5, 95% CI 3.0, 23.8) higher risk of CVD mortality, respectively, after adjustment for confounders. Those with T less than 8 nmol/L, irrespective of sexual symptoms, had a higher risk of mortality compared with eugonadal men (Figure 3B and Table 5). Compared with those with no sexual symptoms, those with all three symptoms were at higher risk of CVD mortality after adjustment for confounders (Figure 3C and Table 5). All three

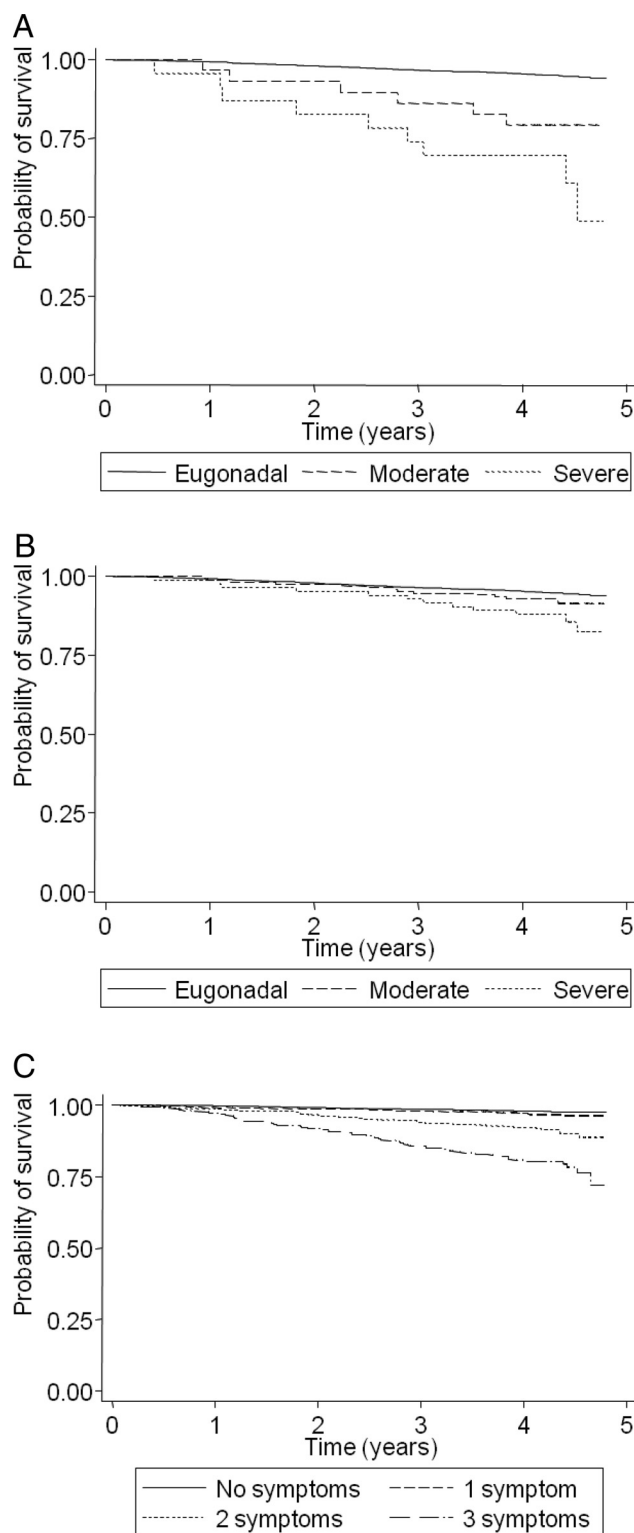


Figure 1. Unadjusted Kaplan-Meier survival curves for LOH status (A), low T irrespective of symptoms (B), and (C) number of sexual symptoms.

sexual symptoms were significantly associated with CVD mortality (Figure 3D).

A broadly similar pattern was observed with cancer related mortality (Supplemental Table 2). Compared

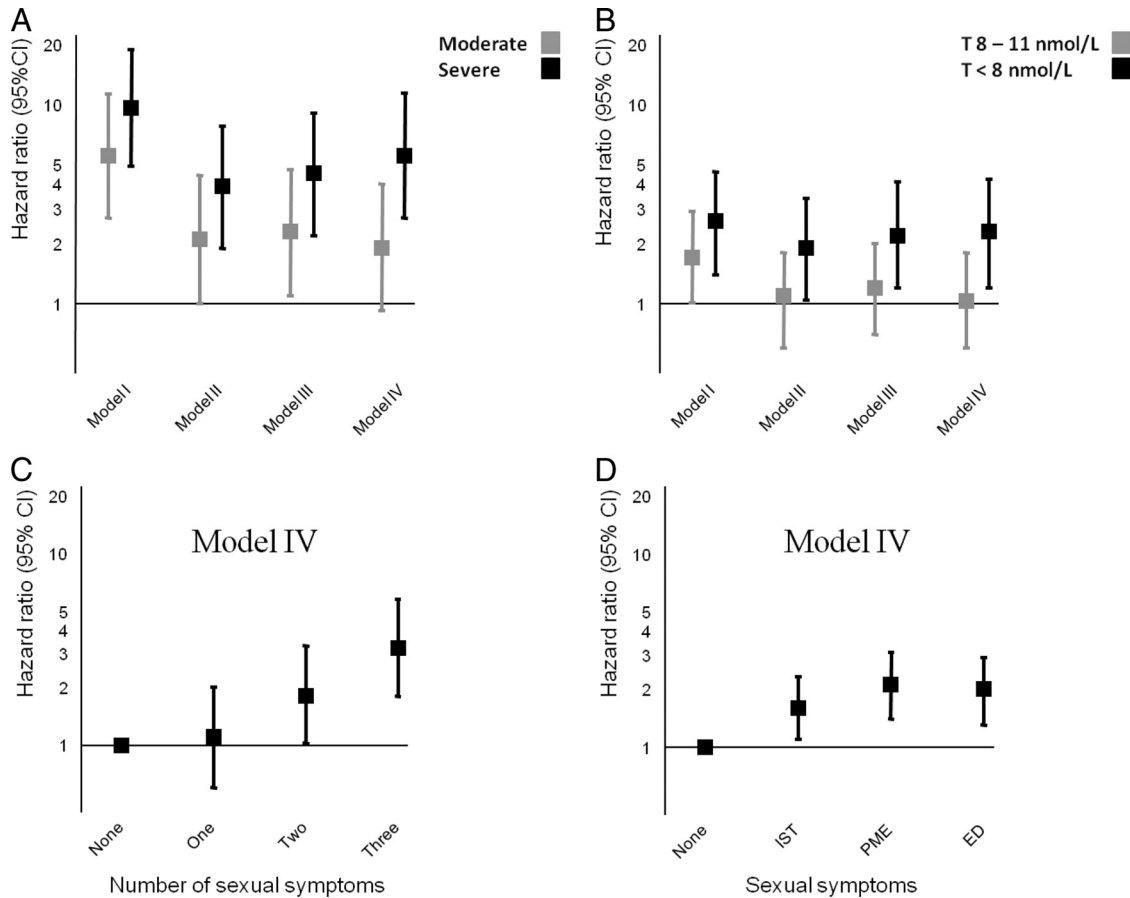


Figure 2. Cox proportional HR plots (95% CI) showing the influence on all-cause mortality of LOH status with eugonadal as the referent (A), low T, irrespective of symptoms, with eugonadal as the referent (B), number of sexual symptoms (C), and individual sexual symptoms (D). Model I is unadjusted; model II is adjusted for age and center; model III is adjusted for age, center, and BMI; and model IV is adjusted for age, center, BMI, smoking, and poor general health. IST, infrequent sexual thoughts; PME, poor morning erection.

with those without LOH, men with severe LOH had a 5-fold higher risk of death from cancer. Those with T less than 8 nmol/L, irrespective of symptoms, had a 3-fold higher risk compared with eugonadal men, and those with all three symptoms, irrespective of T levels, had a 5-fold

higher risk of cancer mortality compared with asymptomatic men. Excluding subjects who reported diabetes at baseline, those who died in the first year of follow-up or subjects with BMI greater than 30 kg/m² did not change the above results (data not shown).

Table 4. Influence of Low T and Number of Sexual Symptoms on Risk of All-Cause Mortality

	Hazard Ratio (95% CI) for All-Cause Mortality			
	Model A	Model B	Model C	Model D
Low T				
Eugonadal		Referent		Referent
T 8–11 nmol/l		1.0 (0.6, 1.8)		1.0 (0.6, 1.8)
T <8 nmol/l		2.3 (1.2, 4.2) ^a		2.2 (1.2, 4.1) ^a
No of sexual symptoms				
0			Referent	Referent
1			1.1 (0.6, 2.0)	1.1 (0.6, 2.0)
2			1.8 (1.0, 3.3) ^a	1.8 (1.0, 3.2) ^a
3			3.2 (1.8, 5.8) ^b	3.1 (1.7, 5.7) ^b
C statistic for model	0.817	0.824	0.837	0.842

Model A included age, center, BMI, current smoking, and poor general health. Model B included low T, age, center, BMI, current smoking, and poor general health. Model C included number of sexual symptoms, age, center, BMI, current smoking, and poor general health. Model D included low T, number of sexual symptoms, age, center, BMI, current smoking, and poor general health.

^a P < .05.

^b P < .001

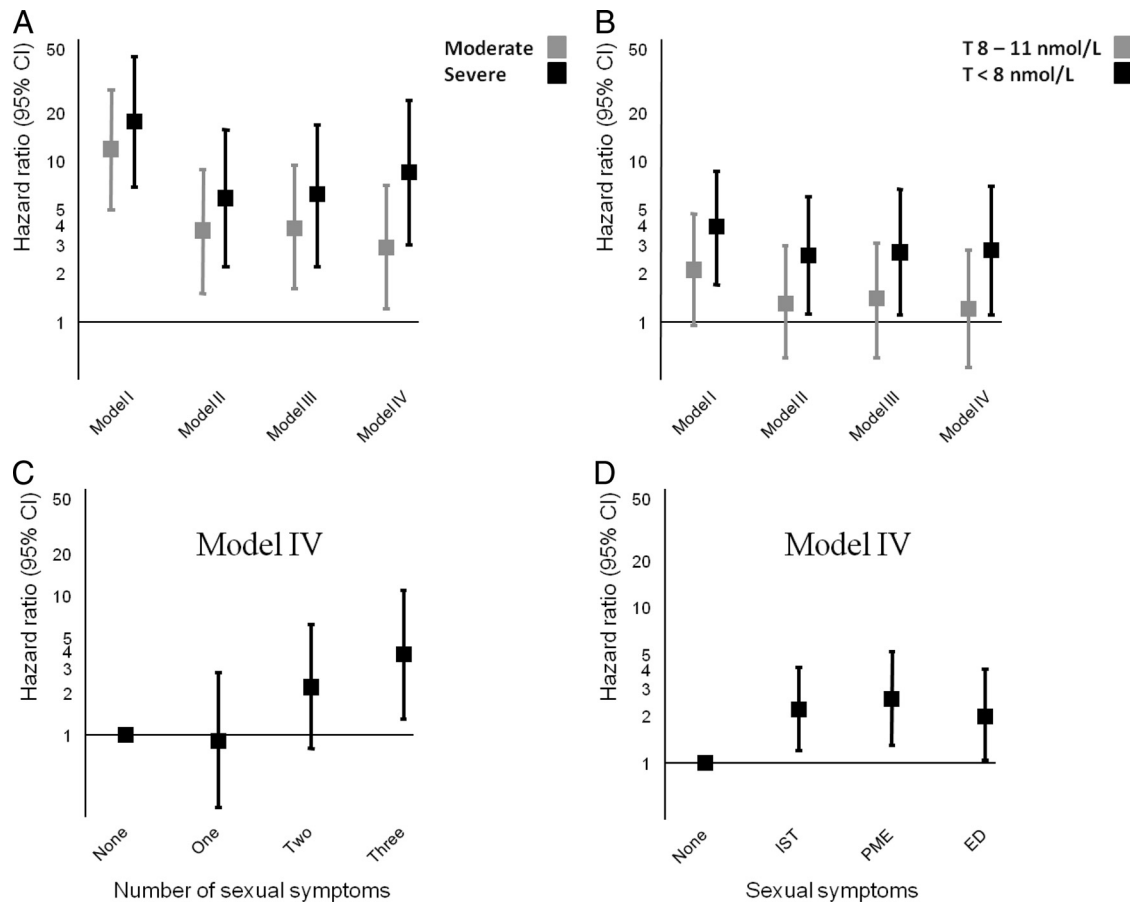


Figure 3. Cox proportional HR plots (95% CI) showing the influence on cardiovascular-related mortality of LOH status, with eugonadal as the referent (A); low T irrespective of symptoms, with eugonadal as the referent (B); number of sexual symptoms (C); and individual sexual symptoms (D). Model I is unadjusted; model II is adjusted for age and center; model III is adjusted for age, center, and BMI; and model IV is adjusted for age, center, BMI, smoking, and poor general health. IST, infrequent sexual thoughts; PME, poor morning erection.

Discussion

In this population-based sample of middle-aged and older men, severe LOH was associated with a 5-fold higher risk of all-cause mortality after adjustment for confounders. The excess risk appeared to be a combination of low T (<8

nmol/L) and the presence of all three sexual symptoms, which were independently associated with a 2- and 3-fold higher all-cause mortality, respectively. There was no interaction between low T and sexual symptoms with respect to mortality risks. LOH was also strongly associated with CVD and cancer-related mortality.

Table 5. Influence of Low T and Number of Sexual Symptoms on Risk of Cardiovascular-Related Mortality

	Hazard Ratio (95% CI) for Cardiovascular-Related Mortality			
	Model A	Model B	Model C	Model D
Low T				
Eugonadal		Referent		Referent
T 8–11 nmol/l		1.2 (0.5, 2.8)		1.2 (0.5, 2.7)
T <8 nmol/l		2.8 (1.1, 7.0) ^a		3.1 (1.2, 7.6) ^a
No of sexual symptoms				
0			Referent	Referent
1			0.9 (0.3, 2.8)	0.8 (0.3, 2.7)
2			2.2 (0.8, 6.2)	2.1 (0.7, 6.0)
3			3.8 (1.3, 10.9) ^a	3.8 (1.3, 10.8) ^a
C statistic for model	0.873	0.884	0.895	0.902

Model A included age, center, BMI, current smoking and poor general health. Model B included low T, age, center, BMI, current smoking and poor general health. Model C included number of sexual symptoms, age, center, BMI, current smoking and poor general health. Model D included low T, number of sexual symptoms, age, center, BMI, current smoking and poor general health.

^a $P < .05$.

The association between endogenous total T and/or free T and all-cause mortality in men has been observed in some (20–27) but not all studies (28–31). A recent systematic review and meta-analysis of 12 community based studies, 11 of which included data on all-cause mortality, concluded that low total T was linked to a higher risk of all-cause and CVD mortality, but there was considerable between-study heterogeneity in results, attributable to differences in subject characteristics (including age, baseline T, and length of follow-up) (9). In our study, mean T levels were similar between men who died and survivors, and even when total T was categorized into quintiles, we found no association with mortality (Table 2). Similar to other studies (10, 27), our results showed that free T was associated with mortality; however, this did not persist after adjustment, suggesting that the relationship was confounded by increasing age. Our observation of a 2-fold increase in risk of mortality only in men with total T less than 8 nmol/L suggests a nonlinear relationship that emerges only when T has declined into the unequivocally hypogonadal range (4, 5).

The association between T deficiency and an increased risk of cardiovascular mortality has been observed in some (21, 22, 26, 27, 29), although not all (24, 25, 28), studies. A meta-analysis of seven population-based studies concluded that there was a borderline significant link between endogenous T and death from a cardiovascular cause (9), in keeping with our findings. The relationships between androgens and cardiovascular disease are complex and inconsistent (32–34). In our analysis, we did not adjust a priori for prevalent CVD on the basis that it could act as a path variable, ie, low T could have a negative influence on the cardiovascular system leading to CVD, which in turn leads to all-cause/CVD-related death. However, a post hoc analysis adjusting for prevalent CVD in the final multivariate models made no difference to the observed mortality risks (data not shown). This would imply that the relationship between low T and increased mortality was not mediated through a direct effect on the cardiovascular system. Thus, whether low T mediates a causal link or represents a marker of poor cardiometabolic health remains uncertain (10, 34).

Our observation of a link between LOH and mortality was not, however, specific to cardiovascular disease. We also found a strong association with cancer-related mortality. This observation is in keeping with some (21, 26) but not all studies (22, 29), further raising the possibility of reverse causality.

ED and CVD frequently coexist and share many risk factors (35). There is increasing evidence to suggest that ED is an independent marker of increased CVD risk and mortality (12–14). It has also been suggested that ED may

be a sentinel symptom of cardiovascular disease (13), preceding coronary events by 2–5 years (36). Our observation of an association between sexual symptoms and CVD mortality is compatible with this. However, our finding that sexual symptoms are also associated with all-cause mortality may indicate that the presence of these symptoms is a marker or consequence of chronic comorbid diseases and general ill health. Erectile/sexual dysfunction and low T frequently coexist in a significant subgroup of men (7). It is therefore interesting to note that the present results showed no interaction between low T and sexual symptoms with regard to mortality, suggesting that the associations are independent and may be additive, although the relatively small number of deaths observed in this study may have precluded detection of such interactions.

The pathophysiological basis of the present findings remains unclear. It is not possible to differentiate whether low T/LOH is the cause or mediator of higher mortality or merely a nonspecific marker of, or specific adaptive response to, poor health. Although there was only a small number of men with severe LOH in this study, nonetheless, the association with multiple causes of mortality makes it less likely that T deficiency per se is the sole explanation, whereas erectile/sexual symptoms (surrogate for poor vascular health) may be even more important than low T. Taken together, the present data suggest that LOH represents a marker of poor health in aging, albeit that a bidirectional relationship cannot be excluded. These considerations have important implications on our approach to clinical management and the rationale for T replacement in symptomatic older men with low T. Although a recent retrospective observational study reported a lower mortality in T-treated compared with untreated veterans (37), it cannot be concluded that the T treatment actually reduced mortality (38). The clinical implication of the present findings is that sexual dysfunction and low T, which often coexist as LOH, should be recognized as an important window of opportunity for improving aging men's general health and survival and subsequent assessment and reduction of adverse health (especially cardiometabolic risk) factors.

Our observation that BMI (or waist circumference; data not shown) did not attenuate the association between LOH and mortality is noteworthy; it confirms other studies that the higher risk of all-cause and CVD death associated with low T was independent of BMI (9, 21). Obesity is an established CVD risk factor and we (and others) have shown that low T is strongly associated with overall or central obesity (17). This raises the possibility that the quality or function may be more important than the quantity of fatty tissue as a risk mediator for CVD. There is also

evidence from population-based studies that BMI has a J-shaped relationship with mortality (39). This could be an alternative explanation for the lack of attenuation when adjusting for BMI in our statistical models.

The main strengths of our study include the prospective, population-based data with detailed phenotyping of men (including documentation of sexual symptoms with a validated questionnaire) stringently identified to be likely candidates for hypogonadism using standardized assessment and state-of-the-art gas chromatography mass spectrometry measurement of T. Methodological limitations inherent to the EMAS study have been described in detail previously (15), as have limitations pertaining to the use of a single, as opposed to repeated, T measurement and the calculation, rather than the direct measurement, of free T (17). In our study the overall loss to follow-up rate was 9.9% (40). Compared with participants, those lost to follow-up had lower 25-hydroxyvitamin D levels (mean 55.2 vs 64.4 nmol/L), lower physical functioning as measured by Reuben's physical performance test rating (mean 23.8 vs 24.2) and a lower mental processing speed as measured by digit symbol substitution score (mean 26.0 vs 28.5) and consequently may be at increased risk of mortality (40). Our findings concerning mortality among the participants may therefore underestimate the true mortality experience of the full cohort. Compared with participants, those lost to follow-up ($n = 367$) had similar total T levels at baseline [mean (SD) 16.6 (5.9) vs 16.3 (6.0), respectively]. Furthermore, because no systematic differences were observed between participants and those lost to follow-up in relation to LOH status, the losses to follow-up are unlikely to have influenced the main findings. The loss to follow-up rate varied across the participating centers (4.4%–16.3%); however, adjusting for the effect of center in the analysis did not alter the main findings. Sixteen percent of the information on CVD-related deaths and 7% of the information on cancer-related deaths came from family members or a contact person of the deceased; hence, these data should be interpreted with caution. However, exclusion of these unverified deaths made no difference to the results (data not shown).

In summary, LOH, as defined by the presence of three sexual symptoms and low T, was associated with a substantial increased risk of all-cause, CVD, and cancer mortality. The excess mortality risk was less marked in men with low T only, underlying the importance of sexual symptoms in the diagnosis and outcome of LOH. Eliciting sexual symptoms and documenting low T offers an important opportunity to identify a small subgroup of men at particularly high risk of dying.

Acknowledgments

We thank the men who participated in the eight countries and the research/nursing staff in the eight centers [C. Pott (Manchester), E. Wouters (Leuven), M. Nilsson (Malmö), M. del Mar Fernandez (Santiago de Compostela), M. Jedrzejowska (Łódź), H.-M. Tabo (Tartu), and A. Heredi (Szeged)] for their data collection and C. Moseley (Manchester) for data entry and project coordination. Dr S. Boonen is senior clinical investigator of the Fund for Scientific Research, Flanders, Belgium (F.W.O.-Vlaanderen); Dr D. Vanderschueren is a senior clinical investigator supported by the Clinical Research Fund of the University Hospitals Leuven, Belgium.

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The European Male Aging Study is funded by the Commission of the European Communities Fifth Framework Program, "Quality of Life and Management of Living Resources," Grant QLK6-CT-2001-00258. Additional support was also provided by Arthritis Research UK and the National Institute for Health Research and the Manchester Biomedical Research Centre. The principal investigator of EMAS is Professor Frederick Wu, MD, Andrology Research Unit, University of Manchester, Manchester, UK.

Disclosure Summary: F.C.W.W. is a consultant for GSK, Bayer-Schering, Jenapharm, Ferring, TAP, Lilly-ICOS, Proctor & Gamble, Ardana Biosciences, Pierre Fabre Medicaments, and Acrux DDS Pty Ltd and has also chaired advisory board meetings and lectured on their behalf. F.C.W.W. has also received lecture fees from Organon, Bayer-Schering, Lilly-ICOS, Ardana Biosciences, and Pierre Fabre Medicaments and has received grant support (2009–2013) from Bayer Schering AG and the New England Research Institute, Watertown, Massachusetts. I.T.H. is a consultant and has received grants from Ferring Pharmaceuticals. All other authors have nothing to disclose.

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