The Association of Testosterone Levels with Overall Sleep Quality, Sleep Architecture, and Sleep-Disordered Breathing

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Context: Little is known about the association of low endogenous testosterone levels and abnormal sleep patterns in older men, although pharmacological doses of testosterone are associated with increased severity of sleep apnea and other sleep disturbances.

Objective: The objective of the study was to examine the association between serum testosterone levels with objectively measured sleep characteristics.

Design: This was a cohort study.

Setting: Community-dwelling men aged 65 yr or older from six clinical centers in the United States participated in the study.

Participants and Main Outcome Measures: A total of 1312 men had baseline total testosterone levels measured in 2000–2002, followed 3.4 yr later by 72-h (minimum) actigraphy and one-night in-home polysomnography to assess sleep duration, sleep fragmentation, and sleep apnea. Analyses were performed by quartile of total testosterone and categorically defined low *vs.* higher total testosterone ($<$250 ng/dl *vs.* $\geq$250 ng/dl). Lifestyle and body size were covariates.

Results: Total testosterone levels were unrelated to age or duration of sleep. Men with lower testosterone levels had lower sleep efficiency, with increased nocturnal awakenings and less time in slow-wave sleep as well as a higher apnea-hypopnea index and more sleep time with O_2 saturation levels below 90%. Low testosterone levels were associated with overweight, and all significant associations were attenuated or absent after adjusting for body mass index or waist circumference. In a *post hoc* analysis in men with higher body mass index ($>$27 kg/m2), testosterone was significantly associated with more periods awake after sleep onset and lower sleep efficiency.

Conclusion: Low total testosterone levels are associated with less healthy sleep in older men. This association is largely explained by adiposity. Clinical trials are necessary to determine whether body weight acts directly or indirectly (via low testosterone) in the causal pathway for sleep-disordered breathing in older men. **(*J Clin Endocrinol Metab* 93: 2602–2609, 2008)**

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Abbreviations: AHI, Apnea-hypopnea index; BMI, body mass index; CV, coefficient of variation; MrOS, Osteoporotic Fractures in Men Study; PIM, proportional integration mode; PSG, polysomnography; REM, rapid eye movement.

Sleep patterns change with age, with older individuals showing prolonged sleep latency, greater sleep fragmentation, poorer sleep efficiency, and lighter sleep (less slow wave sleep) than younger individuals (1, 2). These associations are much stronger in men than women, suggesting a sex-related vulnerability to age-associated sleep problems (2). The prevalence of sleep apnea in older adults ranges from 5% to greater than 80%, depending on the definition, and is both more prevalent and more likely to become severe with aging in men than women (3, 4). The physiological mechanisms that underlie these large sex differences in sleep and sleep-related disorders, including a male predominance for less slow-wave sleep and more sleep apnea are poorly understood.

In most studies, bioavailable but not total testosterone levels decrease with age in apparently healthy men (5–7). The clinical significance of this decline, which often begins in midlife, is uncertain. As reported in the Institute of Medicine monograph (7), low levels of testosterone have been associated with frailty, reduced lean body mass (8) and muscle strength (9), increased total body and central obesity (10–13), reduced cognitive function (14, 15), and low libido (16). There has been little mention of the potential association of sleep disturbance with testosterone levels, and the association between endogenous testosterone levels and sleep disturbance and sleep apnea has not been addressed in large community-based studies.

Most clinical trials of testosterone treatment and sleep were small, short studies of pharmacological doses (at least 200 mg of weekly testosterone enanthate) in older eugonadal (17, 18) or hypogonadal (19, 20) men, and focused on sleep apnea as an outcome. In these trials, testosterone caused or worsened sleep apnea. Intramuscular testosterone therapy does not mimic physiological hormone levels or the circadian rhythm seen in younger men. Transdermal testosterone administration can maintain more stable physiological serum testosterone concentrations, but lacks pulsatility and diurnal rhythm, possibly necessary for beneficial effects. In the largest and longest clinical trial of transdermal testosterone, 108 men without known sleep apnea (whose average testosterone levels were lower than the young male mean) were randomly assigned to daily placebo or scrotal testosterone patch for 3 yr (21); sleep apnea was evaluated by a portable instrument that assessed cessation of airflow and change in saturation of oxyhemoglobin. In this trial testosterone titrated to physiological levels showed no effect on sleep-disordered breathing.

Previous studies of testosterone treatment of sleep disturbance had variable results. For example, one cross-sectional study of 216 men with sleep apnea (22) showed that more severe hypoxia was associated with lower free and total testosterone levels, independent of age and obesity. In that study, treatment with continuous positive airway pressure increased total but not bioavailable testosterone. In another study of eight men with sleep apnea, androgen blockade had no effect on their apnea (23).

Thus, it remains unclear whether restoration to young adult testosterone levels is protective or harmful to sleep patterns in elderly men. No large population-based studies have reported the association of endogenous testosterone levels with objectively measured sleep parameters in older community-dwelling men or examined whether any observed associations are independent of age, body mass index (BMI), and other potential covariates. We report here the independent association of baseline endogenous total and bioavailable testosterone levels in 1312 relatively healthy community-dwelling older men who had overnight sleep duration, sleep architecture, and sleep-disordered breathing measured objectively an average of 3.4 yr later.

Participants and Methods

Participants

Data are from a subset of participants in the Osteoporotic Fractures in Men Study (MrOS). From March 2000 through April 2002, 5995 community-dwelling men at six clinical centers in the United States (Birmingham, AL; Minneapolis, MN; Palo Alto, CA; Monongahela Valley near Pittsburgh, PA; Portland, OR; and San Diego, CA) agreed to participate in a study of healthy aging, with a particular focus on osteoporosis and fractures. Eligibility required that participants be at least 65 yr of age, have no bilateral hip replacements, and be able to walk without the assistance of another person. Details of the MrOS design and cohort have been published (24, 25).

Baseline blood was assayed for testosterone in 2623 participants (44%), who were chosen based on availability of a complete set of skeletal imaging procedures (to be used in planned analyses of the effects of sex steroids on skeletal change). The sampling scheme included all nonwhite participants, an oversampling of men with complete skeletal imaging and an oversampling of participants from the Birmingham and Portland clinics. The sample target was 2643 participants; a sample of 2623 (99%) was achieved.

An average of 3.4 yr after the baseline visit, between December 2003 and March 2005, a subset of MrOS participants were invited to participate in an ancillary study, the Outcomes of Sleep Disorders in Older Men. To participate in the Outcomes of Sleep Disorders in Older Men, men were required to consent to a comprehensive assessment that included objective measures of sleep, including a single night of in-home unattended polysomnography (PSG), plus wrist actigraphy for a minimum of three consecutive 24-h periods. In addition, participants completed an in-clinic examination and interview, which included validated sleep questionnaires. A total of 3135 MrOS men participated in the sleep study.

Although it is possible that some men were less healthy 3 yr later at the time of the sleep tests, we doubt that this explains the observed association because men in MrOS were ambulatory, community dwelling, and relatively healthy, and men who were seriously ill or recovering from a serious illness were excluded from polysomnography or had their scheduled in-home evaluation delayed until they were well.

Overall, 1510 of the men with testosterone assays (58%) attended the sleep examination; of these, 1321 men had both actigraphy and PSG data of sufficient quality for inclusion in the analyses. After excluding one participant whose high testosterone value suggested he was taking unreported testosterone and eight who were on antiandrogen therapy for prostate cancer, there were 1312 men for the present study who had complete data on both testosterone levels and sleep measures. The institutional review board at each clinic site approved the study; written informed consent was obtained from all participants.

Sex steroid and related assays

All but 1% of venipunctures were obtained before 1100 h in fasting subjects at the baseline visit. All blood was prepared immediately after phlebotomy and stored at −70 C. All samples remained frozen until assayed at the Oregon Health and Science University General Clinical

Research Center by a single technician. Pooled serum controls were included in every assay. Total testosterone was measured using a solid-phase ^{125}I RIA [Diagnostic Products, Los Angeles, CA; range: 10–1600 ng/dl; intraassay coefficient of variation (CV): 5.4%; interassay CV 8.2%]. All testosterone assays were completed in duplicate, with the average value used for analyses. Testosterone assays were repeated when there was a 40% or greater difference between initial assay duplicates. In a subset of the MrOS cohort, the results of testosterone assays using RIA were highly correlated with results obtained using mass spectromometry ($r > 0.90$).

Bioavailable testosterone was calculated using mass action equations (26,27) and approximated the sum of free testosterone plus albumin-bound hormone. This calculation used sex hormone binding globulin measured by using an immunometric assay (Diagnostic Products) with a range of 0.2–180 nM/liter; intraassay CV 3.3%; and total assay CV 5.3%; albumin was measured using a Beckman LX 20 analyzer (Beckman-Coulter Instruments, Buckinghamshire, UK; intraassay CV 1.6%; total assay CV 3.4%).

In-home overnight PSG

In-home sleep studies were performed using full-night, unattended, in-home PSG and the same standardized sensors recommended by the American Academy of Sleep Medicine. The recording montage consisted of two central electroencephalograms; a bilateral electrooculogram; a bipolar submental electromyogram; thoracic and abdominal respiratory inductance plethysmography; airflow (by nasal-oral thermocouple and nasal pressure cannula); finger pulse oximetry; electrocardiogram; body position (mercury switch sensor); and bilateral leg movements (piezoelectric sensors). Trained, certified staff members performed home visits for set-up of the sleep study units, using methods developed for the Sleep Heart Health Study, described previously (28). Differences in in-home *vs.* in-laboratory detection of hypopneas or apneas would not be anticipated unless signal quality was degraded. Signal quality for MrOS was closely monitored, and PSG data quality was excellent with less than a 4% failure rate; the quality of more than 70% of studies was graded as excellent or outstanding. Prior work has shown that measurement of the apnea-hypopnea index (AHI) from PSG performed in home settings has excellent agreement with PSG performed in the laboratory: this was formally evaluated in a study using similar equipment in the home and laboratory, which showed similar measurement for the AHI for each type of study (*e.g.* median AHI was 12.4 in home and 9.5 in laboratory; $P = 0.41$) (29). All differences were attributed to night-to-night variability and differences in time spent supine. The other potential differences between laboratory- and home-based full PSG would be attributable to differences in setting.

PSG studies were scored at a central reading center (Case Western Reserve University, Cleveland, OH) by research-certified scorers (28). Apneas were identified if the amplitude of the airflow was flat or nearly flat for longer than 10 sec. Obstructive apneas were scored if persistence of effort on abdominal or thoracic inductance plethysmography was noted, and central apneas scored if there was no evident effort on both the abdominal and thoracic plethysmography bands. Hypopneas were scored using Sleep Heart Health Study criteria (requiring a discernible $>$ 30% reduction in amplitude of respiratory effort or airflow). For the current study, we included only respiratory events associated with 3% or greater oxygen desaturation. Using these approaches, between- and within-scorer reliability for various derivations of the AHI in the same scoring group has been excellent, with intraclass correlation coefficients ranging from 0.76 to 0.99 (30).

Wrist actigraphy

The Octagonal Sleep Watch actigraph (Ambulatory Monitoring, Inc., Ardsley, NY) was used to detect movement. The actigraph contains a piezoelectric linear accelerometer that generates voltage each time the actigraph moves. These voltages were gathered continuously and summarized over 1-min epochs. The actigraphs collect data in three modes: zero crossings, proportional integration mode (PIM), and time above threshold. We used the PIM mode, a high-resolution measure of activity level or vigor of motion. PIM data were scored using Action W software, based on an algorithm developed at the University of California, San Diego (31).

These algorithms calculate a moving average, which takes into account the activity levels immediately before and after the current minute, to determine whether the given time point should be coded as sleep or awake. To minimize night to night variability, the average of the sleep parameters over all nights was used in all analyses.

Men were instructed to wear the actigraph continuously on the nondominant wrist for five consecutive 24-h periods and did so for an average of 5.2 ± 0.8 nights (range 1–13). Data comparing total sleep time assessed using actigraphy in MrOS men with the gold standard PSG recorded concurrently (n = 909 men) indicated a modest correlation ($r = 0.61$). Actigraphy parameters included total hours of sleep per night; sleep efficiency (the percentage of time the participant spent sleeping while in bed); sleep latency (the number of minutes it took for a participant to fall asleep from the time they got into bed); and wake after sleep onset (a measure of sleep fragmentation that represents the number of minutes a participant was awake during a typical sleep period and after the initial onset of sleep of at least 20 min duration). Total sleep duration was categorized as less than 5 h, 5 to less than 7 h, 7 to less than 8 h, or more than 8 h (32). Participants also completed a sleep diary that was used in the editing of the data to determine when the participant got into and out of bed and when the actigraph was removed. Actigraphy data were transferred to the MrOS coordinating center (San Francisco, CA) for centralized processing.

Other measures

Race/ethnicity, education level, and marital status were determined at baseline. At the time of the sleep study, all participants completed a standard self-administered questionnaire that included questions about medical history, current use of medications, self-reported health, alcohol drinks per week, and current smoking status. The Physical Activity Score for the Elderly was used to assess physical activity level (32). Participants were asked to bring in all medications used within the last 30 d; a computerized dictionary, based on the original Established Populations for Epidemiologic Studies of the Elderly (EPESE) coding system (33) and maintained at the MrOS coordinating center in San Francisco, was used to categorize the medications. Height (centimeters) was measured on Harpenden stadiometers, and weight (kilograms) was measured on standard balance beam or digital scales using standard protocols, with participants wearing light clothing without shoes. BMI was calculated as kilograms per square meter. Waist, hip, and neck circumference (centimeters) were measured. Comorbidity was defined as a history of any of the following: osteoarthritis, cardiovascular disease, diabetes, chronic obstructive pulmonary disease, and Parkinson's disease.

Statistical analyses

Characteristics related to sleep or testosterone were summarized using means and SDs for continuous data and counts and percentages for categorical data. Linear trends of participant characteristics across categories of testosterone quartiles were assessed using least-squares models for continuous variables and Mantel Haenszel χ^2 tests for categorical variables. Linear and the least-square regression were used to examine the association between bioavailable or total testosterone as the independent exposure variable and the continuous sleep outcome measures. Logistic regression was used to examine the association between bioavailable or total testosterone levels and categorical sleep measure outcomes (oxygen saturation $< 90\%$ and AHI > 15). For skewed outcome variables, the analyses were repeated using transformations to meet normality assumptions. There were no differences in the results. For ease of interpretation, the original outcome variables were presented.

Total sleep time, sleep efficiency, sleep latency, and wake after sleep onset time were determined using actigraphy, which provided data averaged over several nights. PSG data were used for models including sleep

architecture outcomes [percent of total sleep time spent in stage 3–4 (sleep slow wave sleep) and rapid eye movement (REM) sleep] and indices of sleep-disordered breathing [nocturnal hypoxemia (the percent of sleep time spent with O_2 saturation < 90%) and AHI, the number of apneas and hypopneas associated with at least a 3% oxygen desaturation per hour of sleep]. Results were the same with 4% desaturation (data not shown).

To explore for potential threshold associations, we analyzed total and bioavailable testosterone levels by quartiles and, for total testosterone, by categorical low and not low levels (<250 *vs.* > 250 ng/dl), as defined by the Institute of Medicine (7). Known or suspected determinants of testosterone and each sleep outcome were examined for potential confounding in age-, race-, and clinic-adjusted models. For each outcome, a backward stepwise regression procedure was used for covariate selection. Any covariate that remained in any of the models with a $P < 0.10$ was considered for inclusion in the full multivariable models. To avoid multicollinearity with BMI, the final models excluded waist, hip, and neck circumference.

The initial multivariable models were adjusted for clinic site, race, BMI, comorbidity, smoking status, and alcohol drinks per week. The final multivariable models were adjusted for age, clinic site, race, and BMI only because none of the other covariates changed the results when included in the model (data not shown). All analyses were also adjusted for the stratified sampling scheme; results were unchanged, and this was not included in the final models.

All analyses were performed using SAS software, version 9.1 (SAS Institute, Cary, NC).

Results

The average age of the 1312 men was 72.6 yr (SD 5.4). The distribution of total sleep time estimated from actigraphy was as follows: 10.7% slept less than 5 h, 53.9% slept 5 to less than 7 h, 28.2% slept 7–8 h, and 7.0% slept 8 h or longer. Total sleep duration was not significantly associated with age in these older men but was strongly associated with BMI and neck, waist, and hip circumferences. The highest values of adiposity measures were observed among the 141 men who slept less than 5 h. Proportionately, more Caucasians and Hispanics slept longer than 8 h a day, compared with African-Americans and Asians, who tended to sleep less ($P = 0.03$). Total testosterone levels were highest in men who slept 7–8 h and lowest in men who slept less than 5 h. Bioavailable testosterone did not vary by sleep duration (data not shown).

Table 1 shows cohort characteristics by quartile of total testosterone. Linear trends were observed between decreasing quartiles of testosterone and increasing levels of all body size measures (BMI and neck, waist, and hip circumferences). Body size measures were highest for men in the lowest quartile of total testosterone (<330 ng/dl). Men in the lowest testosterone quartile were also more likely to have more than one medical condition. No significant linear trends were found for physical activity, alcohol consumption, or current cigarette smoking across testosterone quartiles; less than 5% of men were current smokers. No differences by clinic site or race were found among quartiles of testosterone ($P > 0.05$) (data not shown).

Table 1 also shows no differences in sleep duration, time in slow-wave or REM sleep, or arousal frequency across quartiles of testosterone. The two measures of sleep consolidation, sleep efficiency and wake time after sleep onset, showed that older men with lower testosterone levels had (on average) a lower percentage of time in bed spent asleep and a higher proportion spent awake after sleep onset. Individuals with lower testosterone levels also had a higher average AHI and a higher proportion with nocturnal hypoxemia, compared with individuals with higher testosterone levels. The same analyses were repeated by quartile of bioavailable testosterone. Men in the lowest quartile of bioavailable testosterone, with levels less than 6.16 nM/liter, were older, had the highest BMI, waist circumference, and hip circumference but not neck circumference (data not shown). Overall the sleep-bioavailable testosterone results were similar but weaker, except that bioavailable testosterone was significantly associated with REM sleep, whereas total testosterone was not (data not shown).

Table 2 shows the age, race, and clinic site adjusted sleep outcomes by quartiles of total testosterone. Similar to the unadjusted analyses, men in the lowest testosterone quartile had poorer sleep efficiency (P for trend = 0.0008), increased awakenings after sleep onset (P for trend = 0.0006), and higher apnea hypopnea index (P for trend = 0.02) and were more likely to spend 1% or more of sleep time in O_2 desaturation less than 90% ($P = 0.0001$). There were no testosterone trends with sleep duration or sleep stage distribution. Once adjusted for BMI, as shown in Table 3, the linear trends were no longer statistically significant, with the exception that men in the lowest testosterone quartile still had significantly lower sleep efficiency than those in the second and highest quartiles and men in the lowest testosterone quartile had more awakenings after sleep onset than those in the second and highest quartiles.

These results were not changed after further adjustment for other covariates including comorbidity at the time blood was obtained for testosterone assays (data not shown). Although men who listed their health as poor, very poor, or fair had significantly lower testosterone levels than men with better health, reported health explained little of the variance in testosterone levels; partial R^2 for health was 0.004, compared with the R^2 for age (0.053) or BMI (0.031). The results of the final model were not materially changed after excluding the 48 men taking a spironolactone loop diuretic, the 41 men taking benzodiazepines, or the three men taking both medications at the time of the blood draw (data not shown). These were the only medications in this cohort that were both associated with low testosterone levels and used by more then 3% of participants in the sleep study.

Although we did test for an interaction between continuous total testosterone and continuous BMI (which was not significant), we did not look at the effect between sleep outcomes and quartiles of total testosterone stratified by median BMI value, which was 27. In a *post hoc* analysis, the association of total testosterone with sleep efficiency and wake after sleep onset was statistically significant only for those in the upper median BMI group. This interaction was not found with any of the other sleep outcomes.

Only 119 men (about 9%) had testosterone insufficiency, as currently defined (total testosterone < 250 ng/dl) (7). Compared with those with a testosterone greater than 250 ng/dl, men with low testosterone had higher BMI and larger neck, waist, and hip

TABLE 1. Characteristics of the 1312 men by total testosterone (nanograms per deciliter) quartiles

Characteristic	Quartile 1, 5–330 ng/dl (n = 328)	Quartile 2, > 330–414 ng/dl (n = 327)	Quartile 3, > 414–513.4 ng/dl (n = 329)	Quartile 4, > 513.4–1345 ng/dl (n = 328)	*P* for trend
Age (yr) ± SD	72.9 ± 5.3	72.8 ± 5.5	72.4 ± 5.4	72.6 ± 5.3	0.30
BMI (kg/m^2) ± SD	28.4 ± 3.9	27.2 ± 3.6	26.5 ± 3.7	25.9 ± 3.0	<0.0001
Neck circumference (cm) ± SD	40.3 ± 3.0	39.6 ± 2.7	39.3 ± 2.7	39.0 ± 2.7	<0.0001
Waist circumference (cm) ± SD	103.5 ± 11.2	100.4 ± 10.5	98.0 ± 10.4	95.9 ± 9.5	<0.0001
Hip circumference (cm) ± SD	105.9 ± 9.3	103.5 ± 9.2	102.0 ± 7.9	100.5 ± 7.1	<0.0001
Race, %					
White	79.9	80.4	83.0	79.0	0.79
African-American	6.1	6.7	6.4	9.2	
Asian	7.0	7.7	4.9	4.3	
Hispanic	4.6	3.1	3.7	5.2	
Other	2.4	2.1	2.1	2.4	
Site, %					
Birmingham	31.7	26.9	31.3	34.5	0.87
Minneapolis	13.4	10.1	10.3	7.6	
Palo Alto	13.4	12.5	15.5	14.6	
Pittsburgh	9.2	11.6	7.6	5.8	
Portland	20.7	26.0	25.8	27.7	
San Diego	11.6	12.8	9.4	9.8	
Physical activity ± SD[a]	138.6 ± 71.6	142.1 ± 67.7	146.3 ± 70.2	152.2 ± 69.5	0.009
Smoke, %					
Never	34.5	35.8	38.3	39.6	0.31
Past	62.8	62.4	59.6	56.1	
Current	2.7	1.8	2.1	4.3	
Drinks per week, %					
None	40.9	37.1	31.0	33.5	0.06
1–7	47.9	44.8	48.9	54.6	
8+	11.3	18.1	20.1	11.9	
Medical conditions 1+, %[b]	77.4	67.9	67.8	61.3	<0.0001
Total sleep time (h) ± SD	6.41 ± 1.22	6.47 ± 1.29	6.49 ± 1.22	6.53 ± 1.06	0.17
Total sleep time, %					
Less than 5 h	12.8	12.2	10.7	7.0	0.17
5 to less than 7 h	54.9	52.6	52.1	56.6	
7 to less than 8 h	25.0	26.6	30.5	30.9	
8+ h	7.3	8.6	6.7	5.5	
Sleep efficiency (%) ± SD	81.5 ± 10.3	83.7 ± 9.7	83.4 ± 9.8	84.4 ± 8.3	0.0003
Wake after sleep (min) ± SD	84.4 ± 45.2	72.1 ± 40.1	74.7 ± 41.7	71.1 ± 37.1	0.0002
Time in stage 3/4 sleep ± SD, %	11.7 ± 9.6	11.1 ± 8.7	11.7 ± 8.8	11.4 ± 8.7	0.87
Time in REM sleep ± SD, %	18.9 ± 6.6	19.9 ± 6.2	19.8 ± 6.4	19.6 ± 6.8	0.25
Time O_2 desaturation < 90% < 1%, %	56.7	52.6	45.6	42.4	<0.0001
Apnea-hypopnea index 15+, %	45.7	38.2	42.9	37.5	0.10
Apnea-hypopnea index ± SD	17.7 ± 16.0	16.6 ± 14.4	16.2 ± 14.0	14.5 ± 13.3	0.005
Arousal Index ± SD	23.9 ± 12.8	22.3 ± 10.5	22.7 ± 11.6	22.6 ± 9.7	0.26

[a] Score from the Physical Activity Score for the Elderly.

[b] Selected medical comorbidities include diabetes, heart attack, stroke, high blood pressure, or cancer.

circumferences (data not shown). As shown in Table 4, men with testosterone levels less than 250 ng/dl had lower sleep efficiency ($P = 0.01$) and more wake after sleep onset ($P = 0.004$) and included a greater proportion who spent time in REM sleep ($P = 0.04$) than men with higher testosterone levels. They did not differ by sleep duration, slow wave sleep, arousal index, or AHI. When BMI was added to the models, the only associations that remained significant at $P = 0.05$ were wake after sleep onset and percent time in REM sleep (Table 4). No other covariates changed these associations, and they were therefore not included in the final models. No similar analyses were performed for bioavailable testosterone because there is no agreed-on cut point for bioavailable testosterone deficiency.

Discussion

In older community-dwelling men, we found no significant association between duration of sleep or sleep stage distributions and total or bioavailable testosterone. Lower testosterone levels, however, were associated with less consolidated sleep as demonstrated by decreased sleep efficiency and increased nocturnal awakenings. Lower testosterone levels were also associated with more severe sleep-disordered breathing, as evidenced by a higher AHI and more frequent hypoxemia. However, higher levels of adiposity were associated with both increased sleep-disordered breathing and low testosterone levels and adjustment for BMI in the whole cohort attenuated nearly all the observed associations.

TABLE 2. Partially adjusted association between total testosterone and sleep outcomes

	Total testosterone levels in quartiles (ng/dl)				
	Quartile 1, 5–330 ng/dl (n = 328)	**Quartile 2, > 330–414 ng/dl (n = 327)**	**Quartile 3, > 414–513.4 ng/dl (n = 329)**	**Quartile 4, > 513.4–1345 ng/dl (n = 328)**	***P* for trend**
	Adjusted mean (95% CI)				
Total sleep time (h)	6.41 (6.28–6.54)	6.49 (6.36–6.62)	6.48 (6.35–6.61)	6.52 (6.40–6.65)	0.26
Sleep efficiency (%)	81.5 (80.5–82.6)	83.9 (82.9–84.9)[a]	83.2 (82.2–84.2)[a]	84.4 (83.3–85.4)[a]	0.0008
Wake after sleep (min)	84.1 (79.7–88.5)	71.5 (67.1–75.9)[a]	75.5 (71.1–79.8)[a]	71.2 (66.9–75.6)[a]	0.0006
Time in stage 3/4 sleep, %	11.8 (10.8–12.8)	11.1 (10.1–12.0)	11.6 (10.6–12.6)	11.5 (10.5–12.5)	0.88
Time in REM sleep, %	18.9 (18.2–19.7)	20.0 (19.3–20.7)[a]	19.8 (19.1–20.5)	19.5 (18.8–20.2)	0.34
AHI	17.5 (15.9–19.0)	16.3 (14.8–17.9)	16.4 (14.9–18.0)	14.8 (13.2–16.3)[a]	0.02
Arousal index	23.7 (22.5–24.9)	22.1 (20.9–23.4)	22.8 (21.6–24.0)	22.9 (21.6–24.1)	0.48
	Odds ratios (95% CI)				
≥1% sleep time O_2 desaturated < 90%	1.0	0.84 (0.62–1.16)	.65 (0.47–0.89)[a]	0.56 (0.41–0.77)[a]	0.0001
AHI 15+	1.0	0.72 (0.52–0.99)[a]	.94 (0.69–1.29)	0.75 (0.55–1.03)	0.25

Models adjusted for age, race, and site. CI, Confidence interval.

[a] $P < 0.05$, compared with the lowest quartile.

Only the associations between total testosterone with wake after sleep onset and percent time in REM sleep remained marginally statistically significant after BMI and other covariate adjustments. Given the number of sleep-related outcomes reported, this single independent association could be spurious. However, the associations of testosterone with disordered sleep persisted in men with higher BMI, compatible with a low testosterone adverse sleep effect in men who are at greater risk of sleep disturbance because of higher weight.

Although our findings do not support an independent association between endogenous levels of testosterone and sleep duration in older community-dwelling men who were not overweight, we did observe more nocturnal awakenings and low total testosterone levels independent of BMI, lifestyle, and comorbidity. This association persisted after adjusting for AHI, suggesting that differences in sleep-related breathing disturbances are unlikely to account for sleep quality differences observed across levels of testosterone.

Published data relating testosterone levels to sleep are quite limited. Experimental sleep deprivation in young men is associated with reductions in testosterone levels. Penev (34) reported a positive association between sleep duration, as measured by either actigraphy or PSG, and increasing testosterone levels in 12 elderly community volunteers with no underlying medical illnesses. The small, select sample studied limits the generalizability of this observation. The mechanism for any such association is poorly understood but has been postulated to relate to effects of sleep deprivation on hypothalamic pituitary function (34).

The evidence (in unadjusted analysis) of more sleep-disordered breathing associated with low levels of endogenous testosterone contrasts with results from clinical trials of im testosterone enanthate therapy, which produces higher than physiologic testosterone levels and causes or worsens sleep apnea. Only one clinical trial in 12 hypogonadal men (35) showed that administration of testosterone increased meta-

TABLE 3. BMI-adjusted association between total testosterone and sleep outcomes

	Total testosterone levels in quartiles (ng/dl)				
	Quartile 1, 5–330 ng/dl (n = 328)	**Quartile 2, > 330–414 ng/dl (n = 327)**	**Quartile 3, > 414–513.4 ng/dl (n = 329)**	**Quartile 4, > 513.4–1345 ng/dl (n = 328)**	***P* for trend**
	Adjusted mean (95% CI)				
Total sleep time (h)	6.48 (6.35–6.61)	6.50 (6.38–6.63)	6.45 (6.32–6.58)	6.47 (6.34–6.60)	0.76
Sleep efficiency (%)	82.2 (81.2–83.2)	84.0 (83.0–85.0)[a]	83.0 (82.0–84.0)	83.8 (82.8–84.9)[a]	0.10
Wake after sleep onset (min)	81.5 (77.1–85.9)	71.0 (66.7–75.3)[a]	76.5 (72.2–80.8)	73.4 (69.0–77.8)[a]	0.07
Time in stage 3/4 sleep, %	11.9 (10.9–12.9)	11.1 (10.1–12.1)	11.5 (10.6–12.5)	11.4 (10.3–12.4)	0.62
Time in REM sleep, %	19.0 (18.2–19.7)	20.0 (19.3–20.7)	19.8 (19.0–20.5)	19.5 (18.8–20.2)	0.45
AHI	16.1 (14.6–17.6)	16.1 (14.6–17.6)	16.9 (15.4–18.4)	15.9 (14.3–17.4)	0.97
Arousal index	23.4 (22.2–24.7)	22.1 (20.9–23.3)	22.9 (21.7–24.1)	23.1 (21.9–24.3)	0.97
	Odds ratios (95% CI)				
≥1% sleep time O_2 desaturated < 90%	1.0	1.01 (0.73–1.41)	0.88 (0.63–1.23)	0.84 (0.60–1.18)	0.23
AHI 15+	1.0	.80 (0.58–1.11)	1.15 (0.83–1.60)	0.98 (0.70–1.37)	0.58

Models adjusted for age, race, site, and BMI. CI, Confidence interval.

[a] $P < 0.05$, compared with the lowest quartile.

TABLE 4. Association between low total testosterone (<250 *vs.* ≥250 ng/dl) and sleep outcomes

	Adjusted for age, race, and site			Adjusted for age, race, site, and BMI		
	Testosterone < 250 ng/dl (n = 119)	Testosterone ≥ 250 ng/dl (n = 1193)	*P* value	Testosterone < 250 ng/dl (n = 119)	Testosterone ≥ 250 ng/dl (n = 1193)	*P* value
	Adjusted mean (95% CI)					
Total sleep time (h)	6.37 (6.16–6.58)	6.49 (6.42–6.55)	0.31	6.45 (6.24–6.66)	6.48 (6.41–6.54)	0.82
Sleep efficiency (%)	81.2 (79.5–82.9)	83.5 (82.9–84.0)	0.01	82.0 (80.3–83.6)	83.4 (82.9–83.9)	0.11
Wake after sleep (min)	85.7 (78.4–93.1)	74.6 (72.3–76.9)	0.004	82.5 (75.2–89.8)	74.9 (72.6–77.5)	0.05
Time in stage 3/4 sleep, %	12.1 (10.5–13.7)	11.4 (10.9–11.9)	0.41	12.3 (10.6–14.0)	11.4 (10.9–11.9)	0.30
Time in REM sleep, %	18.4 (17.2–19.6)	19.7 (19.3–20.0)	0.04	18.4 (17.2–19.6)	19.7 (19.3–20.0)	0.05
AHI	13.0 (10.8–15.2)	11.0 (10.3–11.7)	0.09	16.2 (13.7–18.7)	16.3 (15.5–17.0)	0.98
Arousal index	23.7 (21.7–25.7)	22.8 (22.2–23.4)	0.39	23.4 (21.3–25.4)	22.8 (22.2–23.5)	0.62
	Odds ratios (95% CI)					
≥1% sleep time O_2 desaturated < 90%	1.0	0.62 (0.42–0.91)	0.02	1.0	0.82 (0.55–1.24)	0.35
AHI 15+	1.0	0.90 (0.61–1.33)	0.60	1.0	1.09 (0.73–1.62)	0.68

CI, Confidence interval.

bolic rate and hypoxic ventilatory responses. The extent to which ventilatory control responses influence propensity to sleep apnea is unclear.

An absent association between testosterone and sleep is consistent with two completely different studies, a clinical trial in which the AHI did not change after testosterone patch treatment (21, 36) and a trial showing that antiandrogen blockade (with flutamide) had no effect on sleep or sleep-disordered breathing in patients with moderate to severe sleep apnea (23).

In analyses adjusted for age, clinic, and race, those with lower levels of testosterone had higher levels of AHI and were more likely to be hypoxemic during sleep. However, these associations were no longer statistically significant after adjusting for BMI in the whole cohort, emphasizing the potential confounding influence of obesity in analyses examining hormonal levels and sleep. Obesity is associated with lower testosterone levels, particularly bioavailable testosterone; the latter is presumed to reflect the effect of obesity on SHBG. It is possible that indices of poor sleep found in association with obesity may be mediated through effects of obesity on lowering testosterone levels. Thus body size could be a confounder, *i.e.* associated with both sleep and testosterone, or an effect modifier, *i.e.* in the causal pathway. Our finding that lower testosterone was independently associated with adverse sleep effects only in men with higher BMI suggests that the association between sex steroids, obesity, and sleep is likely to be complex. Clinical trials of physiological doses of transdermal testosterone are necessary to answer this question.

This study has strengths and limitations. The MrOS sleep study is much larger than any other previously reported sleep study of exclusively older men and has the advantage that the 1312 men were not selected based on testosterone levels or sleep problems. Because the men in this cohort were recruited from six geographic areas in the United States, these results are likely to be generalizable to asymptomatic community-dwelling men. However, although ethnic minorities were oversampled, the MrOS sleep study was underpowered to assess differences by race or ethnicity. Another advantage is that sleep quality was directly measured using in-home recordings and standardized for usual (5 d) sleep patterns measured by actigraphy. This is the first large population-based study of sleep and endogenous testosterone, which more accurately reflects physiological levels than the pharmacologic levels achieved in most reported treatment trials. Also, we were able to adjust for lifestyle and comorbidity, which did not materially change the results once a measure of body size had been included in the analysis. In all studies of elderly people, even those who are relatively healthy and community dwelling as were MrOS participants, residual confounding by subclinical disease or other unexamined attributes is always possible. Such confounding could have obscured but is unlikely to have created associations. Finally, although this is a longitudinal study, causality cannot be assumed. The present results suggest that obesity is in the causal pathway, but we cannot determine whether obesity led to lower testosterone levels or vice versa.

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References

1. **Ohayon MM** 2004 Sleep and the elderly. J Psychosom Res 56:463–464
2. **Redline S, Kirchner HL, Quan SF, Gottlieb DJ, Kapur V, Newman A** 2004 The

effects of age, sex, ethnicity, and sleep-disordered breathing on sleep architecture. Arch Intern Med 164:406–418
3. **Newman AB, Foster G, Givelber R, Nieto FJ, Redline S, Young T** 2005 Progression and regression of sleep-disordered breathing with changes in weight: the Sleep Heart Health Study. Arch Intern Med 165:2408–2413
4. **Stone KL, Redline S** 2006 Sleep-related breathing disorders in the elderly. Sleep Med Clin 1 247–262
5. **Ferrini RL, Barrett-Connor E** 1998 Sex hormones and age: a cross-sectional study of testosterone and estradiol and their bioavailable fractions in community-dwelling men. Am J Epidemiol 147:750–754
6. **Feldman HA, Longcope C, Derby CA, Johannes CB, Aranjo AB, Coviello AD, Bremner WJ, McKinlay JB** 2002 Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts male aging study. J Clin Endocrinol Metab 87:589–598
7. **Institute of Medicine** 2004 Testosterone and aging: clinical research directions. Liverman CT, Blazer DG, eds. Washington, DC: National Academies Press; 1–219
8. **Baumgartner RN, Waters DL, Gallagher D, Morley JE, Garry PJ** 1999 Predictors of skeletal muscle mass in elderly men and women. Mech Ageing Dev 107:123–136
9. **Roy TA, Blackman MR, Harman SM, Tobin JD, Schrager M, Metter EJ** 2002 Interrelationships of serum testosterone and free testosterone index with FFM and strength in aging men. Am J Physiol Endocrinol Metab 283:E284–E294
10. **Abbasi AA, Mattson DE, Duthie Jr EH, Wilson C, Sheldahl L, Sasse E, Rudman IW** 1998 Predictors of lean body mass and total adipose mass in community-dwelling elderly men and women. Am J Med Sci 315:188–193
11. **Couillard C, Gagnon J, Bergeron J, Leon AS, Rao DC, Skinner JS, Wilmore JH, Després JP, Bouchard C** 2000 Contribution of body fatness and adipose tissue distribution to the age variation in plasma steroid hormone concentrations in men: the HERITAGE Family Study. J Clin Endocrinol Metab 85:1026–1031
12. **Marin P** 1995 Testosterone and regional fat distribution. Obes Res 3(Suppl 4):609S–612S
13. **Seidell JC, Bjorntorp P, Sjostrom L, Kvist H, Sannerstedt R** 1990 Visceral fat accumulation in men is positively associated with insulin, glucose, and C-peptide levels, but negatively with testosterone levels. Metabolism 39:897–901
14. **Barrett-Connor E, Goodman-Gruen D, Patay B** 1999 Endogenous sex hormones and cognitive function in older men. J Clin Endocrinol Metab 84:3681–3685
15. **Moffat SD, Zonderman AB, Metter EJ, Blackman MR, Harman SM, Resnick SM** 2002 Longitudinal assessment of serum free testosterone concentration predicts memory performance and cognitive status in elderly men. J Clin Endocrinol Metab 87:5001–5007
16. **Tsitouras PD, Martin CE, Harman SM** 1982 Relationship of serum testosterone to sexual activity in healthy elderly men. J Gerontol 37:288–293
17. **Sandblom RE, Matsumoto AM, Schoene RB, Lee KA, Giblin EC, Bremner WJ, Pierson DJ** 1983 Obstructive sleep apnea syndrome induced by testosterone administration. N Engl J Med 308:508–510
18. **Liu PY, Swerdloff RS, Veldhuis JD** 2004 Clinical review 171: the rationale, efficacy and safety of androgen therapy in older men: future research and current practice recommendations. J Clin Endocrinol Metab 89:4789–4796
19. **Matsumoto AM, Sandblom RE, Schoene RB, Lee KA, Giblin EC, Pierson DJ, Bremner WJ** 1985 Testosterone replacement in hypogonadal men: effects on obstructive sleep apnoea, respiratory drives, and sleep. Clin Endocrinol (Oxf) 22:713–721
20. **Schneider BK, Pickett CK, Zwillich CW, Weil JV, McDermott MT, Santen RJ, Varano LA, White DP** 1986 Influence of testosterone on breathing during sleep. J Appl Physiol 61:618–623
21. **Snyder PJ, Peachey H, Hannoush P, Berlin JA, Loh L, Holmes JH, Dlewati A, Staley J, Santanna J, Kapoor SC, Attie MF, Haddad Jr JG, Strom BL** 1999 Effect of testosterone treatment on bone mineral density in men over 65 years of age. J Clin Endocrinol Metab 84:1966–1972
22. **Grunstein RR, Handelsman DJ, Lawrence SJ, Blackwell C, Caterson ID, Sullivan CE** 1989 Neuroendocrine dysfunction in sleep apnea: reversal by continuous positive airways pressure therapy. J Clin Endocrinol Metab 68:352–358
23. **Stewart DA, Grunstein RR, Berthon-Jones M, Handelsman DJ, Sullivan CE** 1992 Androgen blockade does not affect sleep-disordered breathing or chemosensitivity in men with obstructive sleep apnea. Am Rev Respir Dis 146:1389–1393
24. **Blank JB, Cawthon PM, Carrion-Petersen ML, Harper L, Johnson JP, Mitson E, Delay RR** 2005 Overview of recruitment for the osteoporotic fractures in men study (MrOS). Contemp Clin Trials 26:557–568
25. **Orwoll E, Blank JB, Barrett-Connor E, Cauley J, Cummings S, Ensrud K, Lewis C, Cawthon PM, Marcus R, Marshall LM, McGowan J, Phipps K, Sherman S, Stefanick ML, Stone K** 2005 Design and baseline characteristics of the osteoporotic fractures in men (MrOS) study—a large observational study of the determinants of fracture in older men. Contemp Clin Trials 26:569–585
26. **Sodergard R, Backstrom T, Shanbhag V, Carstensen H** 1982 Calculation of free and bound fractions of testosterone and estradiol-17β to human plasma proteins at body temperature. J Steroid Biochem 16:801–810
27. **Vermeulen A, Verdonck L, Kaufman JM** 1999 A critical evaluation of simple methods for the estimation of free testosterone in serum. J Clin Endocrinol Metab 84:3666–3672
28. **Redline S, Sanders MH, Lind BK, Quan SF, Iber C, Gottlieb DJ, Bonekat WH, Rapoport DM, Smith PL, Kiley JP** 1998 Methods for obtaining and analyzing unattended polysomnography data for a multicenter study. Sleep Heart Health Research Group. Sleep 21:759–767
29. **Iber C, Redline S, Kaplan Gilpin AM, Quan SF, Zhang L, Gottlieb DJ, Rapoport D, Resnick HE, Sanders M, Smith P** 2004 Polysomnography performed in the unattended home versus the attended laboratory setting—Sleep Heart Health Study methodology. Sleep 27:536–540
30. **Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, Langendorfer A, Stein EA, Kruyer W, Gotto Jr AM** 1998 Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. JAMA 279:1615–1622
31. **Cole RJ, Kripke DF, Gruen W, Mullaney DJ, Gillin JC** 1992 Automatic sleep/wake identification from wrist activity. Sleep 15:461–469
32. **Washburn RA, McAuley E, Katula J, Mihalko SL, Boileau RA** 1999 The physical activity scale for the elderly (PASE): evidence for validity. J Clin Epidemiol 52:643–651
33. **Pahor M, Chrischilles EA, Guralnik JM, Brown SL, Wallace RB, Carbonin P** 1994 Drug data coding and analysis in epidemiologic studies. Eur J Epidemiol 10:405–411
34. **Penev PD** 2007 Association between sleep and morning testosterone levels in older men. Sleep 30:427–432
35. **White DP, Schneider BK, Santen RJ, McDermott M, Pickett CK, Zwillich CW, Weil JV** 1985 Influence of testosterone on ventilation and chemosensitivity in male subjects. J Appl Physiol 59:1452–1457
36. **Snyder PJ, Peachey H, Hannoush P, Berlin JA, Loh L, Lenrow DA, Holmes JH, Dlewati A, Santanna J, Rosen CJ, Strom BL** 1999 Effect of testosterone treatment on body composition and muscle strength in men over 65 years of age. J Clin Endocrinol Metab 84:2647–2653