Endogenous Testosterone Levels, Physical Performance, and Fall Risk in Older Men

Eric Orwoll, MD; Lori C. Lambert, MS; Lynn M. Marshall, ScD; Janet Blank, MS; Elizabeth Barrett-Connor, MD; Jane Cauley, MD; Kris Ensrud, MD; Steven R. Cummings, MD; for the Osteoporotic Fractures in Men Study Group

Background: Gonadal steroid levels decline with age in men. Whether low testosterone levels affect the development of common age-related disorders, including physical functioning and falling, is unclear.

Methods: This longitudinal, observational follow-up study sought to determine whether low testosterone levels are associated with physical performance and fall risk in older men. A total of 2587 community-based men aged 65 to 99 years were selected using a stratified random sampling scheme from a study cohort of 5993 volunteers. Bioavailable testosterone and estradiol levels and physical performance measures were determined from baseline. Incident falls were ascertained every 4 months during 4 years of follow-up. Generalized estimating equations were used to estimate risk ratios for the relation of sex steroids to falls.

Results: Fifty-six percent of the men reported at least 1 fall; many fell frequently. Lower bioavailable testosterone levels were associated with increased fall risk. Men with testosterone levels in the lowest quartile had a 40% higher fall risk than those in the highest quartile. The effect of low testosterone levels was most apparent in younger men (65-69 years) (relative risk, 1.8; 95% confidence interval, 1.2-2.7); testosterone level was not associated with falls in the oldest men (≥80 years). Lower testosterone concentrations were associated with reduced physical performance. However, the association between low testosterone levels and fall risk persisted despite adjustment for performance.

Conclusions: Falls were common among older men. Fall risk was higher in men with lower bioavailable testosterone levels. The effect of testosterone level was independent of poorer physical performance, suggesting that the effect of testosterone on fall risk may be mediated by other androgen actions.

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Author Affiliations: Bone and Mineral Unit, Oregon Health & Science University, Portland (Drs Orwoll and Marshall and Mses Lambert and Blank); University of California, San Diego (Dr Barrett-Connor); University of Pittsburgh, Pittsburgh, Pa (Dr Cauley); Minneapolis Veterans Affairs and University of Minnesota, Minneapolis (Dr Ensrud); and San Francisco Coordinating Center of the California Pacific Medical Center Research Institute of Medicine and the University of California, San Francisco (Dr Cummings).

Group Information: The Osteoporotic Fractures in Men Study Group Investigators are listed at the end of this article.
short study of men 65 years and older designed primarily to identify risk factors for falls and fractures. We report the associations among testosterone concentrations, physical performance, and fall risk during a mean follow-up of 4 years.

STUDY METHODS

STUDY POPULATION

Between March 1, 2000, and April 30, 2002, 5995 community-dwelling, ambulatory men 65 years and older were recruited for participation in the baseline examination of the prospective MrOS Study. The recruitment and characteristics of the population have been described elsewhere.25,26 Approximately 1000 participants were recruited at each of 6 academic medical centers: Oregon Health & Science University, Portland; Stanford University, Palo Alto, Calif; University of Alabama at Birmingham; University of California, San Diego; University of Minnesota, Minneapolis; and University of Pittsburgh, Pittsburgh, Pa. Recruitment efforts focused on community mailings from vehicle registration or voter registration lists, although community outreach activities were also used.25,26 The inclusion criteria were (1) age 65 years and older, (2) the ability to walk without assistance, (3) at least 1 native hip suitable for bone density measurements, (4) anticipated residence near a study site for the duration of follow-up, (5) the absence of a medical condition that would result in imminent death, and (6) the ability to understand and sign an informed consent form. The cohort was approximately 89% white.23 As of July 1, 2005, the cohort had 8.2% mortality and 1.1% voluntary termination. The institutional review board at each study center approved the study protocol, and written informed consent was obtained from all the participants.

Sex Steroid Cohort

Assays of sex steroids were performed using baseline serum samples from 2623 participants; results from these men form the basis of the present study. Men were selected from the general MrOS Study population using a stratified random sampling scheme so that the following characteristics were adequately represented: race, availability of an extensive set of skeletal imaging procedures (for analyses of the effects of sex steroids on fracture), and clinic site.27 The sampling target was 2643 participants, and sampling of 2623 (99%) was achieved. Measures of sex steroids were available in 2587 participants. As previously reported, men in whom sex steroids were measured were representative of the entire MrOS Study cohort on numerous characteristics (except for the inclusion, by intent, of a higher proportion of men of a minority race).2 Results from the 34 men being treated with androgens are excluded from these analyses.

At the baseline clinic visit, participants completed questionnaires and interviews regarding medical history, medication use, and lifestyle. Types of medications used regularly for the past month were coded during the clinic visit by trained staff. Information was recorded directly from prescription medications brought in by the participant. Medical history was assessed using self-reports on the questionnaire of several current and past illnesses, including stroke, hypertension, types of cancer, Parkinson disease, and myocardial infarction. General health status was assessed using a self-report of overall health relative to other men of the same age. Lifestyle factors, including smoking and alcohol consumption, history of falls in the past 12 months, and difficulties walking 2 to 3 city blocks or up 10 stairs, were also obtained from self-reports. Height was measured using a wall-mounted stadiometer, and weight was obtained using a balance beam scale. Total body lean and fat mass were assessed by means of dual-energy x-ray absorptiometry (Hologic 4500W; Hologic Inc, Waltham, Mass). Weight, lean mass, and fat mass each were divided by the square of height to provide the body mass index, lean mass index, and fat mass index, respectively.

Physical Performance Measures

Grip strength was assessed using a handheld dynamometer. Leg extension power, measured using the Nottingham power rig (University of Nottingham, Nottingham, England), correlates well with functional measures such as chair-rising speed, stair-climbing speed and power, and walking speed in elderly individuals.10,28 The narrow walk, used as an indirect measure of dynamic balance, involved walking a 6-m course while keeping each foot within a 20-cm-wide lane. A trial was considered successful if the participant had no more than 2 deviations from the lane. Time to complete 3 chair stands without using the arms to rise was used to assess lower extremity muscle capacity. Participants who could not complete the measures were classified as “unable.” The proportion unable was 2.3% for grip strength, 1.6% for leg power, 8.9% for narrow walk, and 2.8% for chair stands.

Ascertainment of Falls

At 4-month intervals, participants were queried by mailed questionnaire about the number of times they had fallen during the interval. Participants who fell in the previous 4 months were asked how many times (1, 2, 3, 4, or ≥5). The first questionnaire was mailed to enrolled participants on July 1, 2000. Participants who did not initially return a tri-annual questionnaire or who did not adequately complete the questionnaire were followed up with a telephone call. The present study includes fall reports from the first through the 15th (March 2005) tri-annual questionnaire cycles. A total of 2382 men (99.8%) completed at least 1 questionnaire; 90% returned 14 or more questionnaires. The mean number of questionnaires completed was 12 (corresponding to a mean of 4 years of follow-up), with a range of 1 to 15.

LABORATORY ANALYSIS

Morning blood samples were collected at the baseline clinic visit after an overnight fast; serum was prepared immediately, frozen at −20°C, and shipped on dry ice to a central facility, where it was stored at −70°C until assay. Assays were performed in duplicate, and all assays used stringent quality control.1 Total testosterone levels were determined using a solid-phase iodine 125 radioimmunoassay (Diagnostic Products Corp, Los Angeles, Calif); total estradiol levels using an ultrasensitive radioimmunoassay (Diagnostic Systems Laboratory Inc, Webster, Tex); sex hormone–binding globulin levels using an immunometric assay (Diagnostic Products Corp); and albumin levels using a Beckman LX 20 analyzer (Beckman-Coulter Instruments, Fullerton, Calif). For total testosterone level, the detectable range was 10 to 1600 ng/dl (0.3-55.5 pmol/L), and the coefficient of variation (CV), derived from repeated assays of a pooled serum sample, was 8.2%, with an intra-assay CV of 5.4%. For total estradiol level, the detectable range was 2.5 to 750 pg/ml (9-2752 pmol/L), the pooled serum sample CV was 13.3%, and the intra-assay CV was 8.3%. Estradiol values in 2 samples were decreased below the sensitivity level of the assay and were reported as half the lowest standard (ie, 1.25 pg/ml.
(5 pmol/L). For sex hormone binding globulin levels, the detectable range was 0.006 to 5.2 µg/dL (0.2-180 nmol/L), and the intra-assay and total assay CVs were 3.3% and 5.3%, respectively. The intra-assay and total assay CVs for albumin level were 1.6% and 3.9%, respectively. Bioavailable testosterone and estradiol levels were calculated using the mass action equations described by Sodergard et al.24 In these equations, the possible binding of other steroids to sex hormone binding globulin was ignored. Measures of free and non–sex hormone binding globulin–bound (bioavailable) estradiol were calculated taking into account the concentration of testosterone. The association constants of testosterone and estradiol used in the equations were taken from Vermeulen et al.30

STATISTICAL ANALYSES

Bioavailable and total testosterone measures were categorized into quartiles. For all analyses, participants who reported current or past use of androgen were excluded (n=34, 1.3%). Comparisons of baseline characteristics by testosterone quartile were made using 1-way analysis of variance. Covariates included age, clinic site, and participant race. Categorical characteristics were compared using χ² analyses. Pearson product moment and Spearman rank correlations were examined to assess linear relationships between age and physical performance measures. Because the performance measures were approximately normally distributed, Pearson product moment correlations are reported. For descriptive analyses, each participant’s fall rate was calculated as the number of falls reported during their entire follow-up divided by their actual follow-up time (range, 4-60 months).

For analysis of longitudinal data, we used generalized estimating equations with a binomial distribution and a logit link function to model the outcome of fall risk calculated from the repeated assessments of falls during each participant’s follow-up. Generalized estimating equation models are an extension of generalized linear models for analyzing longitudinal data31,32 and are advantageous in that they accommodate different lengths of follow-up and, within a participant’s follow-up period, missing intervals. The generalized estimating equation procedure assumes that responses from the same participant are correlated with past responses through a first-order autoregressive process. Risk ratios (RRs) and 95% confidence intervals (CIs) were estimated from the models.33

All analyses examining the association between testosterone concentration and fall risk included the baseline variables that account for the stratified sampling method used to select the sex steroid cohort (clinic site, race, and availability of a complete set of skeletal imaging procedures). Final models also included the baseline covariates age, history of previous falls reported at baseline, history of certain medical conditions (cancer, angina, arthritis, and Parkinson disease), history of dizziness, use of central nervous medications (benzodiazepine, nonbenzodiazepine anticonvulsants, narcotic analgesics, selective serotonin reuptake inhibitors, trazodone, and tricyclic antidepressants), use of walking aids, and mobility limitations (self-reported difficulty walking either 10 steps or 2-3 city blocks). These covariates were significantly associated with fall risk (statistical significance was set at P<.05). During variable selection, the following covariates were also examined: marital status, educational achievement, general health status, body mass index, lean and fat body mass indices, alcohol use, vision, history of myocardial infarction, thyroid conditions, stroke, osteoporosis, hypertension, diabetes mellitus, multiple (>3) co-morbidities, urinary tract symptoms, and current use of any medications. Because none of these variables confounded the association of testosterone level with fall risk or was significantly related to fall risk, we excluded them from the final model.

To evaluate whether the association between testosterone level and fall risk was affected by physical performance, we added variables for each physical performance measure sequentially to the final model. To control for a participant’s inability to perform the physical performance assessments, the statistical models included an indicator variable for participants who attempted but could not complete the performance measure or could not complete the performance measure owing to a physical limitation, and the corresponding physical performance variable was set to a value of zero. When physical performance measures were categorized into quartiles, the additional category representing “unable” was also included in the model.

RESULTS

STUDY POPULATION

The mean (SD) age of the participants was 73 (6) years (Table 1); 14% were 80 years or older. Most participants considered their health (compared with their peers) to be good to excellent. Variation in sex steroid concentrations was substantial, and increasing age was associated with lower bioavailable testosterone and estradiol concentrations. Increasing age was also associated with lower lean body mass (r = −0.21; P = .001), strength (grip strength: r = −0.40; leg power: r = −0.49; P < .001 for both), and physical performance (chair stand time: r = 0.23; narrow walk speed: r = −0.27; P ≤.001 for both).

SEX STEROIDS, BODY MASS, AND PHYSICAL PERFORMANCE AT BASELINE

Men with higher levels of bioavailable testosterone had on average lower body weight, lower body mass index, and lower fat mass index, but lean body mass index did not vary by testosterone level (Table 1). Nevertheless, strength and physical performance were slightly better in men with higher levels of bioavailable testosterone (Table 1). Baseline levels of bioavailable estradiol were not associated with any measure of strength or physical performance.

FALL OUTCOMES

A total of 29 057 completed tri-annual questionnaires were returned by the 2587 participants who had available sex steroid measures. During the period of observation, 56% of the men reported at least 1 fall. Among men who fell, the rate of reported falls is shown in Figure 1. Those who reported at least 1 fall before baseline were at higher risk for falling during follow-up (RR, 2.63; 95% CI, 2.29-3.03; P < .001). In addition, falls occurred more commonly in older men (mean number of falls per year: 0.6 in men aged 65-69 years, 0.7 in men aged 70-79 years, and 1.0 in men ≥80 years), and older men fell more often (P < .001). More than 20% of those older than 80 years reporting falling 5 times or more compared with 10% of men aged 65 to 69 years.

The risk of falls was greater in men with reduced levels of strength or physical performance at baseline. Compared with men in the highest quartile of grip strength, men who could not perform the measure or who could...
perform the measure but were in the lowest quartile were at approximately 40% greater risk for falling (multivariate RR, 1.4; 95% CI, 0.9-2.0; and multivariate RR, 1.7; 95% CI, 1.4-2.1, respectively). Fall risk was similarly increased with low leg power and with inability to complete narrow walk trials.

**TESTOSTERONE LEVELS AND FALL RISK**

With lower baseline bioavailable testosterone levels, there was a progressive increase in the risk of falls during follow-up (Table 2). Fall risk in men in the lowest quartile of baseline bioavailable testosterone concentration was more than 40% greater than that in men in the highest quartile, before and after adjustment for physical performance. To examine whether poorer health affected this association, we repeated the analysis after restricting the cohort to healthier men (self-reported good or excellent health, no history of either Parkinson disease or prostate cancer, no use of walking aids, and no self-report of mobility limitation). The association of testosterone level with fall risk was not materially different from that observed in the entire cohort, with the RR comparing the lowest to highest testosterone quartile being 1.47 (95% CI, 1.16-1.86) (Figure 2). The relative risk of falls for a 1-SD increase in bioavailable testosterone concentration is 0.89 (95% CI, 0.83-0.95; P < .001).

Men with lower levels of bioavailable testosterone were also at higher risk for multiple falls (≥2 per year) (bio-

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**Table 1. Baseline Characteristics of the Study Population and Differences by Quartiles of Bioavailable Testosterone Levels***

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sample Cohort Overall (N = 2587)</th>
<th>Bioavailable Testosterone Level Quartiles†</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 (≤1.75 ng/dL)</td>
<td>2 (1.75-2.12 ng/dL)</td>
<td>3 (2.13-2.50 ng/dL)</td>
</tr>
<tr>
<td>Age, y</td>
<td>73.2 (5.7)</td>
<td>74.8</td>
<td>73.4</td>
</tr>
<tr>
<td>Height, cm</td>
<td>173.9 (6.9)</td>
<td>173.7</td>
<td>174.2</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>82.6 (13.4)</td>
<td>85.4</td>
<td>83.4</td>
</tr>
<tr>
<td>BMI</td>
<td>27.3 (3.8)</td>
<td>28.2</td>
<td>27.4</td>
</tr>
<tr>
<td>Lean BMI</td>
<td>18.7 (1.9)</td>
<td>18.8</td>
<td>18.8</td>
</tr>
<tr>
<td>Fat BMI</td>
<td>7.0 (2.2)</td>
<td>7.9</td>
<td>7.1</td>
</tr>
<tr>
<td>Alcohol consumption, drinks/wk</td>
<td>4.0 (6.6)</td>
<td>3.5</td>
<td>3.7</td>
</tr>
<tr>
<td>Total testosterone, ng/dL</td>
<td>422.8 (157.9)</td>
<td>268.0</td>
<td>381.2</td>
</tr>
<tr>
<td>Total estradiol, pg/mL</td>
<td>173.8 (5.6)</td>
<td>154</td>
<td>17.4</td>
</tr>
<tr>
<td>Bioavailable estradiol, pg/mL</td>
<td>12.1 (4.3)</td>
<td>10.4</td>
<td>11.9</td>
</tr>
<tr>
<td>Average grip strength, kg</td>
<td>38.4 (8.0)</td>
<td>38.6</td>
<td>38.2</td>
</tr>
<tr>
<td>Narrow walk best time, m/s</td>
<td>1.15 (0.27)</td>
<td>1.10</td>
<td>1.16</td>
</tr>
<tr>
<td>Chair stand time, s</td>
<td>10.8 (3.1)</td>
<td>11.6</td>
<td>10.8</td>
</tr>
<tr>
<td>Maximum leg power, W</td>
<td>210.7 (62.4)</td>
<td>199.0</td>
<td>213.0</td>
</tr>
<tr>
<td>Race, %</td>
<td>White, 76.6</td>
<td>75.9</td>
<td>77.2</td>
</tr>
<tr>
<td></td>
<td>African American, 9.0</td>
<td>11.3</td>
<td>7.1</td>
</tr>
<tr>
<td></td>
<td>Asian, 7.0</td>
<td>7.1</td>
<td>8.5</td>
</tr>
<tr>
<td></td>
<td>Hispanic, 4.8</td>
<td>3.9</td>
<td>4.3</td>
</tr>
<tr>
<td></td>
<td>Other, 2.5</td>
<td>1.9</td>
<td>2.9</td>
</tr>
<tr>
<td></td>
<td>Very poor, poor, or fair health status, %</td>
<td>14.4</td>
<td>21.7</td>
</tr>
<tr>
<td></td>
<td>Current smoker, %</td>
<td>4.1</td>
<td>3.7</td>
</tr>
<tr>
<td></td>
<td>Use of walking aids, %</td>
<td>3.6</td>
<td>6.4</td>
</tr>
<tr>
<td></td>
<td>Mobility limitation, %</td>
<td>14.6</td>
<td>23.3</td>
</tr>
<tr>
<td></td>
<td>Unable to complete grip strength, %</td>
<td>2.3</td>
<td>2.3</td>
</tr>
<tr>
<td></td>
<td>Unable to complete a narrow walk trial, %</td>
<td>8.9</td>
<td>13.3</td>
</tr>
<tr>
<td></td>
<td>Unable to complete 5 chair stands, %</td>
<td>2.8</td>
<td>5.0</td>
</tr>
<tr>
<td></td>
<td>Unable to complete power rig trials, %</td>
<td>1.6</td>
<td>2.6</td>
</tr>
</tbody>
</table>

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).
Si conversion factors: To convert testosterone to nanomoles per liter, multiply by 0.0347; estradiol to picomoles per liter, multiply by 3.67.
*Data are given as mean (SD) unless otherwise indicated.
†The number of participants with complete data for bioavailable testosterone measures (testosterone, estradiol, and sex hormone–binding globulin) is 2486.
Statistical tests of continuous variables by quartile were conducted using analysis of variance. Categorical variables were tested by quartile using χ² tests.

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Figure 1. The distribution of fall rates among men who fell during follow-up.
available testosterone quartile 1 vs 4; RR, 1.2; 95% CI, 1.1-1.4; P = .003). Lower levels of total testosterone were associated with higher risk of falling, but the association was less robust than with bioavailable testosterone (lowest vs highest quartile: RR, 1.2; 95% CI, 1.0-1.44; P = .04). Neither the total nor the bioavailable estradiol level was related to risk of falling. There was no interaction among race, sex steroid levels, and fall risk.

The risk of falls was substantially greater in men with reduced levels of strength or physical function at baseline. However, when strength and physical function were included in multivariate models of fall risk, the effect of bioavailable testosterone level on fall risk was unaltered (Table 2). Moreover, whereas leg power was an increasingly robust predictor of fall risk as age increased (Figure 3A), the effects of baseline bioavailable testosterone on the risk of falling tended to decline with advancing age (Figure 3B) (interaction P = .09). The effect of testosterone concentration on fall risk was most apparent in younger men (RR, 1.8; 95% CI, 1.2-2.7), and fall risk was not related to bioavailable testosterone levels in men older than 80 years (RR, 1.15; 95% CI, 0.73-1.8). These results were essentially unchanged when the analyses were performed using age-specific testosterone quartiles.

Aging in men is accompanied by a reduction in circulating testosterone levels. We show that falls are common in older men and that men with low baseline testosterone levels are substantially more likely to fall than those with higher levels. Bioavailable testosterone concentration is associated with measures of physical performance, but the association of testosterone level to the risk of falling is apparent regardless of physical performance. Thus, the mechanisms by which testosterone level affects the propensity to fall may involve other pathways. Finally, the relationship between testosterone concentration and risk of falling tends to diminish with age.

In this cohort, falling was common, and it became more frequent as age increased. Lean mass and physical performance declined as age increased. Fall risk increased with lower grip strength and with measures of lower extremity weakness (use of walking aids, self-reported mobility limitations, and low leg power). In fact, low leg power or low grip strength was increasingly more predictive of fall risk as age advanced. These data supplement other studies in older men,7,19,34,35 in whom the development of sarcopenia and physical dysfunction was associated with increasing morbidity and disability.36,37

Androgen receptors are present in muscle,38 and androgens have pleiotropic effects on the physiologic characteristics of muscle.39 However, the importance of age-related declines in testosterone levels in the causation of changes in physical performance is controversial. In the present study, testosterone was not associated with lean mass. Men with the highest bioavailable testosterone levels tended to have slightly better physical performance measures than men with the lowest levels, but other studies23,40-43 in older men found that circulating testosterone levels have little or no association with similar measures. Although we hypothesized that lower testosterone levels might be linked to increased risk of falling via deficits in physical functioning, the relationship between testosterone levels and fall risk was not attenuated when measures of physical performance were included in the multivariate models. That the relationship between leg power and fall risk increased with age further suggests that the effects of testosterone on falls (most apparent in the younger men) may not be acting solely via effects on strength. There may be other androgen-dependent mechanisms that contribute to the causation of

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**Table 2. Relation of Bioavailable Testosterone Levels and Fall Risk, With and Without Adjustment for Physical Performance**

<table>
<thead>
<tr>
<th>Bioavailable Testosterone Level Quartile</th>
<th>Model 1* RR (95% CI)</th>
<th>Model 1* P Value</th>
<th>Model 2† RR (95% CI)</th>
<th>Model 2† P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (&lt;1.75 ng/dL)</td>
<td>1.42 (1.19-1.70)</td>
<td>&lt;.001</td>
<td>1.40 (1.17-1.67)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>2 (1.75-2.12 ng/dL)</td>
<td>1.27 (1.06-1.51)</td>
<td>.009</td>
<td>1.28 (1.07-1.52)</td>
<td>.006</td>
</tr>
<tr>
<td>3 (2.13-2.50 ng/dL)</td>
<td>1.26 (1.05-1.50)</td>
<td>.02</td>
<td>1.26 (1.06-1.50)</td>
<td>.01</td>
</tr>
<tr>
<td>4 (&gt;=2.51 ng/dL)</td>
<td>1.00</td>
<td>NA</td>
<td>1.00</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; NA, not applicable; RR, risk ratio.

*SI conversion factor: To convert testosterone to nanomoles per liter, multiply by 0.0347.

†Additionally adjusted for grip strength, leg power, and ability to complete narrow walk trials.
falling. For example, although vision was not associated with fall risk in the present cohort, other researchers have hypothesized that testosterone may affect visual performance or cognition\textsuperscript{45-46}.

The apparent independence of the effects of low testosterone levels and reduced physical performance on fall risk in this cohort raises questions about the potential utility of testosterone replacement in older men. Replacement doses of testosterone in hypogonadal men, and supraphysiologic doses in younger men, increase lean mass and strength.\textsuperscript{30} Skeletal muscle in older men retains its responsiveness to testosterone,\textsuperscript{15} and recently Page et al\textsuperscript{16} reported that older men with reduced testosterone levels treated with intramuscular testosterone experienced an increase in muscle mass and strength. These effects of testosterone therapy may reflect pharmacologic actions and a priori cannot be taken as evidence of a role of testosterone deficiency in the genesis of age-related declines in physical capacity. Nevertheless, the positive effects of testosterone treatment on physical function justify interest in the possible benefits of therapy in older men.

The effect of testosterone concentration on falls was strongest in the youngest men studied. In men aged 65 to 70 years, fall risk was substantially higher when levels of bioavailable testosterone were low, but the association between testosterone level and fall risk was much less apparent with increasing age, even after adjustment for multiple covariates. The reason for this interaction with age is unclear. Perhaps the waning effect of testosterone reflects a dominance of nonandrogen-dependent factors later in life or the emergence of relative androgen insensitivity in elderly individuals. The finding that relatively younger men are more affected by testosterone deficiency has potentially important implications for understanding the mechanisms of androgen effects and may affect the design of studies intended to examine the usefulness of testosterone replacement therapy in older men.

To our knowledge, this is the first study of the associations among endogenous sex steroid levels, physical performance, and incident fall risk in older men. It has major strengths, including the large community-based population, careful measurements, and almost complete follow-up for falls. The relatively long duration of observation and the large number of falls provide adequate power to confidently describe the relationships between testosterone level and fall risk. A primary strength of the MrOS Study is that it was specifically designed to investigate skeletal and nonskeletal risk factors for fracture in a diverse cohort of older men. Men in the MrOS Study cohort are geographically and racially diverse, generally healthy, and well educated. Distributions of total hip and femoral neck bone mineral density measured using dual-energy x-ray absorptiometry in the MrOS Study cohort and among men of similar ages in the Third National Health and Nutritional Examination Survey (NHANES III) are comparable, although the MrOS Study participants are slightly heavier and have mean bone mineral density that is 2% to 8% higher depending on age.\textsuperscript{25} Sex steroid levels in this cohort are similar to those in other cohorts.\textsuperscript{2} Thus, the results of this study are likely to be broadly applicable to similarly aged, generally healthy US men. Despite these advantages, there are also limitations. The MrOS Study is composed of volunteers who thus may be healthier than the general population of older men. On the other hand, there was wide variation in levels of physical performance and of fall rates, suggesting that the results are applicable to many men. Although we found no evidence of ethnic differences in the associations described herein, the MrOS Study is primarily composed of white men, and the results may not apply to those in other racial groups. Finally, the use of radioimmunoassay methods to measure sex steroid levels has recently been questioned.\textsuperscript{47,48} However, we used stringent quality control procedures, and measurements of the relatively high levels of testosterone in adult men (unlike those in women and children) are reliable using radioimmunoassay techniques.\textsuperscript{49} We found no association of estradiol to the outcomes considered herein, and the measurement of estradiol levels in men is more challenging using radioimmunoassays. Nevertheless, it is unlikely that a meaningful, independent effect of estradiol was undetected. Finally, although we adjusted for many covariates that may affect the interaction of testosterone and fall risk or physical performance, there may be others that we have not considered.

In summary, we show that older men fall frequently and that those with low levels of bioavailable testosterone are at substantially higher risk for falls. The association between lower testosterone levels and increased fall risk was much less apparent with increasing age, even after adjustment for multiple covariates that we have not considered.
risk persisted after adjustment for measures of physical function and was strongest among relatively younger men. These findings strengthen the link between testosterone and the health of older men, suggesting that the effects of testosterone on fall risk may be via novel mechanisms and provide insight into how testosterone measurements might be useful for identifying men at higher risk for adverse events. Moreover, these results provide additional justification for trials of testosterone supplementation in older men and should aid in the design of those studies.

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Correspondence: Eric Orwoll, MD, Oregon Health & Science University (Box CR113), 3181 SW Sam Jackson Park Rd, Portland, OR 97239 (orwoll@ohsu.edu).

Author Contributions: Dr Orwoll had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Orwoll, Marshall, and Cummings.

Acquisition of data: Orwoll, Marshall, Blank, Barrett-Connor, Cauley, and Ensrud.

Analysis and interpretation of data: Orwoll, Lambert, Marshall, Blank, Barrett-Connor, Cauley, and Ensrud.

DRAFTING OF THE MANUSCRIPT:

Orwoll, Lambert, Marshall, and Barrett-Connor.

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Administrative Center (Oregon Health & Science University): E. Orwoll (principal investigator), K. Phipps (co-investigator), L. Marshall (co-investigator), J. Babich Blank (project director), J. Lambert, B. Chan, D. Neevel.


University of Minnesota: K. Ensrud (principal investigator), H. Fink (co-investigator), D. King (program manager), N. Michaels (assistant program manager), N. Nelson (clinical coordinator), C. Bird, D. Blanks, F. Imker-Witte, K. Moen, M. Paudel, M. Slindee.

Stanford University: M. Stefanick (principal investigator), A. Hoffman (co-investigator), K. Kent, B. Malig, S. Wong.


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