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Serum sex steroid hormones and frailty in older American men of the Third National Health and Nutrition Examination Survey (NHANES III)

Monika Eichholzer[1], **Aline Barbir**[1], **Shehzad Basaria**[2], **Adrian S Dobs**[3,4], **Manning Feinleib**[5], **Eliseo Guallar**[5,6], **Andy Menke**[5], **William G Nelson**[3,7,8], **Nader Rifai**[9], **Elizabeth A Platz**[3,5,7], and **Sabine Rohrmann**[1]

[1]Division of Cancer Epidemiology and Prevention, Institute of Social and Preventive Medicine, University of Zurich, Zurich, Switzerland [2]Section of Endocrinology, Diabetes, and Nutrition, Boston University School of Medicine, Boston Medical Center, Boston, MA, USA [3]Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD, USA [4]Division of Endocrinology and Metabolism, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA [5]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA [6]Division of General Internal Medicine, Department of Medicine, Johns Hopkins School of Medicine, Baltimore, MD, USA [7]James Buchanan Brady Urological Institute, Johns Hopkins Medical Institutions, Baltimore, MD, USA [8]Departments of Oncology, Pathology, Pharmacology and Molecular Sciences, Radiation Oncology and Molecular Radiation Sciences, Johns Hopkins Medical Institutions, Baltimore, MD, USA [9]Department of Laboratory Medicine, Harvard Medical School and Children's Hospital, Boston, MA, USA

Abstract

Objective—To determine whether frailty is associated with circulating total and free testosterone, total and free estradiol, and sex-hormone binding globulin (SHBG) in older men.

Methods—With NHANES III data of 461 men aged 60 years and older, we used logistic regression to analyze the associations between serum concentrations of sex steroid hormones, SHBG and frailty. Participants meeting any 3 or more of the 5 frailty criteria were classified as "frail", all others were considered as non-frail.

Results—2.5% of men were frail. Men with SHBG ≥66 nmol/L had three times the odds of frailty (OR=2.97; 95% CI 1.28–6.86) compared to men with SHBG <66 nmol/L. Men with free testosterone levels below 243 pmol/L had an increased odds of frailty (OR=3.92; 95% CI 1.29–11.89). None of these associations was statistically significant after additionally adjusting for body mass index, smoking and history of cardiovascular diseases (CVD). Total testosterone, and total and free estradiol serum levels were not statistically significantly associated with frailty.

Corresponding author: Monika Eichholzer, MD, MSc, MSc, Division of Cancer Epidemiology and Prevention, Institute of Social and Preventive Medicine, University of Zurich, Hirschengraben 84, CH-8001 Zürich, Switzerland. Phone: +41 44 634 40 12, monika.eichholzer@ifspm.uzh.ch.

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Conclusions—In this US nationally representative study of older men, low free testosterone and high SHBG serum levels were associated with a significantly increased odds of frailty after adjustment for age and race/ethnicity. These associations may, however, be explained by confounding due to obesity, smoking, and the higher prevalence of cardiovascular disease in frail men or by low hormones or high SHBG mediating the association between obesity, smoking, CVD and frailty.

Keywords

Frailty; elderly men; testosterone; SHBG; estradiol

Introduction

With advancing age the risk of frailty increases, but not all elderly become frail (1,2). It has been estimated that 7% of the 65+ year old noninstitutionalized US population can be considered to be frail (3) and this proportion is likely to increase due to the ageing of modern societies. This complex syndrome can be described as a decline in multiple organ systems leading to loss of function and impaired tolerance to stresses. Even minor negative events are likely to result in adverse outcomes such as falls, hospitalization, disability and death (2–4). Presently, no consensus definition of frailty exists and it is not specified in the International Classification of Diseases (4). The most widely used definition is the one by Fried et al. (3). They define overall frailty as the presence of three or more of the following components: unintentional weight loss (10 lbs in past year), self-reported exhaustion, poor grip strength, slow walking speed, or low physical activity. For degree of frailty, an individual can be classified as frail (3 or more components), intermediate (1–2 components), or nonfrail (0 components).

The underlying cause of frailty remains unknown. Interrelated impairment in multiple organ systems is likely to contribute to it. Changes in levels of sex steroid hormones, such as testosterone, could add to the physiological dysregulation that is connected with frailty due to the effects of hormones on multiple physiological systems, such as skeletal muscle and bone, and the cardiovascular system (5). This hypothesis is supported by the simultaneously decreasing total and free testosterone blood levels, and the loss of skeletal muscle mass in ageing men (6–9). In addition, bioavailable estradiol serum concentrations, which are of importance for example for bone mineral density (10), also decrease with age (11).

The association between testosterone serum levels and individual components of the frailty score, such as muscle strength and physical function, has been evaluated in a number of observational and interventional studies (5). However, epidemiological studies on the role of sex steroid hormones in the development of the frailty phenotype are limited and mainly confined to testosterone. Of the five existing studies, two looked at the risk of low hormone levels cross-sectionally (12,13). Two others evaluated the association additionally prospectively (1,14). One survey (15) studied the association between changes in hormone concentrations with time and progression of frailty. Overall, the five studies provided mixed results.

We used the frailty index by Fried et al. (3), which has previously been modified and adapted to information available in the Third National Health and Nutrition Evaluation Survey (NHANES III) by Wilhelm-Leen et al. (3,16), to determine whether frailty is associated with circulating total and free testosterone, total and free estradiol, and sex-hormone binding globulin (SHBG), in older men who participated in NHANES III.

Methods

Data source

For the present analysis we used individual level data from NHANES III. NHANES III was carried out by the National Center for Health Statistics between 1988 and 1994 (17). It is a cross-sectional, multistage, stratified, clustered probability sample of the U.S. civilian noninstitutionalized population at least 2 months old, and in which the elderly, non-Hispanic blacks and Mexican Americans were oversampled. Study participants took part in an interview and an extensive physical examination at the Medical Examination Center (MEC), where blood samples were drawn.

NHANES III was carried out in two phases, between 1988 and 1991 and between 1991 and 1994, such that unbiased national estimates of health and nutrition characteristics can be independently produced for each phase. Within each phase, the subjects were randomly assigned to take part in either the morning or afternoon/evening examination session. Of 33,944 subjects who had been interviewed in NHANES III, 14,781 were men with a physical examination. Of the 2205 men who were at least 12 years old and participated in the morning session of Phase I, 1637 had surplus blood samples available for measurement of sex steroid hormone and SHBG measurements. Participants in the morning session were chosen for our study to reduce the effects of diurnal variation on serum sex hormone concentrations. 461 men who were at least 60 years old and for whom surplus blood samples were available were included in the present analysis.

Assessment of Frailty

We used the frailty score originally developed and validated by Fried et al. (3), which has been adapted to the data available in NHANES III by Wilhelm-Leen et al. (16). This adapted score, which has been found to have strong face validity, consists of the five following items:

1. Low body weight for height, defined as body mass index (BMI) ≤ 18.5 kg m^2.
2. Slow walking, defined as the slowest quintile adjusted for sex, in a timed 8-foot walk.
3. Weakness, defined as present if participants answered ‘some difficulty,’ ‘much difficulty,’ or ‘unable to do’ when asked how much difficulty they have ‘lifting or carrying something as heavy as ten pounds (like a sack of potatoes or rice).’
4. Exhaustion, defined as present if participants answered ‘some difficulty’, ‘much difficulty’, or ‘unable to do’ when asked how much difficulty they have ‘walking from one room to the other on the same level’.

5. Low physical activity, defined as present if participants answered ‘less active’ when asked ‘Compared with most (men/women) your age, would you say that you are more active, less active or about the same?’

In our analysis we included men with valid information on at least three of the five frailty symptoms. One item was missing for 27 men (mainly skipping the “less active” question (n=14), 8 with missing information on walking speed), 2 items were missing for 3 men. In total, 5 of these 30 men who had 1 or 2 components missing were considered to be frail.

Participants meeting any 3 or more of the 5 criteria were classified as “frail”, those with 1 or 2 criteria as "prefrail" and those meeting none of the criteria as "robust". In addition, the frailty variable was dichotomized into "frails" (3+ frailty criteria) and "non-frails" (0–<3 frailty criteria) for the purposes of our analyses (3,16).

Measurement of sex steroid hormones and SHBG serum concentrations

Blood samples were drawn from all participants in the morning between 8.30 and 11.30 a.m. in the Medical Examination Center after an overnight fast. The samples were stored at −70°C until they were taken from the freezer to measure the concentrations of testosterone, estradiol, and SHBG in the laboratory of Dr. Nader Rifai at Children’s Hospital Boston. The blood samples were randomly ordered for testing and the laboratory technicians were blinded to the identities and characteristics of the study participants. A competitive electrochemiluminescence immunoassay on the 2010 Elecsys autoanalyzer (Roche Diagnostics, Indianapolis, IN) was used to quantify serum testosterone, estradiol, and SHBG. The lowest detection limits of the assays were 0.07 nmol/L for testosterone, 18.4 pmol/L for estradiol, and 3 nmol/L for SHBG. For the quality control specimens included during the analyses of NHANES III, the coefficients of variation were as follows: testosterone 5.9% and 5.8% at 8.7 and 19.1 nmol/L; estradiol 6.5% and 6.7% at 376.9 and 1739.9 pmol/L; and SHBG 5.3% and 5.9% at 5.3 and 16.6 nmol/L. In addition, we ran quality control samples with a mean estradiol concentration of 144.6 pmol/L, which is in the range of typical male estradiol concentrations; the intra-assay CV% was 5.2% and the inter-assay CV% was 2.5%. Free testosterone was calculated from measured total testosterone, SHBG, and albumin (available in the NHANES III public use database). Free estradiol was calculated from total estradiol, SHBG, and albumin (18,19).

Other explanatory variables

Cigarette smoking, alcohol consumption, and physical activity were assessed using a questionnaire. Height was measured to the nearest 0.1 cm using a stadiometer and weight was measured to the nearest 0.01 kg using an electronic digital scale while the participant was wearing foam slippers and paper shirt and pants. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Self-reported history of a diagnosis of a heart attack or stroke was used to define prevalent cardiovascular disease (CVD) and self-reported history of a diagnosis of cancer (other than skin cancer) to define prevalent cancer. Participants were categorized as being diabetic when they reported a history of a diagnosis of diabetes or were users of insulin or diabetic medication.

Statistical analysis

Data were analyzed using SUDAAN (20) as implemented in SAS v.9.1 (Cary, NC). Sampling weights were applied to take into account selection probabilities, over-sampling, non-response, and differences between the sample and the total US population (21).

We compared geometric mean concentrations of hormones and SHBG categories of frailty (frail, pre-frail, and robust) using weights to account for sampling probability and non-response using two models.

Logistic regression was used to calculate odds ratios (OR) and 95 percent confidence intervals (CI) of being frail compared to being non-frail in relation to (a) continuous hormones and SHBG concentrations and (b) to having low levels of total testosterone, free testosterone, total estradiol, free estradiol, or having a high level of SHBG. We defined low concentrations using as cut points <10.4 nmol/L for total testosterone (22) <173.5 pmol/L for free testosterone (22), <73.4 pmol/L for total estradiol (23), and <2.2 pmol/L (10th percentile in our study population) for free estradiol. We used ≥66 nmol/L (90th percentile) as the cut point for high SHBG. In the first model, we adjusted for age (1-year increments) and race/ethnicity (non-Hispanic black, non-Hispanic white, Mexican-American, other). To evaluate the possibly confounding effects of factors that influence hormone concentrations, in Model 2 we included age and race/ethnicity as well as BMI (continuous), cigarette smoking (never smoker, former smoker, current smoker), alcohol consumption (never drinker, ≤1 drink/week, >1 drink/week to <1 drink/day, 1+ drink/day), physical activity (moderate or vigorous physical activity on 0 times/week, <3 times/week, ≥3 to <8 times/week, > 8 times/week), and prevalence of CVD. Additionally adjusting for prevalent diabetes and cancer did not appreciably affect the risk estimates; thus, these co-morbidities were not considered in the final model. In addition, ORs and 95% CIs were calculated by polynominal logistic regression for being frail or pre-frail compared with being robust.

All significance tests were two-sided; $p<0.05$ was considered to be statistically significant. The Institutional Review Board of the National Center for Health Statistics, Centers for Disease Control and Prevention approved the protocols for conduct of the NHANES III. All participants provided informed consent. The Institutional Review Boards at the Johns Hopkins Bloomberg School of Public Health and the National Center for Health Statistics, Centers for Disease Control and Prevention approved the assay of stored serum specimens for the Hormone Demonstration Program.

Results

Biochemical, lifestyle and clinical characteristics of men with data on frailty and sex steroid hormones are summarized in Tables 1 and 2. Of the 461 men (unweighted n) included in the present analysis, 70.6% had no components of frailty, 20.6% had one, 6.3% two, and 2.5% at least three components. The most common comment of the frailty score was “low physical activity” (14.2%), followed by “slow walking” (13.3%), and “weakness” (10.4%). “Exhaustion” was present for only 2.4% of men and "low BMI" for only 1.6%. Overall, 70.6% of men belonged to the category “robust”, 26.9% to the category “prefrail”, and 2.5% to the category “frail”.

After taking into account age, frail men were older, had a slightly lower median BMI, lower serum vitamin D levels, but showed almost no differences in serum levels of cholesterol, albumin, and glycated hemoglobin compared with robust men (Table 2). Frail men were less likely to be non-Hispanic white, to be current or former smokers, to be alcohol consumers, to participate in moderate physical activity, to have prevalent CVD and cancer, but were more likely to have prevalent diabetes.

In relation to hormones, a higher percentage of frail than robust men had low free testosterone (< 243 pmol/L) and high SHBG serum levels (≥ 66 nmol/L) (Table 2). Percentages of men with total testosterone concentrations < 10.4 nmol/L were about the same in frail and robust men. The proportions of men with low total (< 73.4 pmol/L) and low free estradiol (< 2.2 pmol/L) were lower in the frail group than in the robust group.

Table 3 shows geometric mean hormone concentrations by frailty status. Adjusting for age and race-ethnicity, frail men appeared to have a lower mean free testosterone and a higher mean SHBG concentration than pre- and robust men. The differences were attenuated when further adjusted for BMI, smoking, and CVD.

Table 4 presents the associations of low hormone and high SHBG concentrations with frailty (frail vs. non-frail). After adjusting for age and race/ethnicity, men with free testosterone levels < 243 pmol/L had a statistically significantly increased odds of frailty of 3.92 (95% CI 1.29–11.89). SHBG levels ≥ 66 nmol/L were also associated with an increased frailty odds (OR = 2.97 (95% CI 1.28–6.86). Total estradiol levels < 73.4 pmol/L and free estradiol concentrations < 2.2 pmol/L were both associated with a higher odds of frailty, but the results were not statistically significant. After additionally adjusting for BMI, smoking, and CVD, the associations were attenuated. Total testosterone levels < 10.4 nmol/L was not associated with frailty (OR = 0.99; 95% CI 0.33–2.91).

Table 5 shows the associations of low hormone and high SHBG concentrations with frailty comparing the frail vs. robust and prefrail vs. robust men. Comparing frail vs. robust men, the associations were stronger for low free testosterone (OR = 4.7; 95% CI 1.48–14.91) and high SHBG (OR = 3.5; 95% CI 1.45–8.45) concentrations than in the analysis comparing to the combination of prefrail and robust men. However, these findings were attenuated after adjusting additionally for BMI, smoking, and CVD (OR = 1.7; 95% CI 0.88–3.28 and 1.58; 95% CI 0.76–3.29, respectively).

Discussion

We studied the associations of serum concentrations of sex steroid hormones and SHBG with odds of frailty in a cross-sectional study representative of American men aged 60 and older. 70.6% of these noninstitutionalized men belonged to the category “robust”, 26.9% to the category “prefrail”, and 2.5% to the category “frail”. This may be an underestimation of the proportion of frails, since NHANES requires participants to come in for examination, and a relatively high proportion of frail persons might have been physically unable to attend. Those with free testosterone levels < 243 pmol/L had a significantly increased odds of frailty. Men with SHBG levels ≥ 66 nmol/L also had a higher odds of frailty. Total

testosterone, and total and free estradiol serum levels were not significantly associated with frailty. The significant age-and race/ethnicity-adjusted odds of frailty described so far were attenuated and no longer statistically significant with additional adjustment for BMI and smoking, both being known to be positively associated with testosterone levels (24–26), and for CVD which seems to be negatively related to testosterone (27). Given the cross-sectional nature of the study one cannot be certain about the directionality of the findings. Although frailty could result from low testosterone, the opposite could also be true. The marked decrease in the estimate of effect following adjustment suggests that low hormones mediate the associations between obesity, smoking, CVD and frailty.

Our findings are consistent with those of some, but not all previous epidemiological studies. Accordingly, Mohr et al. (13) observed in a cross-sectional analysis of 646 50–86 years old participants in the Massachusetts Male Aging Study that SHBG, but not total or free testosterone, was associated with the frailty score proposed by Fried et al. (3) after adjustment for age, diabetes mellitus, and depression (the association for free testosterone was also adjusted for log caloric intake). Data from 1469 men of the Osteoporotic Fractures in Men Study (14), on the other hand, found that decreased serum levels of calculated bioavailable testosterone were related to an increased risk of frailty (using a modified version of the Fried criteria (3)). In cross-sectional analyses, men in the lowest quartile of bioavailable testosterone had 1.39-fold (95% CI 1.02–1.91) increased odds of greater frailty compared to men in the highest quartile after adjustment for covariates including age, body size, health status, and medical conditions. Over a mean follow-up period of 4.1 years, the age-adjusted OR of frailty was 1.51 (95% CI 1.10–2.07) comparing the two groups. However, this association was attenuated by adjustment for covariates. Neither estradiol nor SHBG serum levels were associated with frailty. Similarly, in a prospective cohort study by Hyde et al. (1), both lower total and free testosterone were associated with a significantly increased odds of frailty (assessed with the FRAIL scale (28)) at baseline in 3616 community-dwelling men aged 70–88 years. Adjustments were made for age, body mass index, smoking, diabetes, social support, impairments in vision and hearing. In the 6-year-follow-up, only lower free testosterone levels was associated with a higher risk of frailty (adjusted OR= 1.22; 95% CI 1.05–1.42). Moreover, in a cross-sectional study of 108 Taiwanese men and women aged 65 years and older (12), low total and free testosterone, but not high SHBG serum concentrations were associated with a significantly higher risk of frailty in both men and women based on the Fried criteria (3), after adjusting for age, diabetes mellitus, hypertension, congestive heart failure, BMI and serum albumin. Finally, in a cohort study of 1705 men aged 70 years and older enrolled in The Concord Health and Ageing in Men Project (15), both decreased total testosterone and calculated free testosterone as well as low dihydrotestosterone, estradiol and estrone serum levels, but not SHBG concentrations, were associated with an increased, age-adjusted risk of frailty for both definitions used (assessed with the Fried scale (3) and the one used in the Study of Osteoporotic Fractures (29)). The two frailty indices each showed that about 50% of men were robust at baseline, whereas 41% were prefrail and 9% frail. A one standard deviation, 2-yr decrease in total testosterone and calculated free testosterone, was associated with a statistically significant increase in the odds of progression (increase in severity) of frailty

using the Fried scale. Additional adjustment for CVD, diabetes, prostate cancer, score, glucocorticoid treatment/corticosteroids did not affect results.

In summary, epidemiological evidence on the association of sex steroid hormones with frailty is mixed. This may in part be explained by the variety of study designs, age-groups studied, definition of frailty used, calculations of free testosterone, and the control for confounders in the surveys done so far. Overall, the most consistent results are seen for low free testosterone levels increasing the risk of frailty, but after multivariate adjustment results were attenuated.

Testosterone is the major circulating androgen in men and about 98% is bound to protein, whereas 2% is free. Of the bound portion 40% is tightly bound to SHBG, the rest is loosely bound to albumin. The sum of the albumin-bound and the free (unbound) testosterone is referred to as the “bioavailable”, i.e. the biologically more active amount (1,30). Testosterone supports muscle protein synthesis and increases muscle strength (31), and maintains bone strength and bone mineral density (32). Additionally, young hypogonadal men exhibit decreased muscle and bone mass, and loss of energy (33); grip strength and appetite have been shown to improve when they are treated with testosterone (34–36). Androgen therapy in older men may lead to small increases in muscle strength (5,37). Comparatively, lower levels of baseline free testosterone were correlated with an increased risk of incident or worsening mobility limitation in older men of the Framingham Offspring Study (38). In a randomized trial in 274 elderly hypogonadal prefrail or frail males a 6-month testosterone treatment improved muscle mass and strength, but the effects were not maintained at 6 months after treatment (39,40). Presently, testosterone treatment has not yet been shown to reverse frailty in a large randomized trial (41).

Even though the physiological pathways leading to frailty remain complex, testosterone could influence components of frailty by the discussed mechanisms (42). Furthermore, not only testosterone decreases with age, but also serum estradiol significantly decreases in aging males (43). This may, for example, result in a decrease of bone mineral density (44). No other effects of SHBG other than binding circulating sex steroid hormones are established, although its concentrations increase with ageing and decrease with obesity and hyperinsulinism. It is, however, interesting that both SHBG and free testosterone are associated with frailty. It might be that the association of free testosterone, which is estimated from total testosterone, SHBG, and albumin, simply reflects the association with high SHBG concentration. It might be that higher SHBG captures the loss of fat mass in older people who are frailer than other older people who remain robust/with more fat mass. However, we cannot address this question in our cross-sectional analysis.

Several aspects of the present study should be commented on. The cross-sectional study design does not allow for establishing the temporal sequence of events. Frailty could result from low testosterone, but the opposite could also be true and testosterone could be a marker. The inflammatory state of chronic illness and/or frailty could result in reduced testosterone synthesis. In relation to the main findings of the present study showing that low free testosterone and high SHBG serum levels are associated with an increased risk of frailty, the effects of (residual) confounding cannot be excluded, even though we included a

number of possible confounders into the analysis. Although weight loss, in our definition a BMI ≤ 18.5 kg m^2, is part of the frailty score, we decided to additionally adjust for body fatness, as it was inversely associated with total and free testosterone as well as with SHGB serum levels, and positively associated with total and free estradiol levels in men in NHANES III (24). Three of the other studies (1,3,12) also adjusted for BMI, even though crude measures of low BMI (and low physical activity) were part of the frailty score. Body fatness is better determined by percentage of body fat and waist circumference than the use of BMI as BMI may also indicate muscle mass. However, both alternative measurements were not available for all study participants and adjusting for them would have strongly reduced the number of participants in our analysis. We also adjusted for history of CVD, which has been also been done in most previous studies. However, CVD may also be a mediator of the association between sex hormones and frailty, and thus, adjustment would not be appropriate. However, not adjusting for CVD in the final model did not materially attenuate the observed associations. Also, SHBG in mainly produced by hepatocytes. Therefore, we examined whether an existing liver disease might have affected our results, but we did not observe a statistically significant higher prevalence of elevated liver enzymes in frail compared with non-frail men (data not shown).

In conclusion, low free testosterone and high SHBG serum levels tended to be associated with an increased risk of frailty, but adjustment for modifiable factors that influence hormone levels attenuated these associations. However, based on the cross-sectional design of our study, larger studies with prospective design are needed to address the causal role of sex steroid hormones in frailty.

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References

1. Hyde Z, Flicker L, Almeida OP, Hankey GJ, McCaul KA, Chubb SA, Yeap BB. Low free testosterone predicts frailty in older men: the health in men study. J Clin Endocrinol Metab. 2010; 95(7):3165–3172. [PubMed: 20410223]
2. Ahmed N, Mandel R, Fain MJ. Frailty: an emerging geriatric syndrome. Am J Med. 2007; 120(9): 748–753. [PubMed: 17765039]
3. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McBurnie MA. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001; 56(3):M146–M156. [PubMed: 11253156]
4. Rockwood K, Hogan DB, MacKnight C. Conceptualisation and measurement of frailty in elderly people. Drugs Aging. 2000; 17(4):295–302. [PubMed: 11087007]
5. O'Connell MD, Tajar A, Roberts SA, Wu FC. Do androgens play any role in the physical frailty of ageing men? Int J Androl. 2010; 34(3):195–211. [PubMed: 20722765]
6. Goodpaster BH, Park SW, Harris TB, Kritchevsky SB, Nevitt M, Schwartz AV, Simonsick EM, Tylavsky FA, Visser M, Newman AB. The loss of skeletal muscle strength, mass, and quality in older adults: the health, aging and body composition study. J Gerontol A Biol Sci Med Sci. 2006; 61(10):1059–1064. [PubMed: 17077199]
7. Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. J Clin Endocrinol Metab. 2001; 86(2):724–731. [PubMed: 11158037]

8. Fantin F, Di Francesco V, Fontana G, Zivelonghi A, Bissoli L, Zoico E, Rossi A, Micciolo R, Bosello O, Zamboni M. Longitudinal body composition changes in old men and women: interrelationships with worsening disability. J Gerontol A Biol Sci Med Sci. 2007; 62(12):1375–1381. [PubMed: 18166688]

9. Feldman HA, Longcope C, Derby CA, Johannes CB, Araujo AB, Coviello AD, Bremner WJ, McKinlay JB. 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. 2002; 87(2):589–598. [PubMed: 11836290]

10. Gielen E, Vanderschueren D, Callewaert F, Boonen S. Osteoporosis in men. Best Pract Res Clin Endocrinol Metab. 2011; 25(2):321–335. [PubMed: 21397201]

11. van den Beld AW, Lamberts SW. The male climacterium: clinical signs and symptoms of a changing endocrine environment. Prostate Suppl. 2000; 10:2–8. [PubMed: 11056486]

12. Wu IC, Lin XZ, Liu PF, Tsai WL, Shiesh SC. Low serum testosterone and frailty in older men and women. Maturitas. 2010; 67(4):348–352. [PubMed: 20727696]

13. Mohr BA, Bhasin S, Kupelian V, Araujo AB, O'Donnell AB, McKinlay JB. Testosterone, sex hormone-binding globulin, and frailty in older men. J Am Geriatr Soc. 2007; 55(4):548–555. [PubMed: 17397433]

14. Cawthon PM, Ensrud KE, Laughlin GA, Cauley JA, Dam TT, Barrett-Connor E, Fink HA, Hoffman AR, Lau E, Lane NE, Stefanick ML, Cummings SR, Orwoll ES. Sex hormones and frailty in older men: the osteoporotic fractures in men (MrOS) study. J Clin Endocrinol Metab. 2009; 94(10):3806–3815. [PubMed: 19737923]

15. Travison TG, Nguyen AH, Naganathan V, Stanaway FF, Blyth FM, Cumming RG, Le Couteur DG, Sambrook PN, Handelsman DJ. Changes in reproductive hormone concentrations predict the prevalence and progression of the frailty syndrome in older men: the concord health and ageing in men project. J Clin Endocrinol Metab. 2011; 96(8):2464–2474. [PubMed: 21677041]

16. Wilhelm-Leen ER, Hall YN, M KT, Chertow GM. Frailty and chronic kidney disease: the Third National Health and Nutrition Evaluation Survey. Am J Med. 2009; 122(7):664–671. e662. [PubMed: 19559169]

17. Statistics NCfH. Plan and operation of the Third National Health and Nutrition Examination Survey, 1988–94. Series 1: programs and collection procedures. Vital Health Stat 1. 1994; (32):1–407.

18. Vermeulen A, Verdonck L, Kaufman JM. A critical evaluation of simple methods for the estimation of free testosterone in serum. J Clin Endocrinol Metab. 1999; 84(10):3666–3672. [PubMed: 10523012]

19. Rinaldi S, Geay A, Dechaud H, Biessy C, Zeleniuch-Jacquotte A, Akhmedkhanov A, Shore RE, Riboli E, Toniolo P, Kaaks R. Validity of free testosterone and free estradiol determinations in serum samples from postmenopausal women by theoretical calculations. Cancer Epidemiol Biomarkers Prev. 2002; 11(10 Pt 1):1065–1071. [PubMed: 12376508]

20. Shah, B.; Barnwell, BG.; Bieler, GS., editors. SUDAAN User's Manual: Software for Analysis of Correlated Data. NC: Research Triangle Institute; 1995.

21. National Center for Health Statistics. Plan and operation of the Third National Health and Nutrition Examination Survey, 1988–94. Series 1: programs and collection procedures. 1994:1–407.

22. Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, Montori VM. Testosterone therapy in adult men with androgen deficiency syndromes: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2006; 91(6):1995–2010. [PubMed: 16720669]

23. Greenspan, F., editor. Basic and Clinical Endocrinology. 4th edn. Conneticut: East Norwalk; 1994.

24. Rohrmann S, Shiels MS, Lopez DS, Rifai N, Nelson WG, Kanarek N, Guallar E, Menke A, Joshu CE, Feinleib M, Sutcliffe S, Platz EA. Body fatness and sex steroid hormone concentrations in US men: results from NHANES III. Cancer Causes Control. 2011; 22(8):1141–1151. [PubMed: 21678033]

25. Svartberg J, Jorde R. Endogenous testosterone levels and smoking in men. The fifth Tromso study. Int J Androl. 2007; 30(3):137–143. [PubMed: 17163954]

26. Shiels MS, Rohrmann S, Menke A, Selvin E, Crespo CJ, Rifai N, Dobs A, Feinleib M, Guallar E, Platz EA. Association of cigarette smoking, alcohol consumption, and physical activity with sex steroid hormone levels in US men. Cancer Causes Control. 2009; 20(6):877–886. [PubMed: 19277882]
27. Corona G, Rastrelli G, Monami M, Guay A, Buvat J, Sforza A, Forti G, Mannucci E, Maggi M. Hypogonadism as a risk factor for cardiovascular mortality in men: a meta-analytic study. Eur J Endocrinol. 2011; 165(5):687–701. [PubMed: 21852391]
28. Abellan van Kan G, Rolland Y, Bergman H, Morley JE, Kritchevsky SB, Vellas B. The I.A.N.A Task Force on frailty assessment of older people in clinical practice. J Nutr Health Aging. 2008; 12(1):29–37. [PubMed: 18165842]
29. Ensrud KE, Ewing SK, Taylor BC, Fink HA, Cawthon PM, Stone KL, Hillier TA, Cauley JA, Hochberg MC, Rodondi N, Tracy JK, Cummings SR. Comparison of 2 frailty indexes for prediction of falls, disability, fractures, and death in older women. Arch Intern Med. 2008; 168(4): 382–389. [PubMed: 18299493]
30. Swerdloff RS, Wang C. Androgens and the ageing male. Best Pract Res Clin Endocrinol Metab. 2004; 18(3):349–362. [PubMed: 15261842]
31. Herbst KL, Bhasin S. Testosterone action on skeletal muscle. Curr Opin Clin Nutr Metab Care. 2004; 7(3):271–277. [PubMed: 15075918]
32. Tracz MJ, Sideras K, Bolona ER, Haddad RM, Kennedy CC, Uraga MV, Caples SM, Erwin PJ, Montori VM. Testosterone use in men and its effects on bone health. A systematic review and meta-analysis of randomized placebo-controlled trials. J Clin Endocrinol Metab. 2006; 91(6): 2011–2016. [PubMed: 16720668]
33. Seftel A. Male hypogonadism. Part II: etiology, pathophysiology, and diagnosis. Int J Impot Res. 2006; 18(3):223–228. [PubMed: 16094414]
34. Pagotto U, Gambineri A, Pelusi C, Genghini S, Cacciari M, Otto B, Castaneda T, Tschop M, Pasquali R. Testosterone replacement therapy restores normal ghrelin in hypogonadal men. J Clin Endocrinol Metab. 2003; 88(9):4139–4143. [PubMed: 12970277]
35. Sih R, Morley JE, Kaiser FE, Perry HM 3rd, Patrick P, Ross C. Testosterone replacement in older hypogonadal men: a 12-month randomized controlled trial. J Clin Endocrinol Metab. 1997; 82(6): 1661–1667. [PubMed: 9177359]
36. Asarian L, Geary N. Modulation of appetite by gonadal steroid hormones. Philos Trans R Soc Lond B Biol Sci. 2006; 361(1471):1251–1263. [PubMed: 16815802]
37. Ottenbacher KJ, Ottenbacher ME, Ottenbacher AJ, Acha AA, Ostir GV. Androgen treatment and muscle strength in elderly men: A meta-analysis. J Am Geriatr Soc. 2006; 54(11):1666–1673. [PubMed: 17087692]
38. Krasnoff JB, Basaria S, Pencina MJ, Jasuja GK, Vasan RS, Ulloor J, Zhang A, Coviello A, Kelly-Hayes M, D'Agostino RB, Wolf PA, Bhasin S, Murabito JM. Free testosterone levels are associated with mobility limitation and physical performance in community-dwelling men: the Framingham Offspring Study. J Clin Endocrinol Metab. 2010; 95(6):2790–2799. [PubMed: 20382680]
39. Srinivas-Shankar U, Roberts SA, Connolly MJ, O'Connell MD, Adams JE, Oldham JA, Wu FC. Effects of testosterone on muscle strength, physical function, body composition, and quality of life in intermediate-frail and frail elderly men: a randomized, double-blind, placebo-controlled study. J Clin Endocrinol Metab. 2010; 95(2):639–650. [PubMed: 20061435]
40. O'Connell MD, Roberts SA, Srinivas-Shankar U, Tajar A, Connolly MJ, Adams JE, Oldham JA, Wu FC. Do the effects of testosterone on muscle strength, physical function, body composition, and quality of life persist six months after treatment in intermediate-frail and frail elderly men? J Clin Endocrinol Metab. 2011; 96(2):454–458. [PubMed: 21084399]
41. Morley JE. Should frailty be treated with testosterone? Aging Male. 2011; 14(1):1–3. [PubMed: 20670101]
42. Morley JE, Kim MJ, Haren MT. Frailty and hormones. Rev Endocr Metab Disord. 2005; 6(2):101–108. [PubMed: 15843881]

43. Ferrini RL, Barrett-Connor E. Sex hormones and age: a cross-sectional study of testosterone and estradiol and their bioavailable fractions in community-dwelling men. Am J Epidemiol. 1998; 147(8):750–754. [PubMed: 9554416]

44. Khosla S, Melton LJ 3rd, Atkinson EJ, O'Fallon WM, Klee GG, Riggs BL. Relationship of serum sex steroid levels and bone turnover markers with bone mineral density in men and women: a key role for bioavailable estrogen. J Clin Endocrinol Metab. 1998; 83(7):2266–2274. [PubMed: 9661593]

Table 1

Prevalence of frailty symptoms and distribution of frailty score (unweighted n = 461 men), men aged ≥ 60 years old, NHANES III 1988–1991[a]

Frailty score (16)	
0	70.6%
1	20.6%
2	6.3%
3–5	2.5%
Frailty score components	
Slow walking	13.3%
Weakness	10.4%
Exhaustion	2.4%
Low physical activity	14.2%
Low BMI	1.6%

BMI, Body mass index.

[a]Sampling weights were applied

Table 2

Unadjusted baseline characteristics by frailty status, men aged ≥ 60 years old, NHANES III 1988–1991[a]

	Frail [b]			Pre-frail [b]			Robust [b]		
	median	***Q1***	***Q3***	***median***	***Q1***	***Q3***	***median***	***Q1***	***Q3***
Age (yr)	76.6	67.8	81.5	67.7	62.5	73.8	67.4	63.6	72.3
BMI (kg/m^2)	24.1	21.6	28.4	26.2	23.6	29.1	26.0	23.7	28.9
Serum vitamin D (nmol/L)	63.4	39.7	90.1	70.4	52.2	83.4	71.6	57.2	88.4
Serum cholesterol (mmol/L)	5.6	4.5	6.8	5.2	4.6	6.0	5.6	5.0	6.1
Serum albumin (g/dL)	4.0	3.8	4.1	4.1	3.9	4.3	4.1	3.9	4.4
Glycated hemoglobin: (%)	5.6	5.2	5.7	5.5	5.0	5.8	5.4	5.1	5.8
	%	***SE%***		***%***	***SE%***		***%***	***SE%***	
Smoking status									
Never smoker	68.7	10.0		21.9	4.0		30.9	4.1	
Former smoker	24.6	9.4		62.7	5.5		50.6	3.6	
Current smoker	6.7	4.5		15.4	3.1		18.5	2.4	
Race/ethnicity									
Non-Hispanic white	15.2	3.5		80.7	5.0		86.2	2.8	
Non-Hispanic black	54.5	6.3		11.4	2.2		5.9	1.2	
Mexican-American	4.6	3.4		4.3	1.2		1.7	0.5	
Other	25.7	5.1		3.7	3.2		6.2	2.3	
Alcohol consumption									
0 drinks	43.1	3.0		48.6	5.7		43.4	5.7	
1–3 drinks /month	39.4	10.5		14.4	4.4		12.0	2.2	
1–7 drinks / week	12.0	9.1		13.0	2.9		23.9	3.0	
1+ drink/day	5.6	4.6		23.9	5.0		20.7	4.0	
Moderate physical activity									
None	70.4	4.3		12.7	3.3		6.8	1.5	
0–3/week	9.4	7.8		33.7	4.4		27.0	4.7	
4–6/week	6.3	7.0		16.8	6.3		13.2	2.9	
Daily	13.9	6.4		36.9	7.1		53.0	4.5	
Chronic disease[c]									

	Frail [b]		Pre-frail [b]		Robust [b]	
CVD	11.0	7.3	26.3	3.7	15.1	2.4
Diabetes	10.4	7.8	7.9	2.0	7.6	1.8
Cancer	3.7	2.2	10.3	2.6	6.2	1.6
Low hormone /high SHBG concentrations						
Total testosterone < 10.4 nmol/L	20.4	5.2	20.1	3.5	18.9	3.7
Free testosterone < 243 pmol/L	79.2	10.9	56.2	5.9	46.4	3.5
Total estradiol < 73.4 pmol/L	2.3	1.2	9.2	5.2	6.7	2.6
Free estradiol < 2.2 pmol/L	9.7	4.2	22.6	4.3	15.9	3.0
SHBG >= 66 nmol/L	41.2	6.7	23.6	5.2	16.5	2.6

BMI, Body mass index. SE, standard error.

[a] Sampling weights were applied

[b] “frail”: participants meeting any 3 or more of the 5 criteria of the frailty score; "prefrail": those with 1 or 2 criteria; “robust”: those meeting none of the criteria.

[c] Self-report

Table 3

Geometric mean hormone concentrations by frailty status, men aged ≥ 60 years old, NHANES III 1988–1991

Analyte	Status[a]	Adjusted for age and race/ethnicity		Adjusted for age, race/ethnicity, BMI, smoking, CVD	
		Mean	*95% CI*	*Mean*	*95% CI*
Total testosterone (nmol/L)	frail	12.32	(8.99 –16.90)	11.83	(8.71 –16.07)
	pre-frail	13.01	(11.73 –14.44)	12.97	(11.76 –14.30)
	robust	14.10	(12.32 –15.27)	13.74	(12.39 –15.27)
Free teststosterone (pmol/L)	frail	170	(118 –243)	174	(121 –243)
	pre-frail	212	(194 –229)	212	(194 –232)
	robust	222	(198 –246)	222	(198 –250)
Total estradiol (pmol/L)	frail	124.96	(100.08 –156.01)	129.22	(100.85 –165.55)
	pre-frail	120.52	(109.44 –132.67)	120.08	(109.33 –131.86)
	robust	121.29	(113.62 –129.48)	121.36	(113.37 –129.92)
Free estradiol (pmol/L)	frail	2.75	(2.16 –4.62)	2.94	(2.31 –3.74)
	pre-frail	2.89	(2.64 –3.19)	2.89	(2.64 –3.19)
	robust	2.89	(2.71 –3.08)	2.89	(2.68 –3.08)
SHBG (nmol/L)	frail	55.73	(45.43 –68.37)	52.34	(44.11 –62.11)
	pre-frail	46.09	(40.49 –52.46)	45.86	(40.54 –51.86)
	robust	47.41	(45.07 –49.87)	47.59	(45.14 –50.17)

SHBG, sex hormone-binding globulin. BMI, Body mass index. CVD, Cardiovascular disease.

[a]“frail”: participants meeting any 3 or more of the 5 criteria of the frailty score; "prefrail": those with 1 or 2 criteria; “robust”: those meeting none of the criteria.

Table 4

Associations between low hormone / high SHBG concentrations and frailty[a], men aged ≥ 60 years old, NHANES III 1988–1991

	age, race/ethnicity		age, race/ethnicity, BMI, smoking, CVD		
	OR	**95% CI**	**OR**	**95% CI**	
Total testosterone < 10.4 nmol/L	0.99	(0.33 –2.91)	0.97	0.25	3.82
Free testosterone < 243 pmol/L	3.92	(1.29 –11.89)	2.46	0.77	7.86
Total estradiol < 73.4 pmol/L	1.87	(0.35 –10.04)	1.29	0.10	16.89
Free estradiol < 2.2 pmol/L	2.02	(0.52 –7.87)	1.07	0.23	4.93
SHBG >= 66 nmol/L	2.97	(1.28 –6.86)	2.64	0.71	9.74

SHBG, sex hormone-binding globulin. BMI, Body mass index. CVD, Cardiovascular disease.

[a]Frailty dichotomized into non-frail (robust and prefrail) and frail (3+ components of frailty score)

Table 5

Associations between low hormone/high SHBG concentrations and frailty and pre-frailty, men aged ≥ 60 years old, NHANES III 1988–1991

	Frail vs. robust		Pre-frail vs. robust	
	OR	**95% CI**	**OR**	**95% CI**
Adjusted for age & race/ethnicity				
Total testosterone < 10.4 nmol/L	1.01	(0.32 –3.18)	1.07	(0.58 –1.99)
Free testosterone < 243 pmol/L	4.70	(1.48 –14.91)	1.70	(0.88 –3.28)
Total estradiol < 73.4 pmol/L	2.22	(0.35 –13.99)	1.58	(0.25 –10.00)
Free estradiol < 2.2 pmol/L	2.53	(0.66 –9.69)	1.82	(0.83 –4.00)
SHBG >= 66 nmol/L	3.50	(1.45 –8.45)	1.58	(0.76 –3.29)
Adjusted for age, race/ethnicity, BMI, smoking, CVD				
Total testosterone < 10.4 nmol/L	1.09	(0.30 –3.92)	1.01	(0.48 –2.11)
Free testosterone < 243 pmol/L	3.21	(0.97 –10.65)	1.57	(0.80 –3.05)
Total estradiol < 73.4 pmol/L	1.84	(0.26 –13.18)	1.37	(0.21 –8.98)
Free estradiol < 2.2 pmol/L	1.81	(0.42 –7.82)	2.00	(0.87 –4.60)
SHBG >= 66 nmol/L	2.79	(0.86 –9.09)	1.55	(0.72 –3.36)

SHBG, sex hormone-binding globulin. BMI, Body mass index. CVD, Cardiovascular disease.