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Prevalence of Symptomatic Androgen Deficiency in Men

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Context: Despite recognition that androgen deficiency in men should be defined according to biochemical and clinical criteria, most prevalence estimates are based on low testosterone levels alone.

Objective: The objective of this study was to examine the association between symptoms of androgen deficiency and low total and calculated free testosterone levels and estimate the prevalence of symptomatic androgen deficiency in men.

Design: This study was a population-based, observational survey.

Participants: A total of 1475 Black, Hispanic, and white men, between the ages of 30–79 yr, with complete data on testosterone, SHBG, and symptoms of androgen deficiency, and who are not taking medications that impact sex steroid levels were randomly selected from the Boston Area Community Health Survey.

Outcome: Outcomes were measured as symptomatic androgen deficiency, defined as low total (<300 ng/dl) and free (<5 ng/dl) testosterone plus presence of low libido, erectile dysfunction, osteoporosis or fracture, or two or more of following symptoms: sleep disturbance, depressed mood, lethargy, or diminished physical performance.

Results: Mean age of the sample was 47.3 ± 12.5 yr. Approximately 24% of subjects had total testosterone less than 300 ng/dl, and 11% of subjects had free testosterone less than 5 ng/dl. Prevalence of symptoms were as follows: low libido (12%), erectile dysfunction (16%), osteoporosis/fracture (1%), and two or more of the nonspecific symptoms (20%). Low testosterone levels were associated with symptoms, but many men with low testosterone levels were asymptomatic (*e.g.* in men 50+ yr, 47.6%). Crude prevalence of symptomatic androgen deficiency was 5.6% (95% confidence interval: 3.6%, 8.6%), and was not significantly related to race and ethnic group. Prevalence was low in men less than 70 yr (3.1–7.0%) and increased markedly with age to 18.4% among 70 yr olds. Projection of these estimates to the year 2025 suggests that there will be as many as 6.5 million American men ages 30–79 yr with symptomatic androgen deficiency, an increase of 38% from 2000 population estimates.

Conclusions: Prevalence of symptomatic androgen deficiency in men 30 and 79 yr of age is 5.6% and increases substantially with age. The aging of the U.S. male population will cause a large increase in the burden of symptomatic androgen deficiency. Future work should address the clinical significance of low testosterone levels in asymptomatic men. **(*J Clin Endocrinol Metab* 92: 4241–4247, 2007)**

AS MEN AGE, SERUM testosterone declines gradually after age 40 between 0.4 and 2.6% per year (1–4). This decline has been associated with parallel age declines in bone mass, muscle mass/strength, physical function/frailty, and sexual function (5, 6). More recently, investigators have highlighted the potential metabolic consequences of testosterone decline, showing a potential role for low testosterone in age-associated metabolic changes such as abdominal obesity (7, 8), diabetes (9, 10), and markers of prediabetes (insulin resistance, impaired glucose tolerance, and metabolic syndrome) (9, 11).

Most elderly men have testosterone levels within the normal range, with prevalence estimates of "low" [*e.g.* <300 ng/dl (10.4 nmol/liter)] serum testosterone generally between 10 and 25% (2, 3, 12). Most of these men with low testosterone levels will not come to clinical attention because testosterone levels are not routinely measured in clinical practice. For this reason, it is important to estimate prevalence based on both testosterone levels as well as clinical symptoms (6, 13–15), which is consistent with clinical practice guidelines issued by The Endocrine Society (16). Data from the Massachusetts Male Aging Study (MMAS) indicate that the prevalence of symptomatic androgen deficiency is between 6 and 12% (17). However, these estimates were based on data that were collected in the late 1980s and 1990s, and thus, may not reflect recent trends toward general population aging and our recent observation from MMAS of a secular decline in testosterone levels between 1987 and 2004 (18).

Using data from the Boston Area Community Health (BACH) Survey, a randomly selected, population-based sample that is representative of the city of Boston and which was conducted between 2002 and 2005, we examined the association between symptoms of androgen deficiency and low total and free testosterone levels. We also estimated the crude and age-specific prevalence of symptomatic androgen deficiency [defined according to the latest clinical guidelines by serum total and calculated free testosterone plus clinical symptoms (16)] in men between the ages of 30 and 79 yr.

Subjects and Methods

Overall design

The BACH Survey employed a stratified, two-stage cluster sample that was designed to recruit equal numbers of subjects (n = 250) according to age (30–39, 40–49, 50–59, 60–79 yr), gender, and race and ethnic [African American (Black), Hispanic, and Caucasian (white)]

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Abbreviations: BACH, Boston Area Community Health; BMD, bone mineral density; BRFSS, Boston Behavioral Risk Factor Surveillance System; ED, erectile dysfunction; MMAS, Massachusetts Male Aging Study.

group. The primary sampling units consisted of 4266 census block geographic areas in the city of Boston. These census blocks were classified into 12 strata defined by geographic location within the city and racial/ethnic density. Households were then sampled from within each selected census block. Further details of the methods used are described elsewhere (19).

Data collection

Data were obtained during a 2-h, in-person interview, conducted by a trained (bilingual) phlebotomist/interviewer generally in the subject's home. Following written informed consent (all protocols and informed consent procedures were approved by the New England Research Institutes Institutional Review Board), a venous blood sample (20 ml) and anthropometric measurements (blood pressure, height, and weight) were obtained, along with information on major comorbidities and general health status, prescription and nonprescription medications, lifestyle and psychosocial factors, and detailed self-reported symptoms suggestive of urogynecological conditions.

Serum collection and sex steroid measurements

Nonfasting blood samples were drawn close to the subject's awakening (median time since awakening 3 h, 38 min) to control for diurnal variation in hormone levels (20, 21). Two samples were drawn 30 min apart and pooled for analysis in equal aliquots to smooth episodic secretion (22). Testosterone and SHBG were measured by competitive electrochemiluminescence immunoassays on the 2010 Elecsys system (Roche Diagnostics, Indianapolis, IN). All assays were previously approved by the Food and Drug Administration for clinical use. The lower limits of detection for testosterone and SHBG were 2 ng/dl (0.07 nmol/liter) and 3 nmol/liter, respectively. Reference ranges are 260–801 ng/dl (9–27.8 nmol/liter) for testosterone and 14.5–48.4 nmol/liter for SHBG. The interassay coefficients of variation for testosterone at concentrations of 24, 275, and 700 ng/dl (0.8, 9.5, and 24.3 nmol/liter) were 7.4, 2.2, and 1.7%, respectively. For SHBG at 16.5, 25, and 64 nmol/liter, interassay coefficients of variation were 3.9, 2.4, and 2.2%, respectively. Free testosterone concentrations were calculated from total testosterone and SHBG concentrations using mass action equations (23, 24).

Symptomatic androgen deficiency

Our operational definition of androgen deficiency is based on an approach for the diagnostic evaluation of adult men suspected of having androgen deficiency recently proposed in a Clinical Practice Guideline by The Endocrine Society (16). In this approach, symptoms of low testosterone are used in conjunction with biochemical parameters to define androgen deficiency. This is consistent with our work using a different data set (*i.e.* the MMAS) (17) as well as work by others (14), and reflects the reality of clinical practice (*i.e.* seldom is a testosterone assay ordered in the absence of symptoms of androgen deficiency).

The Clinical Practice Guideline distinguished between two sets of symptoms related to androgen deficiency, with one set being more specific than the other: (1) of the more specific, "suggestive" set of symptoms, we have data available on libido, erectile dysfunction (ED), and osteoporosis/osteoporotic fracture; (2) of the nonspecific, "associated" symptoms, we have data available for lethargy, sleep disturbance, depressed mood, and low physical performance.

The presence of low libido was defined as follows: a response of "low" or "very low" to the question "Over the past 4 wk, how would you rate your level (degree) of sexual desire or interest?" (1, very high; 2, high; 3, moderate; 4, low; or 5, very low). Men with an International Index of Erectile Function score less than 17 were defined as having ED (25). Osteoporosis was defined as physician-diagnosed osteoporosis or fracture after age 50 yr. Nonspecific symptoms were defined as follows: sleep disturbance and depressed mood were measured with questions assessing symptoms over the last week, with yes/no responses; lethargy was assessed by the question "Did you have a lot of energy? (over the past 4 wk)", with presence indicated by responses "none of the time" or "some of the time"; low physical performance was indicated by a score in the lowest quintile of the physical component score of the SF-12 (26). Subjects were considered symptomatic if they had one of the specific symptoms (low libido, ED, or osteoporosis), or two or more of the nonspecific symptoms (sleep disturbance, depressed mood, lethargy, or low physical performance). Men who were symptomatic with total testosterone level less than 300 ng/dl (10.4 nmol/liter) and free testosterone level less than 5 ng/dl (0.17 nmol/liter) were defined as having symptomatic androgen deficiency (16). See Fig. 1 for a flow chart that displays how the algorithm was implemented.

Analytic sample

The BACH sample (n = 5506) was recruited from April 2002 through June 2005; this analysis considers men only (n = 2301). Of the 2301 male participants, blood samples were obtained on 1899 (82.5%). Of these, we excluded 10 men who were missing testosterone or SHBG data, 32 men on medications that are known to affect sex steroid levels (GnRH agonists and antagonists, androgens, estrogens, progestins, 5-α-reductase inhibitors, drospirenone, ketoconazole, danazol, and clomiphine), and 12 men with extreme outlying values (≥4 SD values from mean) of testosterone or SHBG. This left 1845 men as a base analysis sample. An additional 373 men who were missing any data on symptoms of androgen deficiency (low libido, ED, osteoporosis, lethargy, sleep disturbance, depressed mood, and low physical performance) were excluded from analyses focusing on symptoms or symptomatic androgen deficiency, leaving 1475 (78% of 1899).

Statistical analysis

Because of design requirements, BACH subjects had unequal probabilities of selection into the study. To be representative of the city of Boston, sampling weights were used to produce estimates for means and percentages that are representative of the male Black, Hispanic, and white population in Boston, Massachusetts, between the ages of 30 and 79 yr. Sampling weights account for oversampling of particular age, gender, and race and ethnic groups as well as subject nonresponse. Statistical analyses were conducted using SUDAAN 9.0.1 (Research Triangle Institute, Research Triangle Park, NC). χ^2 tests were performed to compare the analytic sample *vs.* those excluded from the analysis. In addition, a Wald test was used to test for age differences in the prevalence of symptomatic androgen deficiency. Results were considered statistically significant if null hypotheses could be rejected at the 0.05 level (two-sided). We estimated the number of existing prevalent cases of symptomatic androgen deficiency [based on 2000 Census data (http://www.census.gov/popest/national/asrh/NC-EST2006-sa.html)] as well as projected prevalence in the year 2025 [based on population projections from the Census (http://www.census.gov/ipc/www/usinterimproj/)] among men between 30 and 79 yr of age. To obtain these estimates, we multiplied the age-specific prevalence estimates times the number of men in each age group; the sum of these products represents an estimate of the number of men with symptomatic androgen deficiency in the specified population.

Results

The mean age of the analysis sample was 47.3 ± 12.5 yr (Table 1). The sample was mostly married or living with a partner

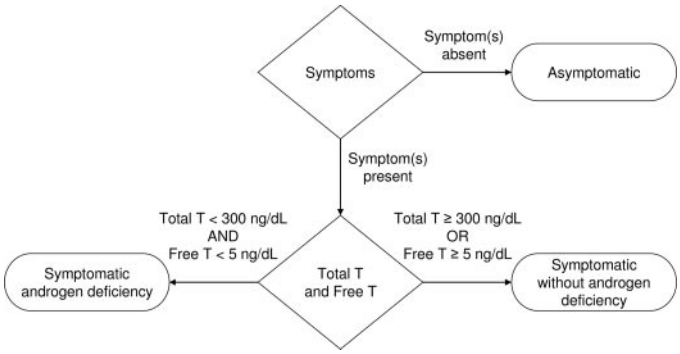

FIG. 1. Operational definition of symptomatic androgen deficiency. To convert from nanograms per deciliter to nanomoles per liter, multiply by 0.0347. T, Testosterone.

TABLE 1. Study sample characteristics overall and by race and ethnic group (n = 1845)

Variable	Overall (n = 1845)	Black (n = 523)	Hispanic (n = 641)	White (n = 681)
Age, yr	47.3 ± 12.5	47.6 ± 12.0	44.1 ± 10.8	47.8 ± 12.9
Age group				
30–39 yr	507 (38.0)	126 (35.2)	209 (47.2)	172 (37.1)
40–49 yr	539 (25.9)	168 (28.4)	191 (28.6)	180 (24.4)
50–59 yr	423 (17.6)	125 (19.0)	137 (14.4)	161 (17.7)
60–79 yr	376 (18.5)	104 (17.3)	104 (9.8)	168 (20.8)
Married or with partner	1,025 (55.2)	238 (48.0)	432 (64.6)	355 (56.1)
Education, yr	14.8 ± 4.1	13.2 ± 3.3	11.4 ± 5.0	16.1 ± 3.6
Household income < $10k	402 (14.1)	138 (24.0)	181 (25.6)	83 (7.8)
Self-reported health, fair/poor	418 (14.9)	109 (17.5)	221 (29.7)	88 (10.7)
Diabetes	221 (9.3)	83 (13.8)	88 (10.5)	50 (7.3)
Alcohol consumption				
No drinks per day	618 (26.1)	183 (33.3)	256 (33.7)	179 (21.5)
Less than one drink per day	674 (40.3)	174 (35.1)	229 (40.0)	271 (42.4)
One or more drinks per day	551 (33.7)	166 (31.6)	155 (26.3)	230 (36.1)
Smoking status, current	530 (25.9)	204 (33.3)	153 (24.4)	173 (23.2)
Smoking pack years				
No pack years	808 (46.2)	210 (45.0)	304 (53.3)	294 (45.1)
<2.5 pack years	243 (13.3)	70 (15.0)	101 (15.9)	72 (12.1)
2.5 to <10 pack years	244 (12.5)	88 (17.0)	82 (11.6)	74 (10.8)
10 to <20 pack years	211 (11.4)	68 (9.1)	65 (10.3)	78 (12.6)
≥20 pack years	339 (16.6)	87 (14.0)	89 (9.0)	163 (19.3)
Weight, kg	89.1 ± 19.4	89.9 ± 20.7	82.5 ± 15.8	90.2 ± 19.4
Body mass index, kg/m^2	28.7 ± 5.6	29.3 ± 6.5	28.5 ± 4.8	28.5 ± 5.4
Obesity, body mass index ≥ 30 kg/m^2	618 (33.5)	197 (40.6)	210 (32.2)	211 (31.0)

Data represent mean ± SD or number (percent). Estimates are weighted inversely to the probability of selection.

(55%), relatively highly educated (mean 15 yr), and in relative good health—with only 15% reporting fair or poor health and 9% reporting diabetes. One quarter of the sample were current smokers, 17% were heavy smokers (≥20 pack years exposure), one third reported consuming one or more drinks per day, average weight was 89.1 kg (196 lb) and the prevalence of obesity (BMI ≥ 30 kg/m^2) was 34%. There was considerable race and ethnic variation in marital status, socioeconomic status, health status, and lifestyle factors. Obesity was significantly more prevalent in Black compared with Hispanic ($P = 0.04$) and white ($P = 0.02$) men. We compared members of the analysis sample with complete symptom data (n = 1475) to those not in the analysis sample (n = 826) on age, self-reported health, smoking status and smoking pack years, and BMI and found no differences between the groups (all $P > 0.45$).

Table 2 shows summary statistics for the serum measures studied by race and ethnic group. Mean total and free testosterone was 437.8 ± 180.1 ng/dl (15.2 ± 6.2 nmol/liter) and 9.1 ± 3.7 ng/dl (0.32 ± 0.13 nmol/liter), respectively, and mean SHBG was 34.0 ± 17.7 nmol/liter. Approximately 24% of subjects had total testosterone less than 300 ng/dl (10.4 nmol/liter), whereas almost 11% of subjects had free testosterone less than 5 ng/dl (0.17 nmol/liter). Most subjects (75%) had both normal total and free testosterone levels and 9.3% had both low total and free testosterone levels. Consistent with analyses reported previously (27), we found little evidence of variation in these serum parameters by race and ethnic group. Therefore, remaining analyses were conducted without consideration of race and ethnicity.

Age trends in the prevalence of low total/free testosterone and elevated SHBG are shown in Fig. 2. The age trend in the proportion of men with low free testosterone increased at a faster rate than the proportion of men with low total testosterone due to a sharp rise in the proportion of men with elevated SHBG.

Table 3 shows associations between the cross-classification of total and free testosterone category and symptoms of androgen deficiency. With the exception of osteoporosis, we

TABLE 2. Total/free testosterone and SHBG overall and by race and ethnic group (n = 1845)

Variable	Overall (n = 1845)	Black (n = 523)	Hispanic (n = 641)	White (n = 681)
Total T, ng/dl[a]	437.8 ± 180.1	447.3 ± 196.5	439.4 ± 186.8	433.7 ± 171.7
Free T, ng/dl[a]	9.1 ± 3.7	9.3 ± 4.0	9.4 ± 3.9	9.0 ± 3.5
SHBG, nmol/liter	34.0 ± 17.7	35.2 ± 20.7	31.9 ± 16.2	34.0 ± 16.6
Total T < 300 ng/dl	457 (24.3)	122 (26.6)	156 (21.2)	179 (24.0)
Free T < 5 ng/dl	218 (10.6)	63 (12.4)	70 (8.8)	85 (10.2)
Total T by free T category				
Total T < 300 ng/dl, free T < 5 ng/dl	186 (9.3)	49 (10.2)	63 (7.9)	74 (9.2)
Total T > 300 ng/dl, free T ≥ 5 ng/dl	271 (15.0)	73 (16.4)	93 (13.3)	105 (14.8)
Total T ≥ 300 ng/dl, free T > 5 ng/dl	32 (1.3)	14 (2.2)	7 (0.9)	11 (1.0)
Total T ≥ 300 ng/dl, free T ≥ 5 ng/dl	1356 (74.4)	387 (71.2)	478 (77.9)	491 (75.0)

Data represent mean SD or number (percent). Estimates are weighted inversely to the probability of selection. T, Testosterone.
[a] To convert to nanomoles per liter, multiply values by 0.0347.

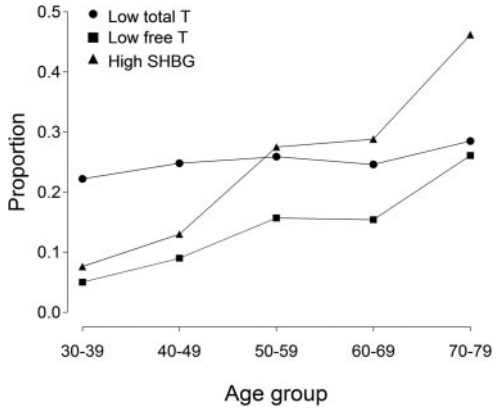

FIG. 2. Proportion of men with low total testosterone [<300 ng/dl (10.4 nmol/liter)], low free testosterone [<5 ng/dl (0.17 nmol/liter)], and high SHBG (>46.25 nmol/liter, defined as highest quintile of SHBG) by 10-yr age group. T, Testosterone.

observed substantial variation in the prevalence of symptoms among the four total/free testosterone groups. The validity of our definition of symptomatic androgen deficiency is supported by a higher prevalence of low libido, ED, and two or more of the nonspecific symptoms among men with low total and free testosterone levels compared with other total/free testosterone groups. Sensitivity analyses examining the effect of increasing the free testosterone cutpoint from 5 ng/dl (0.17 nmol/liter) to 6 ng/dl (0.20 nmol/liter) or 7 ng/dl (0.24 nmol/liter) showed lower specificity in terms of symptom prevalence among the group low on both total and free testosterone. As an example, among men with total testosterone less than 300 ng/dl (10.4 nmol/liter), the prevalence of low libido in men with free testosterone less than 5 ng/dl (0.17 nmol/liter) was 28.1% (*vs.* a base rate of 11.6%). Increasing the cutpoint to free testosterone less than 6 ng/dl (0.20 nmol/liter) and less than 7 ng/dl (0.24 nmol/liter) decreased the prevalence of low libido to 23.9 and 19.8%, respectively. Similar results were obtained for ED and two or more of the nonspecific symptoms.

Depicted in Fig. 3 are Venn diagrams showing the interrelationships among symptoms, low total testosterone [<300 ng/dl (10.4 nmol/liter)], and low free testosterone [<5 ng/dl (0.17 nmol/liter)] among men less than age 50 yr and age 50+ yr. Positive symptom reports and low total and free testosterone were more common among older men. The presence of symptoms was more strongly related to testosterone levels in older as compared with younger men, as indicated by a greater degree of overlap between symptom presence and low total and free testosterone among older (52.4% with low total or free testosterone had symptoms) compared with younger (43.1% with low total or free testosterone had symptoms) men. It is noteworthy that, even in men aged 50+ yr, 47.6% of men with low testosterone levels were asymptomatic.

A total of 86 men met the criteria for symptomatic androgen deficiency, yielding a crude prevalence of 5.6% (95% confidence interval: 3.6%, 8.6%). Prevalence was not significantly related to race and ethnic group, with estimates as follows: Black (5.2%), Hispanic (4.4%), and white (5.9%). Restricting attention to trends in symptomatic androgen deficiency by age decade (Fig. 4A), prevalence was low in men younger than 70 yr (3.1%–7.0%), did not appear to rise in a dose-response fashion with age, but was significantly greater in the oldest age group (18.4%) compared with other groups (all pairwise comparisons, $P < 0.05$). However, the apparent lack of dose-response appears to be related to instability among men 60+ yr, as sample sizes within decade of age are relatively small. Figure 4B shows the clear increasing age trend in estimated prevalence of symptomatic androgen deficiency with a moving-average approach, which is not as impacted by small sample size. Projection of age-specific prevalence estimates to 2000 population data would suggest that there are 4.7 million American men 30–79 yr old with symptomatic androgen deficiency. Further projection to 2025 suggests that as many as 6.5 million American men in this age range will have symptomatic androgen deficiency.

Discussion

In this random-sample population-based study of 1475 men with complete symptom and testosterone data, we found that 5.6% of men had symptomatic androgen deficiency using a definition that incorporates both clinical symptoms and testosterone levels. The prevalence increased substantially with age. We found no evidence of a difference in prevalence by race and ethnic group, consistent with BACH data on race and ethnic differences in hormone levels reported previously (27).

Researchers have expressed concern about the nonspecific nature of the symptoms of androgen deficiency (13, 28), concerns that are supported by the relatively low specificity of screening instruments for androgen deficiency (29–31). We showed that the relative percentages of low libido, ED, and two or more of the nonspecific symptoms were elevated

TABLE 3. Prevalence of symptoms overall and by total and free testosterone (nanograms per deciliter) category ($n = 1475$)

Variable	Overall (n = 1475)	Total T < 300 ng/dl, free T < 5 ng/dl (n = 145)	Total T < 300 ng/dl, free T ≥ 5 ng/dl (n = 228)	Total T ≥ 300 ng/dl, free T < 5 ng/dl (n = 25)	Total T ≥ 300 ng/dl, free T ≥ 5 ng/dl (n = 1077)
Low libido	202 (11.6)	38 (28.1)	37 (12.4)	6 (14.1)	121 (9.4)
ED	309 (16.3)	54 (27.7)	54 (21.1)	8 (17.8)	193 (13.9)
Osteoporosis/osteoporotic fracture	24 (1.4)	3 (1.3)	4 (3.1)	2 (4.4)	15 (1.1)
Two or more of the non-specific symptoms[a]	360 (20.0)	55 (42.8)	52 (17.6)	10 (23.8)	243 (17.6)

Data represent number (percent). Estimates are weighted inversely to the probability of selection. To convert to nanomoles per liter, multiply values by 0.0347. T, Testosterone.

[a] Overall number (prevalence): sleep disturbance [528 (33.0%)], lethargy [149 (11.2%)], depressed mood [298 (15.4%)], or low physical performance [348 (18.2%)].

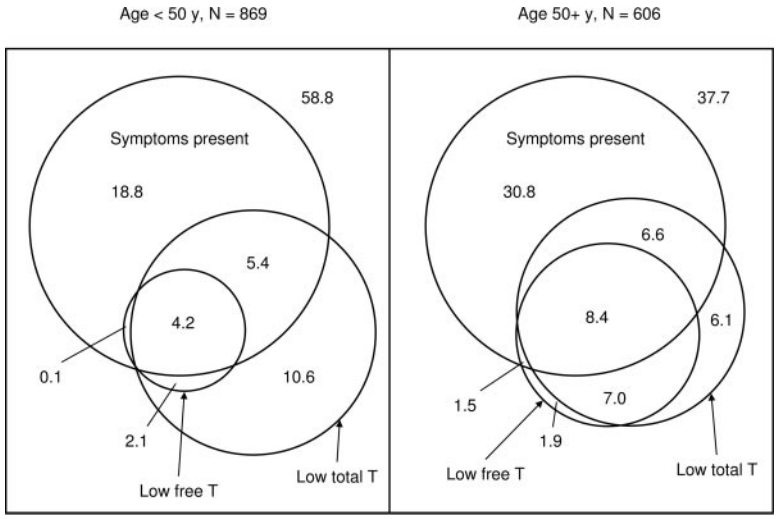

FIG. 3. Venn diagrams showing the interrelationships among symptoms, low total testosterone [<300 ng/dl (10.4 nmol/liter)], and low free testosterone [<5 ng/dl (0.17 nmol/liter)] among men less than 50 yr (left) and age 50+ yr (right). *Numbers* displayed are percentages within each area. Positive symptom reports and low total and free testosterone were more common among older men. The presence of symptoms was related more strongly to testosterone levels in older as compared with younger men as indicated by a greater degree of overlap between symptom presence and low total and free testosterone among older (52.4% of men with low total or free testosterone had symptoms) compared with younger (43.1% of men with low total or free testosterone had symptoms) men. The intersection of symptoms and low total and free testosterone levels was more common in older men (prevalence of symptomatic androgen deficiency was 4.2% among men < 50 yr and 8.4% among men 50+ yr). Note: *Circles* for the Venn diagrams are proportional within age strata. T, Testosterone.

in men with low testosterone levels compared with men with testosterone levels in the normal range. Also, with increasing age, the specificity of symptoms for low testosterone appeared to increase. Furthermore, there was a suggestion that low libido was more prevalent than ED in men with low total and free testosterone, despite the lower marginal probability of low libido. This is consistent with the work of Zitzmann *et al.* (32), showing that some symptoms of androgen deficiency might appear at higher concentrations of androgens than others. However, consistent with our previous work from MMAS on the association between low libido and testosterone (33), we also found that the majority of men with symptoms of androgen deficiency had normal testosterone levels and conversely, a considerable portion of men with low testosterone were asymptomatic. It is difficult to speculate on why these men with low testosterone levels do not exhibit symptoms, but recent data indicate that testosterone thresholds may be symptom-specific (32) or individual-specific (34), the latter potentially related to genetic differences that affect androgen sensitivity (35, 36). It could also be that the phenotype on which the symptoms of androgen deficiency are based (*i.e.* the generalized phenotype of hypogonadism observed in young men) does not apply in all respects to the aging male. Regardless of the mechanism, because these men would not likely come to clinical attention, it may be important to ask the question: what are the clinical risks of "missing" these asymptomatic men with low testosterone levels, if any? In future analyses, it will be of interest to determine whether symptomatic and asymptomatic men with low testosterone levels are at differential risk of poor skeletal health, frailty, anemia, metabolic syndrome/prediabetes, diabetes, and other outcomes postulated to have an underlying androgen component.

We previously have reported data from the MMAS on the prevalence of symptomatic androgen deficiency, showing a prevalence rate of 6% in the baseline data, which is comparable to BACH on mean age. Despite the potential impact of the age-independent population-level decline in testosterone levels reported in MMAS (18), we find no difference in the prevalence of symptomatic androgen deficiency in a cohort measured 20 yr later. This is mainly due to differences in how we operationally defined symptomatic androgen deficiency in the two studies, with the current approach consistent with the most recent (2006) clinical guidelines issued by The Endocrine Society (16). Specifically, in this analysis, more weight was given to specific symptoms (*e.g.* libido, ED, and osteoporosis) and we used more stringent testosterone cutpoints. Others have provided estimates of the percentage of men with symptoms and low testosterone. In a study of Hong Kong men between the ages of 45 and 64 yr, Wong

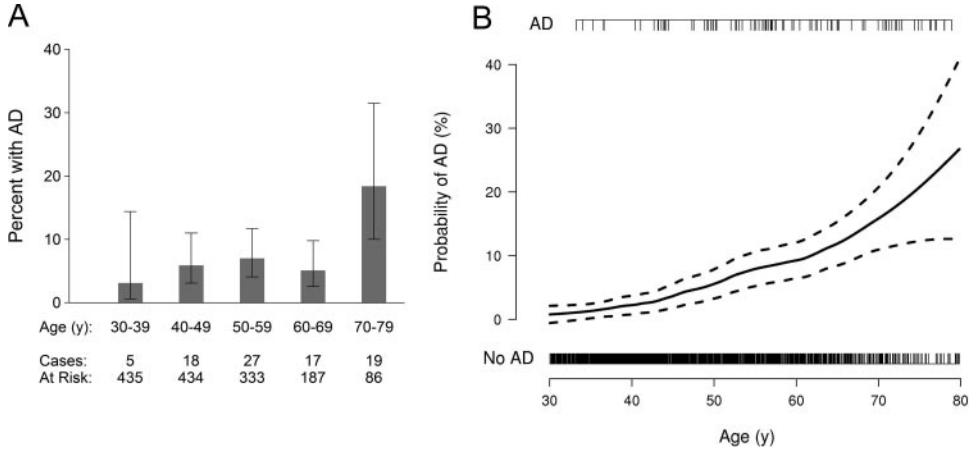

FIG. 4. A, Age-specific prevalence (95% confidence interval) of symptomatic androgen deficiency (AD). B, Estimated probability of AD (*solid line*) with 95% confidence intervals (*dotted lines*), *vs.* age. Estimates were obtained using a generalized additive model (43) for binary outcomes. The model uses a lowess smoothing term to approximate the relation between age and the log odds of AD. The one-way "rug" plots at the *top* and *bottom* depict the age distribution of subjects with and without AD.

et al. (37) reports a 9.5% prevalence of symptomatic androgen deficiency, using the same definition as in our previous MMAS publication. In that study, the prevalence was considerably higher only in the oldest group (60–64 yr: 16.7%). Kapoor *et al.* (38) estimated that 17% of diabetic subjects with a mean age of 58 yr had androgen deficiency defined as positive on symptoms and low total testosterone levels. Tan and Pu (39) reported that among 71 patients averaging 73 yr of age with at least one androgen deficiency symptom, 31% had low total testosterone levels [<300 ng/dl (10.4 nmol/liter)].

Potential limitations and strengths

Limitations and strengths of the current study should be noted. It has been shown that the Elecsys immunoassay has a low bias as compared with isotope-dilution gas chromatography-mass spectrometry (40), although other data indicate no difference with respect to liquid chromatography-tandem mass spectrometry (41). If there is a low bias associated with the Elecsys system, the prevalence of symptomatic androgen deficiency reported herein would be inflated. In analyses not presented, arbitrarily lowering the total testosterone cutpoint reduced the estimated prevalence, as one would expect. However, the association with age remained unchanged and the prevalence of symptoms was not markedly higher when using a lower cutoff (*e.g.* 200 ng/dl), especially for more specific symptoms of androgen deficiency such as libido or ED. A second limitation is that BACH was not designed to estimate the prevalence of symptomatic androgen deficiency, and the symptoms that might be the most sensitive and specific indicators of low testosterone [*e.g.* decreased testes size, low sperm count, low bone mineral density (BMD), or low muscle strength] were not measured, which might have caused us to underestimate the prevalence of symptomatic androgen deficiency. A subset of 1219 male BACH respondents participated in a study on skeletal health (42) where detailed measures of BMD and muscle strength were taken. We used these data to examine how supplementing the osteoporosis/fracture symptom with BMD-defined hip osteoporosis and replacing the low physical function symptom with grip strength affected our results. The effects of these modifications on the association between testosterone category and symptoms (reported in Table 3) or on prevalence estimates were very minor. Also, we were able to assess a broad range of symptoms identified in The Endocrine Society's Clinical Practice Guideline that are arguably more prevalent than those we were unable to measure, and therefore, might reflect the realities of time-constrained everyday clinical practice where rare symptoms are less likely to be discovered. Because testosterone is not a front-line biochemical measure in clinical practice, we made *a priori* decision rules with respect to symptom presence that might prompt a clinician to order a testosterone measurement. A particular strength of this study is that we gave more weight to the more specific indications of low testosterone (*i.e.* libido, ED, and osteoporosis), as might be done in a clinical setting. In addition, the racial and socioeconomic diversity of the sample is an advantage, supporting the potential ability to generalize these estimates. In fact, comparisons of the BACH sample with local [Boston Behavioral Risk Factor Surveillance System (BRFSS)] and national (the National Health and Nutrition Examination Survey, the National Health Interview Survey, and the national BRFSS) data bases shows that BACH is very comparable with respect to sociodemographic and health-related variables. Small differences were observed in the percentage likely to be employed (lower *vs.* BRFSS) and a higher prevalence of asthma in Boston than nationwide (19).

Conclusion

In conclusion, we provide data on the descriptive epidemiology of androgen deficiency in a racially and socioeconomically diverse representative sample of men. Consistent with our previous work (17), we estimate that there are a substantial number of men in the United States with symptomatic androgen deficiency, and that the aging of the U.S. population alone will increase this burden considerably. In no way do we mean to imply that all of these men who meet our operational criteria are candidates for testosterone therapy. Future clinical trials that enroll symptomatic patients with low testosterone levels are required to evaluate the risk-benefit ratio of testosterone therapy. Future work should also examine treatment patterns among men with symptomatic androgen deficiency and the profile of asymptomatic men with low testosterone levels, which might assist in understanding the mechanisms by which low testosterone levels increase risk of disease.

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