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What Is a Normal Testosterone Level for Young Men? Rethinking the 300 ng/dL Cutoff for Testosterone Deficiency in Men 20-44 Years Old

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Study Need and Importance: Testosterone reference ranges for older men are long established in the urological literature. However, few studies have examined testosterone levels in young men. As a result, clinicians have struggled to counsel and evaluate young men presenting with concerns about testosterone deficiency. Contributing to this struggle is the fact that testosterone levels decline with age, yet we use the same age-independent cutoffs to evaluate young men for testosterone deficiency as we do for older men. In response, we performed the first study evaluating population-based testosterone levels for younger men in the United States. We also used the 2018 American Urological Association guideline for testosterone deficiency definition of a "normal testosterone" as the middle tertile of the population, to provide age-specific cutoffs for low testosterone levels in younger men.

What We Found: The mean total testosterone of men 20-44 years old was 466 ng/dL. Middle tertile, "normal" testosterone levels were 409-558 ng/dL (20-24 years old), 413-575 ng/dL (25-29 years old), 359-498 ng/dL (30-34 years old), 352–478 ng/dL (35-39 years old), and 350-473 ng/dL (40-44 years old). Age-specific cutoffs for low testosterone levels were 409, 413, 359, 352, and 350 ng/dL, respectively (see Figure).

Limitations: Our age-specific cutoffs for testosterone are modeled on the American Urological Association guideline definition that a normal testosterone level is within the middle tertile. However, no randomized controlled trials have been performed to select the middle tertile as a cutoff value. Additionally, our study is limited by some shortcomings of the National Health and Nutrition Examination Survey database. Namely, the National Health and Nutrition Examination Survey does not specifically query men for hypogonadal signs and symptoms, and only 1 serum testosterone value was obtained from each subject.

Interpretation for Patient Care: Clinicians should integrate age-specific cutoffs into the evaluation of younger men presenting with testosterone deficiency. Age-specific cutoffs will be useful in evaluating younger patients with hypogonadal symptoms who have historically been disqualified from treatment based on age-independent cutoffs.

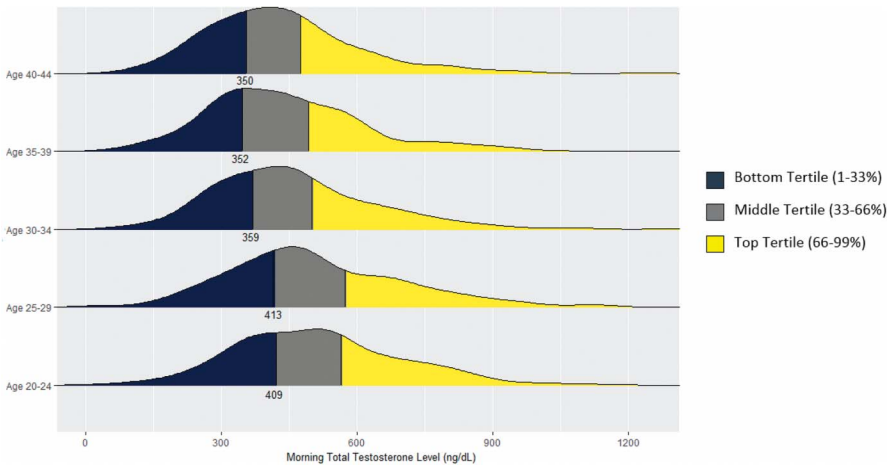

Figure. Morning total testosterone level (ng/dL) distributions by age group.

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What Is a Normal Testosterone Level for Young Men? Rethinking the 300 ng/dL Cutoff for Testosterone Deficiency in Men 20-44 Years Old

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Conflict of Interest: SD-N: American Urological Association; JMD: NICHD, Blue Cross Blue Shield of Michigan, Posterity Health, Lipocine.

Ethics Statement: In lieu of a formal ethics committee, the principles of the Helsinki Declaration were followed.

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Editor's Note: This article is the fifth of 5 published in this issue for which Category 1 CME credits can be earned. Instructions for obtaining credits are given with the questions on pages 1362 and 1363.

Purpose: There is an age-related decline in male testosterone production. It is therefore surprising that young men are evaluated for testosterone deficiency with the same cutoff of 300 ng/dL that was developed from samples of older men. Our aim is to describe normative total testosterone levels and age-specific cutoffs for low testosterone levels in men 20 to 44 years old.

Materials and Methods: We analyzed the 2011-2016 National Health and Nutrition Examination Surveys, which survey nationally representative samples of United States residents. Men 20 to 44 years old with testosterone levels were included. Men on hormonal medications, with a history of testicular cancer or orchiectomy, and with afternoon/evening laboratory values were excluded. We separated men into 5-year intervals and evaluated the testosterone levels of each age group, and for all men 20 to 44 years old. We used the American Urological Association definition of a "normal testosterone level" (the "middle tertile") to calculate age-specific cutoffs for low testosterone levels.

Results: Our final analytic cohort contained 1,486 men. Age-specific middle tertile levels were 409-558 ng/dL (20-24 years old), 413-575 ng/dL (25-29 years old), 359-498 ng/dL (30-34 years old), 352-478 ng/dL (35-39 years old), and 350-473 ng/dL (40-44 years old). Age-specific cutoffs for low testosterone levels were 409, 413, 359, 352, and 350 ng/dL, respectively.

Conclusions: Diagnosis of testosterone deficiency has traditionally been performed in an age-indiscriminate manner. However, young men have different testosterone reference ranges than older men. Accordingly, age-specific normative values and cutoffs should be integrated into the evaluation of young men presenting with testosterone deficiency.

Key Words: testosterone, hypogonadism

Testosterone deficiency, which is defined as a combination of low serum testosterone levels plus signs and symptoms of hypogonadism, affects 4.0 to 13.8 million[1,2] men in the U.S. Although traditionally thought of as a disease affecting elderly men, young men are increasingly presenting with concerns related to testosterone deficiency. In addition, testosterone levels, sperm counts, and fertility have declined in young men over the past 2 decades.[3] However, the diagnosis of testosterone deficiency in young men remains challenging. Whereas symptoms such as decreased libido or erectile dysfunction are common in older men, young men often present with less specific symptoms such as low energy and fatigue.[4]

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Another significant challenge in evaluating young men for testosterone deficiency is uncertainty about what constitutes a "normal" testosterone level in these men. Testosterone levels decline with age,[5] yet we historically have used the same age-independent cutoffs to evaluate young men as we use for older men. The American Urological Association (AUA) guideline suggests using a cutoff for low testosterone of 300 ng/dL when evaluating adult men.[6] However, this age-independent 300 ng/dL cutoff has 3 problems for young men. First, this cutoff was derived from testosterone replacement trials that primarily studied men above the age of 45.[6] Second, as described above, it is known that testosterone levels decline with age.[5] Third, there are competing cutoffs reported in literature[2,7] and from professional societies such as the American Association of Clinical Endocrinologists (200 ng/dL),[8] Endocrine Society (264 ng/dL),[9] British Society of Sexual Medicine (345 ng/dL),[10] European Association of Urology (345 ng/dL),[11] International Society of Sexual Medicine (350 ng/dL),[12] and the International Society for Study of Aging Male (350 ng/dL;[13] Table 1). The 2018 AUA guideline for testosterone deficiency recognized our knowledge gap about normal testosterone levels for men of different ages and specifically called for the development of age-specific reference ranges for testosterone.[6]

Therefore, we used the National Health and Nutrition Examination Survey (NHANES) to evaluate normative total testosterone levels and to estimate age-specific testosterone reference ranges for men 20 to 44 years old. We also calculated age-specific cutoffs for low testosterone levels by utilizing the 2018 AUA guideline's definition of a "normal testosterone" as residing within the middle tertile of testosterone levels. With over 55 million men in the U.S. between 20 and 44 years old,[14] our findings can help clinicians improve their counseling of young men presenting with concerns about testosterone deficiency.

MATERIALS AND METHODS

Data Source

We used the 2011 to 2016 NHANES data to evaluate testosterone levels in U.S. men 20 to 44 years old. The NHANES are cross-sectional, population-based surveys run by the Centers for Disease Control and Prevention. These surveys combine personal interviews with standardized physical examinations and laboratory tests to collect data on a nationally representative sample of the U.S. population.[15] Each year, NHANES surveys approximately 5,000 people from a sampling of U.S. counties. NHANES samples participants across 60-80 sampling domains (eg, age, sex, race, income), and oversamples various groups to produce reliable estimates of the U.S. population.[15] Sampling weights are used to account for differential probabilities of selection and nonresponse among different groups.[16] In lieu of a formal ethics committee, the principles of the Helsinki Declaration were followed.

Table 1. *Total Testosterone Cutoffs for Testosterone Deficiency Recommended by Different Professional Organizations*

Guideline	Total testosterone cutoff (ng/dL)
American Association of Clinical Endocrinologists[8]	200
Endocrine Society[9]	264
American Urological Association[6]	300
British Society of Sexual Medicine[10]	345
European Association of Urology[11]	345
International Society of Sexual Medicine[12]	350
International Society for Study of Aging Male[13]	350

Study Population

We included 20- to 44-year-old men with morning total testosterone levels (6:00 a.m. to 10:00 a.m.). We focused on morning testosterone levels because there are diurnal variations in testosterone levels, especially for young men.[17] We excluded men on hormonal medications (eg, testosterone injections; n=11), men with a history of testicular cancer (n=0), men with history of orchiectomy (n=5), and men with afternoon or evening blood draws (n=1,936). Additionally, among men with morning laboratory values, men with missing testosterone levels (n=106) were excluded (Fig. 1).

Testosterone Testing

From 2011 to 2016, NHANES used isotope dilution high-performance liquid chromatography/tandem mass spectrometry for quantification of total testosterone in accordance with the National Institute for Standards and Technology's reference method. Mass spectrometry is considered the gold standard for evaluating testosterone levels.[18] Isolation of the analyte was achieved using liquid-liquid extraction. Additional details about the reliability, validation, and quality control of testosterone levels is available in NHANES laboratory methods.[19]

Data Analyses

We obtained total testosterone results from the NHANES database and grouped men into 5-year age intervals (20-24, 25-29, 30-34, 35-39, and 40-44 years old). We calculated the 2.5th, 5th, 10th, 25th, 33rd, 50th, 66th, 75th, and 90th percentile testosterone levels for the final analytic cohort of

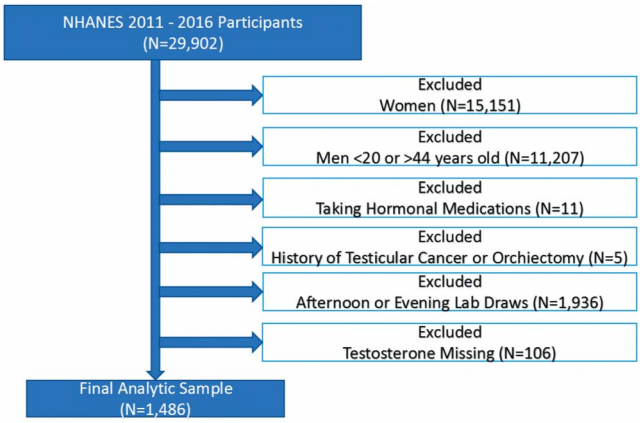

Figure 1. Consort diagram. NHANES indicates National Health and Nutrition Examination Survey.

Table 2. *Population Description (N= 1,486)*

Age, median (IQR), y	31.7 (25.1-38.4)	
Body mass index, median (IQR), kg/m^2	27.9 (24.0-37.8)	
No. race, weighted percentage (SE)		
Mexican American	229, 13	(1.6)
Non-Hispanic Black	265, 9.7	(1.1)
Non-Hispanic White	554, 60	(2.6)
Other Hispanic	151, 8.4	(1.1)
Other race	287, 9.3	(1.0)

Abbreviation: SE, standard error.

20- to 44-year-old men overall and for each 5-year age group. Additionally, we fit a linear regression model with testosterone as the dependent variable and age as a continuous variable to assess the association between a per year increase of age and testosterone levels. All analyses were performed using survey procedures in SAS to account for the complex sampling design. Weights were divided by one-third to account for combining 3 NHANES study periods in accordance with NHANES standard analysis procedures.[20] We used SAS 9.4 at the 5% significance level for all analyses with 95% confidence intervals based on the multistage stratified design of NHANES.[21]

Determining "Low" Testosterone Levels for Young Men

The 2018 AUA guideline for testosterone deficiency defines normal testosterone levels as the middle tertile of the population.[6] The guideline also states that "age-adjustments should be made to define this middle range." Therefore, we calculated the middle tertile, the 33rd and 66th percentiles to define normal testosterone levels for each 5-year age grouping and for all men aged 20 to 44 years old. We then used the 33rd percentile to determine age-specific cutoffs for low testosterone levels for men in each 5-year age grouping as well as in all men 20 to 44 years old.[6]

RESULTS

Our final analytic cohort contained 1,486 men 20 to 44 years old. This cohort represents a weighted sample of 22, 496, 685 U.S. men. The age, race, and BMI characteristics of the study population are presented in Table 2. The average age was 32 years old. There was a relatively equal distribution of men in each age grouping; 20% of the weighted population was 20-24 years old, 19% was 25-29 years old, 19% was 30-34 years old, 20% was 35-39 years old, and 22% was 40-44 years old. Since NHANES is a weighted sample, the distribution of race was representative of the U.S. population.

Total morning testosterone levels are described in Table 3. The mean total testosterone of men 20-44 years old was 466 ng/dL. There was an age-related decline in testosterone levels, with 25- to 29-year-old men having the highest mean testosterone (514 ng/dL) and 40- to 44-year-old men having the lowest mean testosterone (430 ng/dL; Fig. 2). Between 20 and 44 years old, each increase in 1 year of age was associated with a decrease in testosterone of 4.3 ng/dL ($P < .0001$, SEM 0.669).

The middle tertile of testosterone levels for men 20 to 44 years old overall was 374 ng/dL to 511 ng/dL. Age-specific middle tertile levels were 409-558 ng/dL for men 20-24 years old, 413-575 ng/dL for 25-29 years old, 359-498 ng/dL for 30-34 years old, 352-478 ng/dL for 35-39 years old, and 350-473 ng/dL for 40-44 years old. Age-specific cutoffs for low testosterone levels—representing the 33rd percentile per the AUA guideline—were 409 ng/dL (20-24 years old), 413 ng/dL (25-29 years old), 359 ng/dL (30-34 years old), 352 ng/dL (35-39 years old), and 350 ng/dL (40-44 years old), and are described in Table 3 and Figure 2.

DISCUSSION

In this study, we provide the first evaluation of normative, population-based testosterone levels for young men in the United States. We also used the 2018 AUA guideline's definition of "normal testosterone" levels to provide the first age-specific cutoffs for low testosterone levels from a nationally representative population. These findings will provide valuable information that clinicians can use in the evaluation and management of young men presenting with concerns about testosterone deficiency.

Testosterone reference ranges for older men are long established in the urological literature.[22] However, few studies have examined testosterone levels in young men. In an attempt to bridge this gap, the Endocrine Society commissioned a study in 2017 to evaluate testosterone reference ranges for young men.[23] This study pooled morning testosterone samples from the Framingham Heart Study and Sibling Study of Osteoporosis and found that average testosterone levels for 19- to 39-year-old men were between 228 and 895 ng/dL.[23] However, there are multiple issues with the makeup of the Framingham Heart Study and Sibling Study of Osteoporosis cohorts. The Framingham Heart Study was composed exclusively of sons and brothers from Framingham, Massachusetts consisted entirely of European Americans, and excluded patients with most comorbid conditions.[24] The Sibling Study of Osteoporosis was similarly composed of 92% brothers who resided in Ghent, Belgium, and who were all Caucasian and healthy.[25] Other studies evaluating testosterone levels in young men suffer from a similar lack of diversity in their study populations.[26]

Our study builds upon these previous attempts to evaluate normal testosterone levels in younger men by utilizing the strengths of the NHANES database to examine testosterone levels in a diverse, comorbid, and nationally representative population. Whereas previous studies examined "healthy, nonobese young men without major comorbidities,"[23] our study includes all men regardless of comorbidities, as long as they were not on hormonal medications or had a history of

Table 3. *Total Morning Testosterone Levels by Age Group*

Age group, y	Mean morning testosterone (ng/dL)	SEM	Percentile								
			2.5th	5th	10th	25th	33rd[a]	50th	66th	75th	90th
20-24	501	12.7	189	225	283	376	409	484	558	604	757
25-29	514	17.6	177	217	273	372	413	491	575	643	771
30-34	456	12.8	178	222	266	326	359	421	498	559	678
35-39	438	11.8	169	193	259	323	352	423	478	533	632
40-44	430	11.0	184	220	247	311	350	418	473	504	640
All men	466	8.0	177	216	261	337	374	444	511	563	712

Abbreviation: SEM, standard error of mean.
[a] The 33rd percentile was used to determine age-specific cutoffs for low testosterone levels for men in each 5-year age grouping as well as in all men 20 to 44 years old.

testicular cancer or orchiectomy. Additionally, our cohort was selected from a weighted sample of U.S. counties, which is useful since testosterone levels can vary by 20% depending on location of residence.[27] Furthermore, men in our study were not from related families, and ethnic/racial subgroups were weighted and sampled to ensure a nationally representative result. This diversity is important because ethnic/racial heritage has been associated with differences in testosterone levels as well.[28] Taken together, the intentional heterogeneity of our NHANES cohort may provide a more accurate representation of the normative testosterone levels for young men in the U.S., regardless of comorbidities, location, or ethnic/racial background.

Our study has several limitations. First, our decision to use the 33rd percentile as a cutoff for low testosterone is based on the AUA guideline recommendation that normal testosterone lies within the middle tertile. No randomized control trials were performed to select the 33rd percentile as a cutoff value. Nevertheless, the AUA guideline committee analyzed multiple population epidemiological studies to arrive at this suggested cutoff. Even if one were to choose a different cutoff, our age-specific normative testosterone ranges still provide young men and their physicians a framework for counseling (Table 3). Second, NHANES only obtained 1 serum testosterone value from each subject. Studies have shown that 30%-35% of men who are classified as hypogonadal based on a single low total testosterone subsequently have normal total testosterone levels over the next 24 hours. Thus, 2 low total testosterone values are recommended to confirm the diagnosis of low testosterone.[29] The NHANES do not perform second blood draws, however, we believe the strengths of the NHANES data source outweigh this weakness. Third, the NHANES does not contain data about hypogonadal symptoms—it only contains serum testosterone laboratory values. However, lab values are a key component of counseling for testosterone deficiency, and reference ranges are often

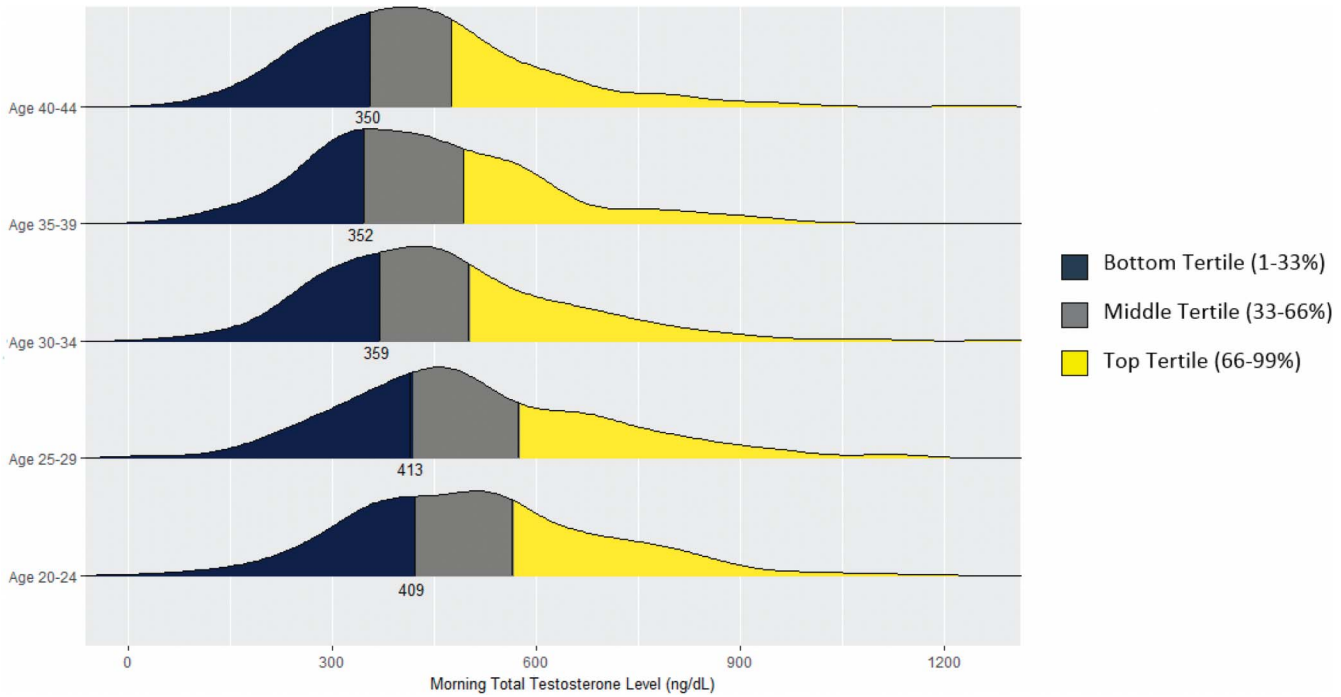

Figure 2. Morning total testosterone level (ng/dL) distributions by age group.

questioned by young men in clinic. Additionally, because NHANES does not ask about hypogonadal symptoms, our population invariably contained some men with symptomatic, clinical hypogonadism. Thus, the normative values we provide may underestimate the testosterone values for asymptomatic men. Nevertheless, patients with hypogonadal symptoms are present within the general population and their testosterone levels are part of the physiological range of testosterone levels for all men. Fourth, the NHANES does not provide information about bioavailable or free testosterone. Bioavailable or free testosterone are unable to be calculated due to a lack of data regarding sex hormone-binding globulin in the 2011 to 2012 NHANES data. Finally, we chose to use 5-year age intervals when creating our normative values to strike a balance between longer, 10-year intervals that have been used in other testosterone studies and narrower 1-year age intervals that could be more difficult to remember. Nevertheless, if clinicians needed wider or narrower age-based values, they could be derived from NHANES using the methods we described above.

These limitations notwithstanding, our findings have important implications for clinicians, patients, payers, and policy makers. Our age-specific cutoffs for low testosterone levels can help clinicians who have struggled with diagnosing testosterone deficiency in young men. In today's age of personalized medicine, clinicians can now use age-specific testosterone levels to evaluate young men instead of relying on a "one size fits all" approach. For patients, we offer normative reference ranges that can be used to compare their testosterone levels to age-matched peers. Our cutoffs also benefit young men who experience hypogonadal symptoms but who have historically been disqualified from treatment based on the age-independent 300 ng/dL cutoff. Patients may also receive financial benefit from these cutoffs, as many insurance companies currently do not cover testosterone therapies if a man's testosterone is >300 ng/dL. For payers and policy makers, these age-specific cutoffs may serve as evidence-based benchmarks to guide coverage decisions for treatment of hypogonadism. Notably, young men in their reproductive years must understand that testosterone therapy can suppress spermatogenesis and must be pursued with caution if they are interested in current or future paternity.[30]

CONCLUSIONS

Our findings suggest that young men have different testosterone reference ranges than older men; management of young men should accordingly reflect these differences. In particular, providers should question the use of an age-independent cutoff for young men and should integrate age-specific cutoffs into their evaluation of young men presenting with testosterone deficiency. Future research should correlate these age-specific cutoffs to hypogonadal symptoms and responses to treatment. Development of age-specific reference ranges and cutoffs for free testosterone and sex hormone-binding globulin may also be useful in the future management of young men with hypogonadism.

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EDITORIAL COMMENTS

In this study, the authors have undertaken the task of more appropriately characterizing the testosterone cutoffs for testosterone deficiency in men aged 20-44 years. The authors did this through analysis of 2011-2016 National Health and Nutrition Examination Survey (NHANES) data to obtain nationally representative samples of United States residents in 5-year age increments. Men with confounding medical histories including hormonal medications, testicular cancer, orchiectomies, and non-morning labs were appropriately excluded. The authors found age-specific cutoffs for low testosterone that differed from the American Urological Association guideline standard of 300 ng/dL.[1]

The NHANES database remained consistent in measurement of total testosterone in serum using isotope dilution liquid chromatography tandem mass spectrometry from 2011 to 2016.[2] This method is the gold standard for testosterone level determination and has demonstrated high accuracy and precision in serum evaluation. Still, caution should be taken when exploring the NHANES data set for hypogonadism, as associated survey data is obtained from physical functioning and sexual behavior questionnaires, none of which contain validated investigation that reflects signs and symptoms of low testosterone. Thus, reliable conclusions towards hypogonadal diagnoses from this dataset are not readily drawn.

The ranges proposed herein by the authors may determine eligibility of therapy to those who may otherwise be overlooked or held to a standard by which men are judged on the basis of non-aged-matched counterparts. The referenced age-specific middle tertiles, combined with hypogonadal symptoms, would provide a reasonable target for restoration of testosterone to normal levels in men aged 20-44 years. As this particular population of men may not otherwise have routine health screenings and have other health considerations, such as preservation of fertility, it's important they be evaluated in a care capacity that will investigate and identify problems through a comprehensive men's health evaluation.

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Hypogonadism is a common concern among men in the United States and is only becoming more common in younger men.[1] This article uses the well-regarded National Health and Nutrition Examination Survey study to better define age-specific low testosterone levels, specifically in men under the age of 44. For years we have used an age independent cutoff to define hypogonadism, using values (200-350 ng/dL) that the major medical societies cannot even agree upon. As most of those data are based on men over the age of 45 years, they have little applicability to younger men.[2] This study attempts to define what is a "normal" testosterone level in young men. Unfortunately, given the high incidence of hypogonadism in the population, at least some of these men would have hypogonadism, which likely skewed these data. Like many previous studies on low testosterone published before, I do not know if this study definitively gives us "normal" testosterone ranges in this cohort and may have actually underestimated the true testosterone levels. Regardless, this study provides important data for urologists and other men's health professionals that will only further our care of this patient population. Medical societies and guideline committees should take note of these and other similar findings and begin to develop more nuanced recommendations for the treatment of hypogonadism, especially in younger men.

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REPLY BY AUTHORS

In 2018, the American Urological Association released its guideline on the management of testosterone deficiency.[1] In this guideline, clinicians were recommended to use a total testosterone of <300 ng/dL as the cutoff for low testosterone. As noted by Tadros and Campbell, the applicability of this cutoff for may be limited for younger men.

We thank Tadros and Campbell for their thoughtful editorials. They helpfully point out that since the National Health and Nutrition Examination Survey (NHANES) does not query patients about hypogonadal symptoms, the men in NHANES with lower testosterone levels likely include those with and without hypogonadal symptoms. As a result, we believe that the age-specific cutoffs for low testosterone we propose are likely conservative estimates of a "low" testosterone. If men with symptomatic hypogonadism (and presumably lower testosterone levels) were excluded, our cutoff values would likely be higher. Despite this limitation, our potentially conservative cutoffs are a step in the right direction for evaluating younger men with real hypogonadal symptoms who are currently excluded from treatment due to the age-independent <300 ng/dL cutoff. It should be noted that other medical societies, such as the Endocrine Society, European Association of Urology, and the International Society for Sexual Medicine, also use age-independent cutoffs in their guidelines. Age-specific cutoffs such as the ones we propose from NHANES allow clinicians to identify the lower range of testosterone levels for younger men and provide improved baselines to consider therapy. We believe our cutoffs fill knowledge gaps about what constitutes a "low" testosterone in younger men and addresses the American Urological Association guideline's explicitly stated need to develop age-specific reference ranges for testosterone.

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