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The association of cardiorespiratory fitness, body mass index, and age with testosterone levels at screening of healthy men undergoing preventive medical examinations: The Cooper Center Longitudinal Study

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ABSTRACT

Background: Currently, exogenous hormone replacement is used in many men with hypogonadism without clear organic cause. This study examines the contribution of modifiable health behaviors, i.e., physical activity and weight control, to the maintenance of testosterone levels with aging.
Methods: In a cross-sectional study of 2994 healthy men aged 50–79 years examined at a preventive medicine clinic from January 2012 to March 2016, screening morning total testosterone levels were measured and categorized as low (< 250 ng/dL), low normal (250–399 ng/dL), and normal (> 400 ng/dL). Cardiorespiratory fitness (fitness) was estimated from a maximal exercise treadmill test. Multiple logistic regression models were used to test the associations between low testosterone levels and age, body mass index (BMI), and fitness.
Findings: Mean testosterone levels were in the normal range for each age group (50–59, 60–69, and 70–79). There was a similar prevalence of low testosterone in each age group (11·3%, 10%, and 10·5%, respectively). The prevalence of low testosterone was positively associated with BMI and negatively associated with fitness but was not associated with age.
Interpretation: This study found no evidence that low testosterone is an inevitable consequence of aging. Maintenance of healthy weight and fitness may help maintain normal testosterone levels.

1. Introduction

Most previous cross-sectional and longitudinal studies report declines in total testosterone levels in men with increasing age. [1–3] Estimates of these reductions range from 0.2% per year in cross-sectional studies to 1.6% per year in longitudinal studies [1,2]. However, other have reported no changes in total testosterone with age. [4–6] In the midst of this uncertainty, the contribution of age to lower testosterone levels, versus what might be attributable to weight gain, decreased physical activity, chronic illness, and other factors that become more prevalent as men age, has not been adequately addressed.

There has been a 12-fold increase in testosterone prescriptions from 2000 to 2011 globally, and a 3-fold increase in testosterone prescriptions in U.S. men over the past decade. [7,8] These trends have raised concerns given that the potential risks associated with testosterone use have not been robustly studied in large groups of healthy and unhealthy men across a broad age spectrum [9–11]. The potential benefit of healthy lifestyle behaviors on maintenance of testosterone levels is not well characterized and could be one way to avoid unnecessary use of exogenous testosterone. One study evaluating lifetime exercisers versus sedentary males showed that testosterone levels were similar between the two groups [12]. On the other hand, in a study of 40 moderately-trained younger men, those treated with combined sprint and resistance activity did show an increase in testosterone levels [13]. Thus, there is inconsistency in the known relationship between exercise and testosterone in small populations.

In this cross-sectional study, we evaluated a substantial population of 50–79 year old men who presented for a preventive medical

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examination that included measures of morning total testosterone, body mass index (BMI), and estimated cardiorespiratory fitness (fitness), a marker of habitual physical activity. The purpose of this study was to evaluate the association of BMI and fitness with testosterone levels in middle aged and older men as a preliminary step in determining whether maintaining a healthy body weight and remaining physically active are avenues to maintaining normal testosterone levels at older ages.

2. Materials and methods

Data were collected from 3974 men who were self-referred or employer-referred to the Cooper Clinic between January 2012 and March 2016 for a preventive medical examination. All participants were 50–79 years of age and had a total morning testosterone measurement as part of routine screening. Participants were generally healthy Caucasian men, well-educated, and all had access to preventive health care. Men with missing BMI or fitness measurement (n = 701) or using any form of androgens, any form of estrogens, anti-estrogens, or 5-alpha reductase inhibitors (n = 278) were excluded, as well as one individual with a total testosterone level > 3000 ng/dL who reported no medication usage. This resulted in a final sample of 2994 men. Informed consent allowing data collection for the Cooper Center Longitudinal Study, a prospective longitudinal study evaluating the relationship between preventive medicine, fitness, and health, was signed by all participants. [14,15] The data are maintained by The Cooper Institute, a nonprofit research organization. The study protocol was annually reviewed and approved by The Cooper Institute's institutional review board.

The medical examination consisted of a self-reported medical history and demographic questionnaire which was reviewed and confirmed by the clinic physician. In addition, the participants had a physical examination, anthropometric assessments, blood pressure measurements, blood chemistry tests following an overnight 12-hour fast and 24 hours of no leisure-time physical activity, and a maximal exercise test. Height and weight were measured using a standard physician's scale and stadiometer, and BMI was calculated as weight in kilograms divided by height in meters squared. BMI was categorized as normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), or obese (> 30 kg/m^2). Blood pressure was measured using the auscultatory technique with a standard sphygmomanometer per routine clinic protocol.

All participants underwent a single morning total testosterone measurement as a screening test. The clinical nature of this population led to only a single measure of morning testosterone. In addition, routine testing of free testosterone, serum-hormone binding globulin (SHBG), luteinizing hormone, follicle stimulating hormone or prolactin was not performed. Blood was drawn between 7–9 a.m. and samples were assayed within two hours. The serum was separated at 2600 rpm for ten minutes. Serum total testosterone levels were analyzed on the Centaur Instrument (Seimen ADVIA Centaur CP, Tarrytown, NY), using the standard Chemiluminescence method. Mean intra-assay coefficients of variation (CVs) were less than 10% and mean inter-assay CVs less than 10%. Total testosterone levels were categorized into low (< 250 ng/dL), low normal (250–399 ng/dL), and normal (≥ 400 ng/dL) based on laboratory norms and commonly used clinical ranges.

All participants completed a maximal exercise treadmill test using a modified-Balke protocol and attained at least 85% of predicted maximal heart rate. The treadmill speed began at 1.48 $m{\cdot}s^{-1}$ at 0% grade for the first minute, a 2% grade for the second, and 1% increases per minute until the 25th minute. After 25 min, the elevation continued at 25% and the speed increased by 0.089 $m{\cdot}s^{-1}$ each minute until volitional exhaustion. [14] The test was terminated for exhaustion, medical indications such as chest pain, and by the physician if it appeared that the participant would not be able to perform the next workload level. Duration of the treadmill test has a strong correlation with measured maximal oxygen uptake in men (r = 0.92) [16]. For the current study, maximal METs (metabolic equivalents, 1 MET = 3.5 mL O_2 uptake/kg/min) were calculated based on the final treadmill speed and grade in order to standardize exercise test performance. The results were classified into age-specific categories of fitness based on sample quintiles from this population of men. Participants were then classified into three groups: low fitness (quintile 1), moderate fitness (quintiles 2 and 3), and high fitness (quintiles 4 and 5).[14]

2.1. Statistical analysis

We summarized characteristics of the sample within categories of age, BMI, fitness and testosterone. We used the Jonckheere-Terpstra nonparametric method to test all unadjusted, doubly ordered trends. We used multiple logistic regression models of testosterone < 250 ng/dL to sequentially test for unadjusted or adjusted associations with age, BMI and fitness. Post-hoc power to detect a partial correlation between testosterone and age controlling for BMI was based on the Fisher z transformation. Our sample size provides 80% power to detect a correlation as small as 0·08 between testosterone and age, adjusting for BMI using a two-sided test at a 5% significance level. All analyses were programmed in SAS/STAT®, version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

Table 1 shows the characteristics of the study population. Most of the men (92.7%) were between ages 50 and 69. Mean testosterone levels were within the normal range (> 400 ng/dL) in all three age groups. Mean BMI for all three testosterone groups was in the overweight category. A decline in fitness was observed across age decades, with men in the 70–79 year age range having a mean fitness level 2 METs lower than men in the 50–59 year age range. Fig. 1 illustrates the association between age, mean testosterone, and fitness/BMI. Mean testosterone level varied across fitness and BMI levels but not in a clinically meaningful way with age.

Table 2 first shows the percentage of men in each testosterone category by decade. There was no association between age and testosterone levels across decades (p for trend = 0.885). On the other hand, Table 2 reveals that BMI has a strong inverse relationship with testosterone. A higher prevalence of low testosterone was seen in the obese BMI group when compared to the normal weight BMI group (p for trend < 0.001). Conversely, fitness had a strong direct association with testosterone levels as shown at the bottom of Table 2 (p for trend < 0.001). Men with high fitness (quintile 4–5) had the lowest prevalence of low testosterone compared to moderate (quintile 2–3) and low fitness (quintile 1) groups. As shown in Fig. 2, low testosterone was more prevalent as BMI increases, but was not more prevalent with increasing age. Likewise, low testosterone was more prevalent as fitness decreases but was not more prevalent with increasing age. Spearman correlation coefficients showed the following relationships between testosterone categories and age (r = -0.00271 (p = 0.8823), BMI category (r = -0.28035 (p < 0.0001), and fitness category (r = 0.24599 (p < 0.0001).

Table 3 indicates that in the unadjusted model, age was not associated with the prevalence of low testosterone (OR: 0.98, 95% Confidence Interval (CI): 0.97, 1.00). The relationship between age and low testosterone remained non-significant after adjusting for BMI (OR: 0.99, 95% CI: 0.97, 1.01). In the model adjusting for both fitness and BMI and in the fully adjusted model, older age was associated with a lower likelihood of having a low testosterone level (OR: 0.96, 95% CI: 0.94, 0.98).

Table 3 further shows that BMI was positively associated with low testosterone in the unadjusted model as well as the adjusted models. When expressed as a categorical variable, men who were high fit (Q4–5) had lower odds of a low testosterone level (OR: 0.75, 95% CI: 0.71, 0.79) compared to low fit (Q1) men. When expressed as a

Table 1
Characteristics of 2994 Men Undergoing Testosterone Screening by Age Decade from 50 to 79 Years Old.

	Ages 50-59 n = 1906	Ages 60-69 n = 868	Ages 70-79 n = 220	p value for trend
Age (yr)	54.1 (2.8)	63.6 (2.8)	73.5 (2.8)	
Total testosterone (ng/dL)	443.1 (170.4)	436.4 (172.1)	447.3 (162.7)	0.60
Total testosterone (nmol/L)	15.4 (5.9)	15.1 (6.0)	15.5 (5.7)	0.60
Body mass index (kg/m^2)	28.0 (4.0)	28.0 (3.9)	26.7 (3.5)	0.02
Waist girth (cm) (n = 2961)	94.5 (11.1)	96.3 (10.5)	95.0 (11.9)	< 0.001
Cardiorespiratory fitness (METs)	11.3 (2.1)	10.1 (2.0)	9.3 (2.1)	< 0.001
History of Diabetes	2.1	3.8	3.2	0.02
History of Hypertension	25.4	35.0	39.5	< 0.001
Current smoker	12.4	6.8	0.9	< 0.001
Systolic blood pressure (mmHg)	120.5 (11.8)	123.3 (14.4)	126.8 (17.1)	< 0.001
Diastolic blood pressure (mmHg)	80.2 (8.6)	79.8 (8.8)	78.0 (8.5)	0.01
Fasting blood glucose (mg/dL)	99.2 (14.8)	101.4 (16.0)	101.8 (19.5)	< 0.001
Hemoglobin A_{1c} (%)	5.5 (0.5)	5.6 (0.5)	5.7 (0.6)	< 0.001

Data are mean (SD) or % unless otherwise specified.
METS = metabolic equivalent of task.
SI conversion factors: To convert cholesterol to mmol/L, multiply values by 0.0259. To convert glucose to mmol/L, multiply values by 0.0555. To convert testosterone to mmol/L, multiply values by 3.467.

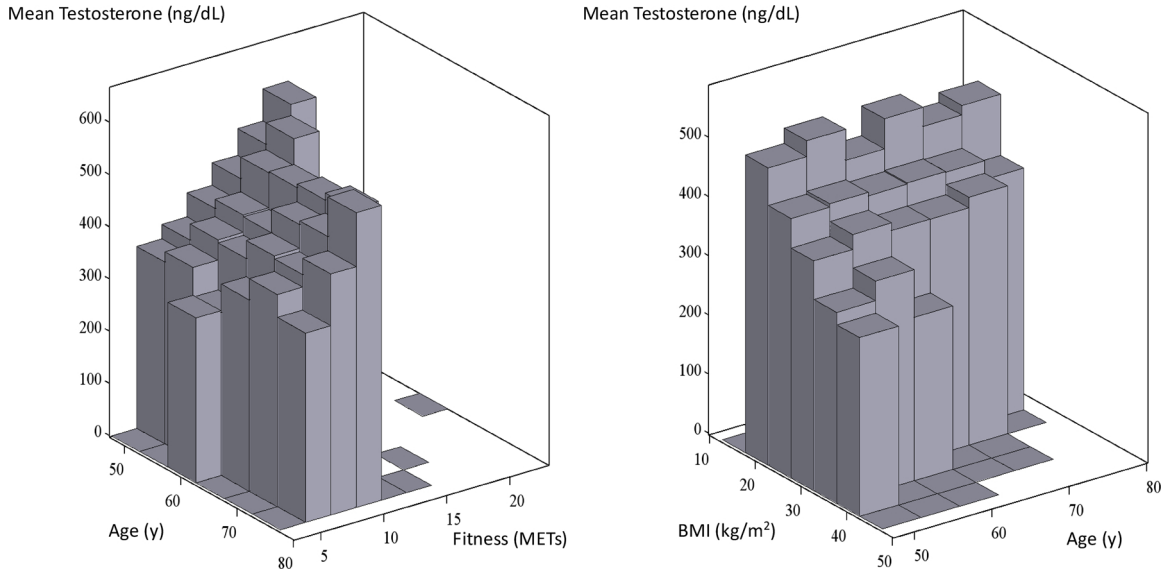

Fig. 1. (A) Mean Testosterone Levels by Age and Cardiorespiratory Fitness Levels. Mean testosterone increases steeply with CRF but not with age. (B) Mean Testosterone Levels by Age and Body Mass Index Levels. Mean testosterone decreases steeply with BMI but not with age.
BMI = body mass index, METS = metabolic equivalent of task.

Table 2
Distribution of Testosterone within Categories of Age, Body Mass Index and Cardiorespiratory Fitness.

		Testosterone (ng/dL)			
	n	< 250 Low, % 326	250-399 Low Normal, % 994	≥400 Normal, % 1674	*p* for trend
Age (years)					
50-59	1906	11.3	32.1	56.6	0.885
60-69	868	10.0	37.1	52.9	
70-79	220	10.5	27.3	62.3	
BMI (kg/m^2)					
18·5-24·9 (normal)	692	4.6	21.1	74.3	< 0.001
25-29·9 (overweight)	1554	9.2	33.3	57.5	
≥30 (obese)	748	20.2	44.1	35.7	
Cardiorespiratory Fitness (METs)					
High (quintiles 4-5)	1101	5.4	25.2	69.3	< 0.001
Moderate (quintiles 2-3)	1382	11.3	36.5	52.2	
Low (quintile 1)	511	21.5	41.5	37.0	

METS = metabolic equivalent of task.

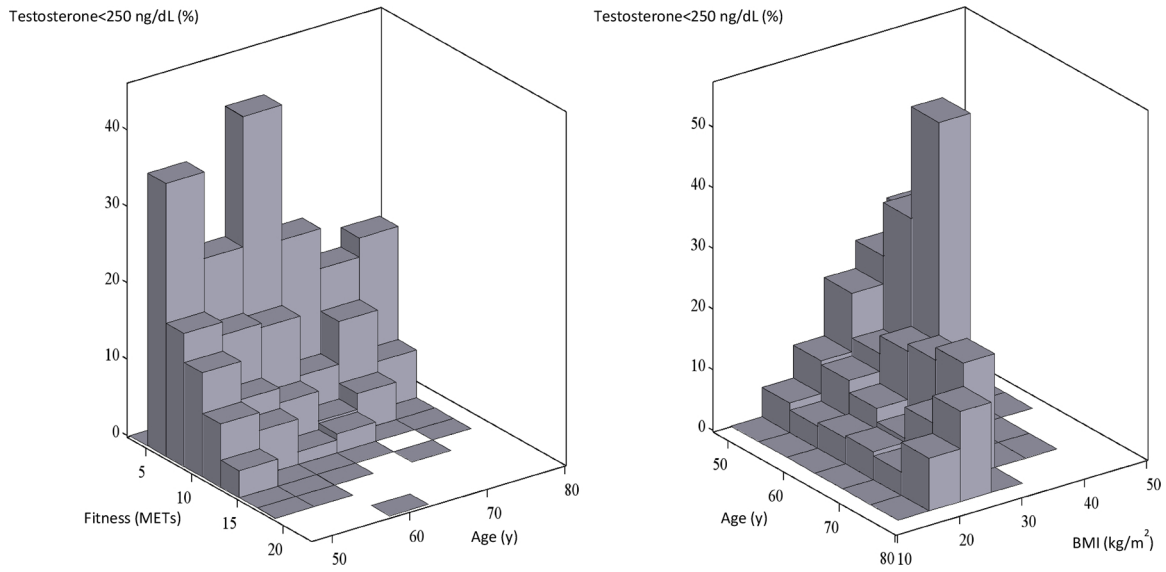

Fig. 2. (A) Prevalence of testosterone < 250 ng/dL versus Age and CRF. The prevalence of testosterone < 250 ng/dL decreases steeply with CRF but not with age. (B) Prevalence of testosterone < 250 ng/dL versus Age and BMI. The prevalence of testosterone < 250 ng/dL increases steeply with BMI but not with age. BMI = body mass index, METS = metabolic equivalent of task.

Table 3
Odds Ratios and 95% Confidence Intervals from Models of Low Testosterone (< 250 ng/dL).

	Age	BMI	Fitness
Unadjusted Models			
Age	0.98 (0.97, 1.00)		
BMI		1.16 (1.13, 1.19)	
Fitness			0.75 (0.71, 0.79)
Age and BMI Adjusted Model[a]	0.99 (0.97, 1.01)	1.16 (1.13, 1.19)	
Age, BMI, and Fitness Adjusted Model[b]	0.96 (0.94, 0.98)	1.08 (1.05, 1.12)	0.78 (0.72, 0.84)
Fully Adjusted Model[c]	0.96 (0.94, 0.98)	1.09 (1.05, 1.12)	0.79 (0.72, 0.84)

a.Multivariate Model with Age per year and BMI per kg/m$^{2.}$
b.Multivariate Model with Age per year, BMI per kg/m^2, and Cardiorespiratory Fitness per MET.
c.Multivariate Model with Age per year and BMI per kg/m^2, Cardiorespiratory Fitness per MET, and Current Smoker.

continuous variable, an increase of one MET in treadmill performance was associated with a 21% decrease in the likelihood of having a low (< 250 ng/dL) testosterone level. This relationship between low testosterone and low fitness persisted after adjustment for age, BMI, and current smoking status.

4. Discussion

In this group of generally healthy and homogenous men who had screening morning total testosterone levels, no clinically significant differences in mean total testosterone levels across age groups were found. The prevalence of low testosterone did not increase across age decades. Further, two key modifiable lifestyle factors appear to play a role in maintaining normal testosterone levels. The two components of lifestyle evaluated were body weight status and fitness level. Given the frequent use of testosterone therapy and the knowledge gaps in the risk-benefit of chronic testosterone use in various populations, the potential to preserve normal testosterone levels with aging through maintenance of a healthy body weight and physical fitness is an important public health message.

Some but not all studies have reported decreasing testosterone levels with increasing age. In the Baltimore Longitudinal Study on Aging cohort (890 men between the ages of 22.5 and 91.3), the percentage of men with decreased testosterone levels (defined as total testosterone < 325 ng/dL) increased with each decade of age (< 10% between ages 20–50, 20% over age 60, and 50% over age 80). [17] In the Massachusetts Male Aging Study (MMAS) of 1156 men, total testosterone declined by 1.6% annually over 7–10 years [1]. Conversely, Sartorius et al reported on 325 men age 40 and older who were in very good or excellent health by self-report and showed no decrease in serum testosterone with age. [5] Others have reported similar results such as in a small study comparing testosterone levels in older and younger men in which testosterone remained fairly stable into the 80′s [18,19]. Further, in the Normative Aging Study, basal testosterone levels were similar between older and younger men although HCG stimulation suggested diminished testis reserve with age [4]. In our population of generally healthy men, older age groups did not have lower testosterone levels and the mean level remained above 400 ng/dL into the 8th decade.

Investigators evaluating the impact of aging on testosterone levels face numerous methodological challenges which may account for conflicting reports in this regard including variability in included ages, testing methodology, and analytical method. Furthermore, other phenotypic covariates appear to effect testosterone levels. In a study evaluating testosterone levels in 400 men between 40 and 80 years of age, BMI, waist circumference, tobacco use, general health status, and physical activity levels were all related to testosterone levels. [2] The Boston Area Community Health study found that waist girth was the

most important contributor to low testosterone [20]. A recent study showing a strong negative correlation between testosterone and BMI was done in 1599 men reported by Clifton et al in 2016 [21]. However, a study evaluating 991 Air Force veterans over 20 years found no secular trend between change in BMI and declining testosterone [22]. Further, chronic diseases, such as new onset diabetes, were associated with the longitudinal decline in testosterone in the MMAS [23]. The authors of this study concluded that a substantial proportion of the apparent aging effect on testosterone levels was attributable rather to changes in health status. Finally, in a community-based study of 3200 men, aged 40–79, from eight European countries demonstrating the apparent contribution of age, obesity, and chronic disease to testosterone levels led the authors to conclude that the apparent age induced decline in testosterone may instead be a decline related to overall health and thus be potentially preventable and or reversible. [24]

There is limited research evaluating the relationship between testosterone levels and reported physical activity or objectively measured fitness. In the Muller study evaluating 400 men ages 40–80 years old, testosterone levels increased with increasing quartiles of self-reported physical activity. [2] The CARDIA study cohort of 604 white and 391 black men, age 24–32, did not show a correlation between total testosterone, bioavailable testosterone, sex hormone binding globulin and self-report physical activity. However, there was a suggestion that fitness may have been associated with SHBG, but not with total testosterone in the subgroup of white men [25]. A double-blind, randomized controlled clinical trial evaluating the impact of transdermal testosterone on atherosclerosis progression as well as other outcomes including fitness. This study showed that those receiving testosterone replacement over a three-year period were less likely to have a significant decline in their VO_2max, or fitness level. [26] Our study demonstrates a highly significant association between low fitness and lower levels of testosterone, after controlling for potential confounders. Thus, fitness may help moderate the tendency for those with higher BMI to have lower testosterone levels. It is interesting to note in our population that the inverse association of BMI and the direct association of fitness with testosterone are evident in the high and low ranges of BMI and fitness but not in the intermediate ranges. Our cross-sectional study cannot determine causation but this finding suggests that modest changes in BMI or fitness may not have a significant effect on testosterone levels.

The strengths of this study include a large sample size with extensive phenotyping. The uniform nature of the cohort (primarily Caucasian, well-educated, and with access to preventive healthcare) decreases the likelihood of unmeasured socioeconomic and unknown potential co-morbidity confounders affecting the outcomes. While there is a lack of racial/ethnic diversity, prior work has shown that race and ethnicity have no significant impact on testosterone. [27] The range for “low total testosterone” was chosen to reflect levels utilized in the literature (230–350 ng/dL) and the recommended ranges of the utilized assay. Finally, fitness estimated from maximal treadmill exercise testing provides an objective marker of habitual physical activity and is more reliable than self-reported physical activity.[16]

Limitations to this study include lack of testing for free testosterone, SHBG, luteinizing hormone, and follicle stimulating hormone levels to definitively categorize hypogonadism. This may affect the findings as some research has suggested an impact of exercise on free testosterone but not total. [28] Other studies have suggested that SHBG increases with age and thus affects bioavailable testosterone levels [17]. In addition, only a single total testosterone level was obtained. This is, nonetheless, clinically informative as many testosterone clinics use either a single, random testosterone level or none at all to make treatment decisions [8] Additionally, due to the single morning measurement, we were unable to address changes in testosterone with circadian rhythm. Finally, this is a cross- sectional study and is unable to show longitudinal changes in testosterone or define causality.

5. Conclusion

In conclusion, this cross-sectional study does not support the contention that testosterone decreases uniformly with aging in healthy middle-aged to elderly men. Finding similar testosterone levels across decades of age suggests that lower testosterone is not an inevitable consequence of aging. Testosterone levels were inversely associated with BMI and positively associated with fitness. This new finding of a strong association between objectively measured fitness and normal testosterone in the oldest age groups has intriguing implications. Further research is needed to better understand the implications of our findings including understanding the expected testosterone levels in healthy aging, whether low testosterone levels will increase if fitness increases, and whether testosterone levels can be maintained despite excess weight and/or the presence of chronic disease in the setting of moderate to high fitness.

Contributors

Laura F. DeFina designed and performed the experiments, and analyzed the data.

Nina B. Radford designed the experiments and analyzed the data.

David Leonard designed and performed the experiments, and analyzed the data.

Rick K. Wilson analyzed the data.

Tyler C. Cooper designed the experiments, and analyzed the data.

S. Michael Clark designed the experiments, and analyzed the data.

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Larry W. Gibbons designed the experiments, and analyzed the data.

Bulent O. Yildiz analyzed the data.

Ugis Gruntmanis designed the experiments, and analyzed the data.

All authors contributed to the writing of the paper.

Conflict of interests

The authors declare that they have no conflicts of interest.

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Ethical statement

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us. We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property. We further confirm that any aspect of the work covered in this manuscript that has involved either experimental animals or human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

We understand that the Corresponding Author is the sole contact for the Editorial process (including Editorial Manager and direct communications with the office). She is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs. We confirm that we have provided a current, correct email address which is accessible by the Corresponding Author.

Provenance and peer review

This article has undergone peer review.

Research data (data sharing and collaboration)

There are no linked research data sets for this paper. The authors do not have permission to share data.

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