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Sleep restriction and testosterone concentrations in young healthy males: randomized controlled studies of acute and chronic short sleep☆

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ABSTRACT

Objective: Low testosterone in men increases the risk for various disorders. Severe sleep restriction (SR) may reduce testosterone, but the effects of long-term short sleep are unknown. This study tested the effects of SR on circulating testosterone in healthy young men.
Design: Randomized controlled studies of SR vs habitual sleep (HS) in inpatient (study 1, n=14) and outpatient (study 2, n=13) settings.
Methods: Study 1 involved severe, acute SR (4 hours time in bed [TIB]) vs HS (9 hours TIB) for 5 nights; study 2 consisted of mild, long-term SR (HS 1.5 hours of sleep/night) vs HS for 6 weeks. Plasma testosterone levels were measured at baseline and end point (study 1) or baseline, week 3, and week 6 (study 2) of each phase. Linear model analyses to assess the effects of SR on testosterone were performed separately for each study.
Results: Study 1: There were no significant sleep-time interaction on testosterone concentrations (change in testosterone levels during HS = 22.86 ± 163.79 ng/dL; SR = 43.73 ± 159.96 ng/dL, $P = .41$) and no main effect of sleep duration ($P = .13$). Study 2: There were a trend for a sleep-time interaction ($P = .067$) and a main effect of sleep on testosterone concentrations from 6 weeks of SR ($P = .0046$). Testosterone concentrations were slightly lower but increased over time with SR relative to HS.
Conclusions: Sleep restriction does not adversely affect plasma testosterone levels in healthy young men. Given prior contradicting evidence, confirmatory studies should be done to ascertain the influence of sleep duration and quality on testosterone concentrations in men throughout life.

Introduction

Hypogonadism, or low testosterone, in men leads to a wide range of sexual symptoms including erectile dysfunction, decreased sex drive, and decreased fecundity.[1] In addition, low testosterone may lead to an increased risk for certain nonsexual conditions such as diminished cognitive function,[2] depression,[3] and loss of muscle mass.[4] Beyond the immediate signs and symptoms, low testosterone may also be associated with an increased risk for cardiovascular disease,[4] coronary artery disease,[5] stroke,[6] metabolic syndrome,[7] osteoporosis,[8] and all-cause mortality.[9] Because testosterone levels naturally decline due to aging,[10,11] with up to 39% of men over the age of 45 having low testosterone,[12] many of the aforementioned complications have largely been observed in elderly populations.[3,13–16]

Interestingly, an age-independent decline in testosterone levels among men has been observed since the 1980s.[17–19] Concurrent with this temporal decline in testosterone levels has been a similar decline in average sleep duration between 1985 and 2004 in the United States.[20] Although concurrence of events does not support causality, that the majority of daily testosterone production in men occurs during sleep[21,22] lends biological plausibility to a potential causal role of inadequate sleep on the development of low testosterone. Indeed, several epidemiological studies have observed an inverse relation between obstructive sleep apnea severity and testosterone levels in males.[23,24] Others have found that lower

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testosterone levels were associated with shorter sleep duration or sleep fragmentation, independent of sleep disorders.[25–28] Likewise, after a 24-hour period of experimentally induced sleep fragmentation, as commonly observed in obstructive sleep apnea patients, the characteristic spike in testosterone production during sleep was disrupted.[22] Although no change was detected in mean testosterone levels, the finding that the nocturnal rhythm of testosterone was altered by impaired sleep quality further supports a potential causal influence of sleep on testosterone production. Furthermore, one night of experimentally induced total sleep deprivation in 11 healthy young men significantly reduced testosterone concentrations relative to a control group given an 8-hour sleep opportunity.[29] In one particularly noteworthy randomized controlled trial, 8 consecutive nights of experimentally induced sleep restriction (SR) to 5 hours per night caused reductions of up to 15% in testosterone levels in 10 healthy young men.[30] Moreover, the current body of evidence suggests an association between the aforementioned sexual and nonsexual consequences of low testosterone and shorter sleep, potentially mediated by lower levels of testosterone.[31–33] Yet, despite accumulating evidence linking short sleep with low testosterone and associated conditions, the relation between chronic, mild SR and the development of low testosterone in healthy young males is largely unknown.

The primary goal of the present study was to examine the effects of SR on circulating testosterone levels. We hypothesized that both severe SR and milder, sustained SR would lead to reductions in circulating testosterone concentrations in healthy young males.

Methods

Participants

Study 1

Participant and study protocol details have been presented elsewhere.[34,35] Briefly, males ages 30-45 years, with body mass index (BMI) between 22 and 26 kg/m^2, were recruited and enrolled in a randomized, controlled crossover inpatient study of 2 phases of 6 days each. Screening procedures and general inclusion and exclusion criteria were identical to those described in detail below for Study 2.

Study 2

Participants were between 20 and 40 years, with a BMI between 25 and 29.9 kg/m^2 or 23-24.9 kg/m^2 and with at least 1 parent with obesity. Participants were included if they met all of the following criteria: (1) average habitual sleep (HS) duration for 14 nights was >7 hours per night but <9 hours per night; (2) nightly sleep duration was >7 hours for at least 10 of 14 nights; and (3) nightly sleep duration was not <6 hours for more than 4 nights. These sleep criteria were assessed using actigraphy (Actigraph GT3X+, Pensacola, FL) over a 2-week period. Subjective sleep diaries were used to assess bed- and wake-time. In addition, participants were required to have normal scores on the following assessments of sleep and psychiatric disorder: Pittsburgh Sleep Quality Index,[36] Epworth Sleepiness Scale,[37] Berlin Questionnaire,[38] Sleep Disorders Inventory Questionnaire,[39] Beck Depression Inventory,[40] Composite Scale of Morningness/Eveningness,[41] and Three Factor Eating Questionnaire.[42] Exclusionary criteria included history of smoking (both current and ex-smokers for <3 years were excluded), drug or alcohol abuse, excessive caffeine intake (>300 mg/d), rotating or daytime shift-work, diabetes, or cardiovascular disease. Individuals with recent weight or dietary changes (weight change ≥5% over the prior 3 months) or participating in a weight loss program were excluded, as were adults living with an infant <1 year of age. Finally, individuals with plans for future travel across time zones were excluded because of the effects of jet lag on sleep quality and duration. Participants agreed not to drive any vehicle during the SR phase. Daytime napping during the study phases was not permitted. Participants were blinded to the original purpose of the study.

Study protocols

Study 1

Participants were randomized to either SR (4 hours time in bed at 1-5 AM) or HS (9 hours time in bed at 10 PM-7 AM) for 5 nights each. Study phases were conducted 3 weeks apart. Fourteen men were enrolled, of which 11 had adequate sample volume to determine end point (n = 10 using day 5 or 6 samples; n = 1 using day 4 sample) testosterone levels. Because this was an ancillary study to the main project, sample aliquots had been used for primary research aims. The main study was conducted 8-10 years ago and had not accounted for this assay. Two participants lacked baseline samples from both study phases, and 5 participants only had baseline sample for 1 phase. All blood samples were taken at 7:30 AM in both phases (Fig. 1A)

Study 2

Participants were randomized to either HS (sleep duration based on screening actigraphy data) or SR (HS – 1.5 hours per night) for 6 weeks in a crossover, outpatient study. During HS, participant bedtimes and wake-times corresponded to their 2-week screening data, whereas during SR, participants were instructed to delay bedtimes by ~1.5 hours to achieve a reduction in sleep. On average, participant bedtimes and wake times during screening were 12:14 AM (SD 1 hour 8 minutes) and 8:45 AM (1 hour 10 minutes), respectively. During both phases, sleep was monitored by wrist actigraphy and verified by the investigators weekly for compliance. Adjustments to the prescribed sleep schedules were made to ensure per-protocol sleep duration for each phase. One participant was disqualified due to nonadherence. Following phase 1, participants underwent a washout period of at least 2 weeks prior to the initiation of phase 2. During this washout period, average sleep duration was required to return to screening status, as verified by actigraphy. An additional 2-4 weeks of washout was provided if sleep had not returned to baseline. As a result, the washout period ranged from 2 to 8 weeks, with an average duration of 37.2±11.9 days.

Fasting plasma samples were collected for each participant at baseline, week 3, and week 6 of each study phase (Fig. 1B). Of the 13 male participants enrolled, 11 completed both study phases, and 2 did not complete due to personal reasons/nonadherence (n = 1) and noncompliance with the washout protocol (n = 1). Of those 11 participants, 10 had adequate sample volume to determine baseline and midpoint values for each study phase; all 11 had end point samples for each study phase up to at least 4 weeks (n = 1 with 4-week end point; n = 10 with 6-week end points). Except for 3 participants, blood samples were obtained between 9 and 11 AM. For those 3 participants, one had 1 end point sample midafternoon (2-3 PM), another had 1 end point sample mid-day (11:45 AM-1 PM), and the other had all samples, except for 1 baseline, in the afternoon (12:30-4 PM).

Institutional Review Board approval

Both studies were approved by the Columbia University Irving Medical Center Institutional Review Board, and participants were given the opportunity to ask questions and obtain additional information about the studies prior to providing informed consent. Studies were registered on clinicaltrials.gov (study 1: NCT00935402; study 2: NCT02960776).

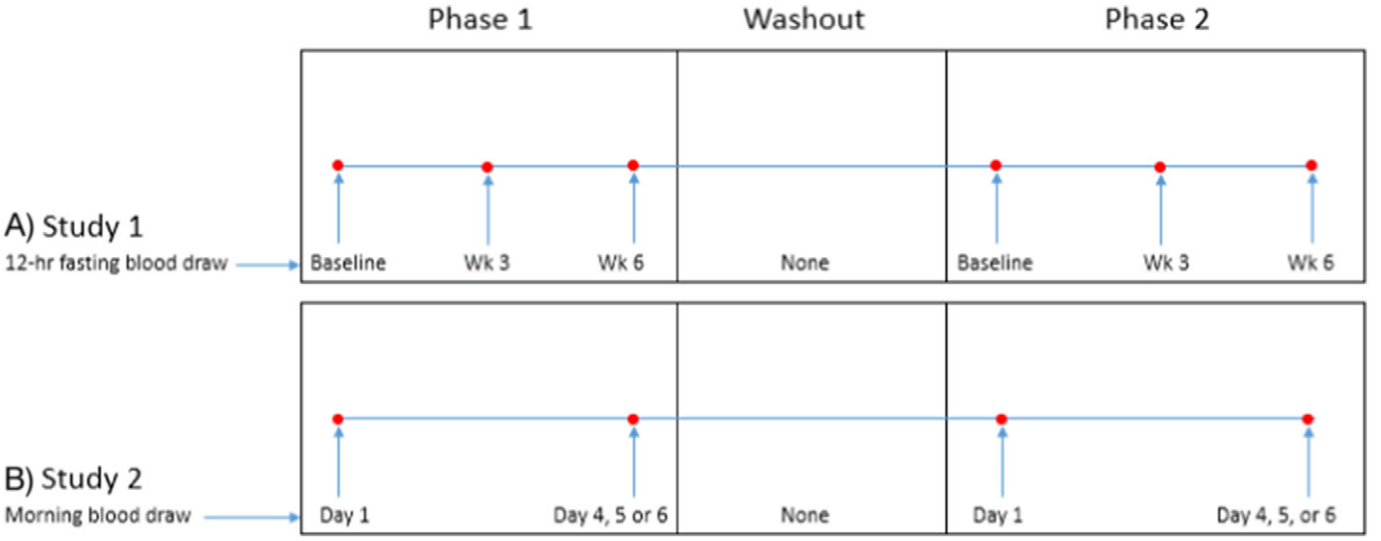

Fig. 1. Design and aliquot times during study 1 (A) and study 2 (B).

Assay methods

For both study 1 and study 2, whole blood samples were collected in EDTA-coated tubes. Samples were centrifuged, and plasma was separated and aliquoted into 0.5- to 0.75-mL samples and stored at −80°C. Plasma testosterone concentration was quantified by solid phase enzyme-linked immunosorbent assay (IB79106; Immuno-Biological Laboratories, Minneapolis, MN). All samples were assayed in batch with all samples from each individual participant assayed at once. The intraassay coefficients of variability for the low- and high-concentration quality controls were 2.30% and 5.03%, respectively. The interassay coefficient of variability for low- and high-concentration quality controls were 2.75% and 5.17%, respectively.

Statistical analyses

Linear mixed-model analyses were performed separately for study 1 and study 2 with testosterone as the outcome variable. No independent variables (predictors or covariates) were missing. One testosterone observation was missing for study 1, and 10 were missing from study 2. As only outcome values were missing, we excluded the missing outcome values from our analyses. Subject was used as random effect. Age, race (categorized as white vs other), and BMI were used as covariates. Additionally, time (either day, for study 1, or week, for study 2) and sleep condition-time interaction, with time as continuous variables, were used as covariates as well. In each case, phase order and carryover (phase-sleep condition) effects were tested at an initial model. If they were not found to be significant, they were dropped from the final analysis. For study 2, phase effect was significant and the carryover effect was near significant. If both phase and carryover effects were kept in the model, then the effect of SR was significant as well. The significance of SR disappeared if near-significant carryover effect was removed from the model. Any phase and carryover effects, when present, have been statistically adjusted; the estimated effects are free from carryover and phase effects. Data presented are raw means ± SD. Significance level was set at $P < .05$.

Results

Participants enrolled in study 1 were slightly older ($P = .0040$) and had a lower BMI ($P < .0001$) than participants in study 2 (Table 1). Racial distribution of participants was not different between the 2 studies ($P = .74$). Total sleep time during study 1 was restricted by 3.57 ± 0.34 hours during the SR phase relative to HS ($P < .0001$), whereas total sleep time during study 2 was reduced by 1.44 ± 0.24 hours during the SR phase compared to HS ($P < .0001$) (Table 2 and Fig. 2). On average, throughout each 6-week period, participants went to bed at 12:13 AM (1 hour 11 minutes) during HS and 1:20 AM (53 minutes) during SR. Corresponding wake times were 8:40 AM (1 hour 15 minutes) and 8:09 am (44 minutes) during HS and SR, respectively. In study 2, sleep efficiency was not different between the 2 phases ($P = .47$).

Table 1
Participant characteristics at baseline

Characteristic	Study 1 (n = 11)	Study 2 (n = 11)	*P* values
Age, y	36.6 ± 5.6*	30.1 ± 5.6	.0040
Height, cm	178.6 ± 6.4	174.0 ± 6.5	.1375
Weight, kg	77.5 ± 8.6	81.3 ± 8.3	.2298
BMI, kg/m^2	24.1 ± 1.1	26.8 ± 1.9	<.0001
Screening sleep duration, h	NA	7.79 ± 0.60	NA
Screening sleep efficiency, %	NA	90.5 ± 2.6	NA

Data are means ± SD. NA, not applicable.

Table 2
Average sleep duration during sleep restriction and habitual sleep phases of each study

Study	Sleep variable	Habitual sleep	Sleep restriction	*P* value
1	TST, h	7.31 ± 0.41	3.74 ± 0.10	<.0001
	Sleep efficiency, %	81.20 ± 4.53	93.32 ± 2.42	<.0001
2	TST, h	7.60 ± 0.60	6.15 ± 0.50	<.0001
	Sleep efficiency, %	89.8 ± 3.50	90.1 ± 3.13	.6360

Data are means ± SD.
TST, total sleep time.

In study 1, there were no main effects of sleep condition ($P = .13$), time ($P = .32$), or sleep condition × time interaction ($P = .41$) on testosterone concentrations from 4-5 nights of severe SR (Fig. 3). Change in testosterone from baseline during HS was 22.86 ± 163.79 ng/dL vs 43.73 ± 159.96 ng/dL during SR. Results were unchanged when nonsignificant covariates (age, race, BMI) were removed from the models.

In study 2, there were trends for carryover effect (sleep condition × phase interaction, $P = .062$) and sleep condition × time interaction ($P = .067$) on testosterone concentrations from 6 weeks of mild SR. After taking into consideration these interactions, there were main effects of sleep condition ($P = .0046$) and phase ($P = .038$) and a trend for a main effect of time ($P = .056$) on testosterone concentrations. Positive coefficients for the interaction terms were smaller than the negative coefficient for the main effect of SR, and our data show that although there was a slight increase in testosterone over time (Fig. 4), overall values were lower in SR than HS (main effect of sleep shows lower values during SR vs HS). However, end point testosterone concentrations were 475.74 ± 204.18 ng/dL after HS vs 483.30 ± 186.19 ng/dL after SR. When nonsignificant covariates (age, race, BMI) were removed from the models, main effects of sleep condition ($P = .027$), time ($P = .038$), and trend for sleep condition × time interaction ($P = .070$) remained, but phase became nonsignificant ($P = .37$).

In study 2, 8 of 11 participants had their blood samples collected at the same time of day for each time point. We have repeated our analyses without the 3 participants whose blood was drawn at a different time points and did not find any material difference from our original analysis.

Conclusions

In the present study, neither severe and acute (<4 hours per night for 5 nights) nor mild and chronic (1.5 hours per night for 6 weeks) SR significantly affected plasma testosterone levels in healthy young men. The changes observed during chronic SR (study 2) were not clinically meaningful and do not support a conclusion that SR reduces testosterone concentrations, at least in the conditions tested, in the short or longer term.

At first glance, the present findings seem to conflict with the current biological understanding of the diurnal secretion of testosterone in young men. Testosterone production reaches a peak during sleep and a nadir during wakefulness.[21,22] Thus, our hypothesis was that a reduction in sleep duration would inhibit secretion of testosterone in healthy young men and would lead to the development of low testosterone. Indeed, prior studies have found a significant decline in serum or salivary testosterone levels after acute SR,[30] total sleep deprivation,[29] or sleep fragmentation,[22] relative to adequate sleep.

Given the seemingly contradictory findings reported herein, careful consideration should be paid to potential explanatory factors. One could consider lack of blinding to be a potential factor. Indeed, given the nature of the interventions, it was impossible for participants to be blinded to the sleep condition. However, testosterone was not a main primary outcome of either studies and, being a biological variable, could not be readily modified by a placebo effect. Moreover, participants were blinded to the purpose of both study 1 and

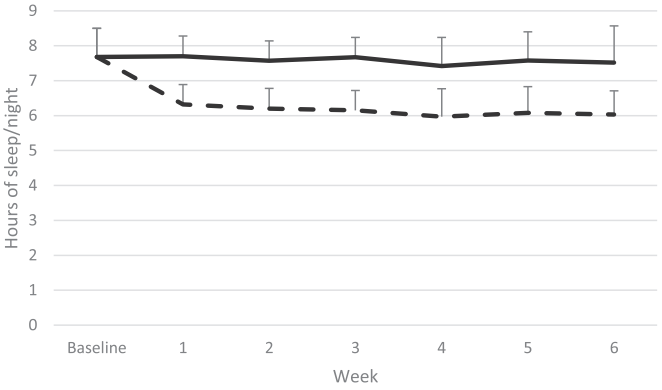

Fig. 2. Average weekly sleep duration during HS (black line) and SR (hatched line) of study 2. Baseline represents screening sleep duration; each weekly time point is the average of the previous 7 days. Data are means ± SD, n = 11.

study 2, and our investigators were blinded during analysis to participant phase. In addition, every other sleep restriction study would suffer from this same limitation, and thus, this cannot explain the difference in findings between studies. Differences in study designs are a second explanation. The observed relationship between sleep restriction and lowered testosterone concentrations in young men from which our research diverges is based on observational studies that did not randomize or blind participants. Finally, the divergent results obtained in the studies reported herein may also be partly explained by the timing of our sleep episodes. Indeed, in a study combining 2 independent, crossover, SR experiments, serum testosterone levels were reduced relative to adequate sleep (2230-0600 hours) when sleep occurred during the first part of the night (2230-0330 hours)[43] and were not affected when sleep occurred during the early morning hours (0245-0700 hours)[43] as compared to adequate sleep (2200-0700 hours). The authors concluded that an advance in wake time, rather than a delay in bedtime, contributed to the adverse effects of acute SR on morning testosterone. It is worth noting that the most prominent study to report an adverse effect of SR on testosterone (in this case, 5 hours vs 9 hours time in bed for 8 nights) was conducted via an advance in participant wake time rather than a delay in participant bedtime,[30] further supporting the prior observations. In contrast, our model for chronic, mild SR (study 2) was executed via a delay in bedtime, and our acute SR study (study 1) was performed by maintaining a constant midpoint of sleep between conditions and thus combined a delay in bedtime and an advance in wake time.

In the context of prior findings, it seems reasonable to postulate that our results may have been partially influenced by the timing of our sleep episodes. It is plausible that SR lowers testosterone concentrations only after an advance in participant wake time, whereas a delay in participant bed times does not. Our results contribute to the pool of evidence suggesting that SR may not adversely affect testosterone concentrations if it occurs via delays in bedtimes. Interestingly, observational studies have demonstrated that, along with reduced total sleep time and sleep quality, elderly males often experience both advanced bedtimes and wake times,[44,45] which, based on evidence highlighted above, may contribute to the lower levels of circulating testosterone observed in this population.[46] To our knowledge, the relationship between advanced awakening and low testosterone in the elderly has not been directly examined.

It is important to note that neither experiment presented herein was designed to assess the impact of SR on circulating testosterone. Rather, those studies were designed to assess the impact of SR on

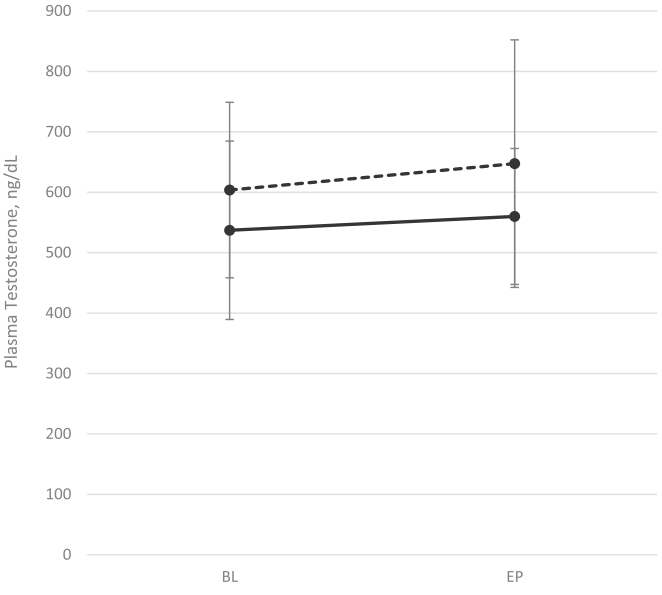

Fig. 3. Plasma testosterone concentrations during HS (black line) and SR (hatched line) of study 1. Abbreviations: BL, baseline, EP, end point. Data are means ± SD, n = 9 for BL and 11 for EP.

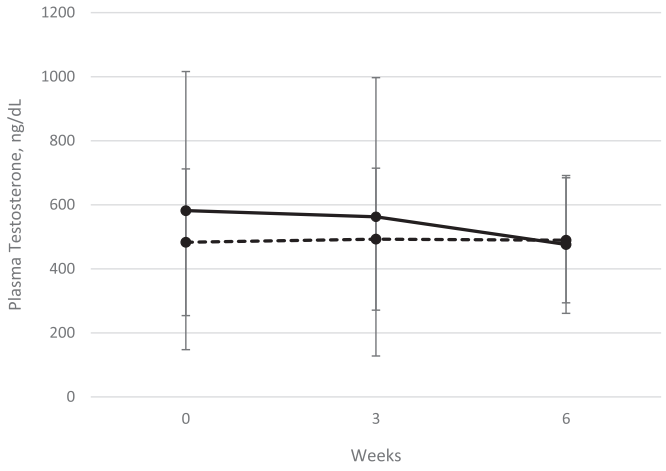

Fig. 4. Plasma testosterone concentrations during HS (black line) and SR (hatched line) of study 2. Data are means ± SD, n = 11.

energy balance regulation. Therefore, inclusion/exclusion criteria that would have improved the present study, such as exclusion of individuals with previous diagnoses of infertility, erectile dysfunction, or clinically relevant hypogonadism and inclusion of individuals at high risk for developing low testosterone, were not present and this information was not available. Also, neither study was powered to detect changes in plasma testosterone levels. Given that the data point in the opposite direction as predicted, it is unlikely that a larger sample size would have reversed the trend toward lower testosterone concentrations after SR. Moreover, studies that have demonstrated a significant effect of inadequate or poor sleep quality on testosterone have done so with comparable sample sizes.[29,30,43] Lastly, given the diurnal secretion of testosterone, it would have been relevant to assess testosterone levels over a 24-hour period and to measure testosterone levels for all participants at the same time of day. However, testosterone levels are relatively stable over the morning hours (ie, 0700-0900 hours).[47] In study 1, all samples were taken at the same clock time. In study 2, samples for each participant were generally taken in the same time period except for a few individuals in which the time period differed on one occasion. Therefore, variability related to time of day was minimal.

Limitations specific to study 1 derive from the fact that it was a post hoc analysis of a study completed in 2010. The blood samples analyzed had been stored at −80°C for >8 years, which may have reduced sample stability. However, the data presented are within the physiological range, suggesting that degradation due to prolonged storage was likely not substantial. Furthermore, any potential degradation would have affected all samples equally, and thus, the comparison between the HS and SR phases, in this within-subjects design, would not have been compromised. Limitations specific to study 2 are largely due to the weight status of our participants. Specifically, participants presented with overweight/obesity or risk of obesity. Higher body weight is associated with lower testosterone levels in men,[48] which may be a more important factor in affecting testosterone levels than shortened sleep duration. However, participants from both studies had similar testosterone levels, and the study outcomes were equivalent. Therefore, it is unlikely that the lack of effect of SR on testosterone in study 2 was masked by the weight status of participants.

The present research has several strengths to note. Our model for chronic short sleep duration in study 2 is representative of the typical short-sleeping adult man, unlike previously conducted acute SR studies, including our own study 1, which drastically reduced sleep time. As a result, its findings are more generalizable to short-sleeping adult populations. Similarly, clinically significant low testosterone in otherwise healthy young males may develop from a multitude of long-term lifestyle factors (potentially including sleep) that cannot be adequately replicated by a short-term intervention as in previous studies and study 1. In our attempt to replicate one of these long-term lifestyle factors, we report the first experimental evidence that details the effect of long-term short sleep duration on circulating testosterone concentrations. The outpatient, crossover design of study 2 similarly contributes to the generalizability of these results.

Finally, the studies described herein support the joint conclusion that reducing sleep duration by delaying bed time, with minimal or no advance in wake time, does not adversely affect testosterone and may have no effect on the development of low testosterone in young men. Additional studies in older adults, for whom testosterone changes are observed, are necessary.

Declaration of interest

The authors have no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Data reported herein are from 2 clinical trials registered on Clinicaltrials.gov

Study 1: NCT00935402: https://clinicaltrials.gov/ct2/show/NCT00935402

Study 2: NCT02960776: https://clinicaltrials.gov/ct2/show/NCT02960776

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