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SCIENTIFIC INVESTIGATIONS

Sleep Duration Is Associated With Testis Size in Healthy Young Men

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Study Objectives: Sleep is increasingly recognized to influence a growing array of physiological processes. The relationship between sleep duration and testis size, a marker of male reproductive potential, has not been studied.

Methods: This was a preliminary cross-sectional analysis of the baseline data from 92 healthy men (mean ± standard deviation, age 33 ± 6 years, body mass index [BMI] 24.7 ± 6.1 kg/m^2), of whom 66 underwent at-home actigraphy and 47 underwent in-laboratory polysomnography. Sleep duration and architecture were measured by actigraphy and polysomnography, testicular volume by Prader orchidometer, total testosterone by liquid chromatography tandem mass spectrometry, free testosterone by equilibrium dialysis, and luteinizing hormone and follicle-stimulating hormone (FSH) by immunochemiluminometric assay.

Results: Sleep duration was correlated with testicular volume (r = .31, P = .046) and with FSH (r = −.30, P = .035), and rapid eye movement sleep was correlated with FSH (r = .44, P = .006). The significance of these findings did not change after adjustment for age and BMI, and were confirmed nonparametrically by resampling. A putative inverse U-shaped relationship between testicular volume and sleep duration was observed by polynomial regression (P = .049), but not with resampling (P = .068).

Conclusions: There is a positive linear and a possible inverse U-shaped relationship between sleep duration and testis volume. Longitudinal or interventional studies manipulating sleep are required to better define causality, and ultimately to establish how much sleep is needed to maximize male reproductive potential.

Clinical Trial Registration: Title: Hormonal Mechanisms of Sleep Restriction, Registry: ClinicalTrials.gov, Identifier: NCT02256865, URL: https://clinicaltrials.gov/ct2/show/NCT02256865

Keywords: actigraphy, fertility, male, sleep, testis

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Sleep is important for neurobehavioral performance and cardiometabolic health. Increasingly it is becoming recognized that sleep may be important for reproductive health.

Study Impact: Here we show for the first time that sleep duration is related to testis size, which is a measure of male reproductive health and highly valued by men. The potential existence of an inverse U-shaped relationship suggests that there may be an optimal amount of sleep that maximizes testis volume and male reproductive potential.

INTRODUCTION

Sleep is important for performance, and inadequate sleep is widely recognized to cause hypersomnolence and trigger neuropsychological deficits[1] that can lead to catastrophic errors.[2–6] Insufficient sleep is now increasingly recognized to also have important cardiometabolic sequelae such as the development of insulin resistance[7] and hypertension.[8] Insulin resistance is induced in part because inadequate sleep promotes poor food choices, increases weight, curtails fat loss while dieting, and reduces the effectiveness of weight loss programs.[3,7,9–13] The mechanisms underpinning these neuropsychological and cardiometabolic consequences of insufficient sleep are being elucidated. Effects on other critical physiological processes are less well studied, especially in humans.

Reproduction is a fundamental physiological process that is essential for the continuation of the species. In mammals, it is intricately linked to development through puberty and is regulated by the hypothalamic-pituitary-gonadal (HPG) axis, which exhibits infradian (ie, menstrual) rhythms in women, and circadian and ultradian (ie, pulsatile) rhythms in men and women. Restricting sleep reduces testosterone concentrations in men,[14,15] but effects on gonadotropins and on ultradian rhythms have not been studied. Nevertheless, these changes suggest that restricting sleep dysregulates the HPG axis through multiple mechanisms (reviewed in Andersen and Tufik[16]), which could in turn lead to multiple andrological diseases including impaired spermatogenesis and prostate diseases. Epidemiological studies support this hypothesis because sleep restriction accompanies circadian misalignment from shift work, and shift work is associated with male infertility,

symptoms of hypogonadism, and prostate diseases.[17] Interventional studies to directly test the effect of sleep restriction on semen parameters have not been performed because longer term sleep restriction to alter the 3-month spermatogenic cycle may be required. Cross-sectional studies are first needed to better justify such a major undertaking.

Available cross-sectional studies are suboptimal. No study has actually measured sleep duration, quantified sleep architecture, or assayed blood hormones by gold standard methods including total testosterone by mass spectrometry or free testosterone by equilibrium dialysis. All have required volunteers to produce semen samples by masturbation and this is known to cause marked selection bias.[18] Nevertheless, limited data from three cohorts are available, two of which suggest the possibility of inverse U-shaped relationships. The other (third) cohort is less relevant because it was conducted in men seeking fertility treatment and evaluated sleep disturbances, not sleep duration.[19] The first cohort was of Danish military recruits, and assessed sleep disturbances. Inverse U-shaped relationships with sperm concentration, total sperm count, and testis size were uncovered,[20] but are difficult to conceptualize because low and high sleep disturbances were both associated with poorer markers of male reproductive potential. The second cohort was of military cadets in China, and did assess sleep duration, but only by self-report. Inverse U-shaped relationships showing associations between short or long sleep with reduced semen volume, reduced total sperm count,[21] and high sperm deoxyribonucleic acid (DNA) stainability,[22] but not with other semen analysis parameters or with DNA fragmentation, were unveiled. However, daytime napping is common in China, and difficult to capture accurately, and the sleep patterns of college students, including military cadets, is highly variable. Furthermore, detailed andrological examinations may not have been systematically collected, as relationships with testis volume were not reported.

To address these limitations, we examined a cohort of normal healthy men who underwent a detailed andrological assessment as part of a comprehensive clinical, biochemical, and laboratory evaluation to rule out the presence of any illnesses including sleep, reproductive, and endocrine disorders. These men were being screened for an unrelated prospective study that was not primarily focused on reproductive potential. Sleep duration and architecture were comprehensively assessed: initially by self-report, and then by actigraphy to measure sleep at home and finally by formal polysomnography in a sleep laboratory to determine sleep architecture. Semen analysis was not required and total testosterone was measured by mass spectrometry and free testosterone by equilibrium dialysis in a laboratory certified by the Centers for Disease Control and Prevention hormone standardization program. Potential linear and U-shaped (inverse or otherwise) relationships among andrological parameters, sleep duration, and sleep architecture were evaluated.

METHODS

Study Design

The study was conducted in the sleep laboratory of the Clinical and Translational Research Center of Los Angeles Biomedical Research Institute at Harbor UCLA Medical Center, as part of an ongoing prospective study designed to determine the hormonal mechanisms by which sleep restriction induces insulin resistance. This report is of the baseline data, before any study interventions. Men aged 22 to 45 years were included in the study if they met inclusion and exclusion criteria, as listed in full in the following paragraphs. All participants provided written informed consent and the study protocol was approved by the Institutional Review Board. An independent study monitor periodically reviewed safety and progress, and the study was registered at clinicaltrials.gov: NCT 02256865.

Participants

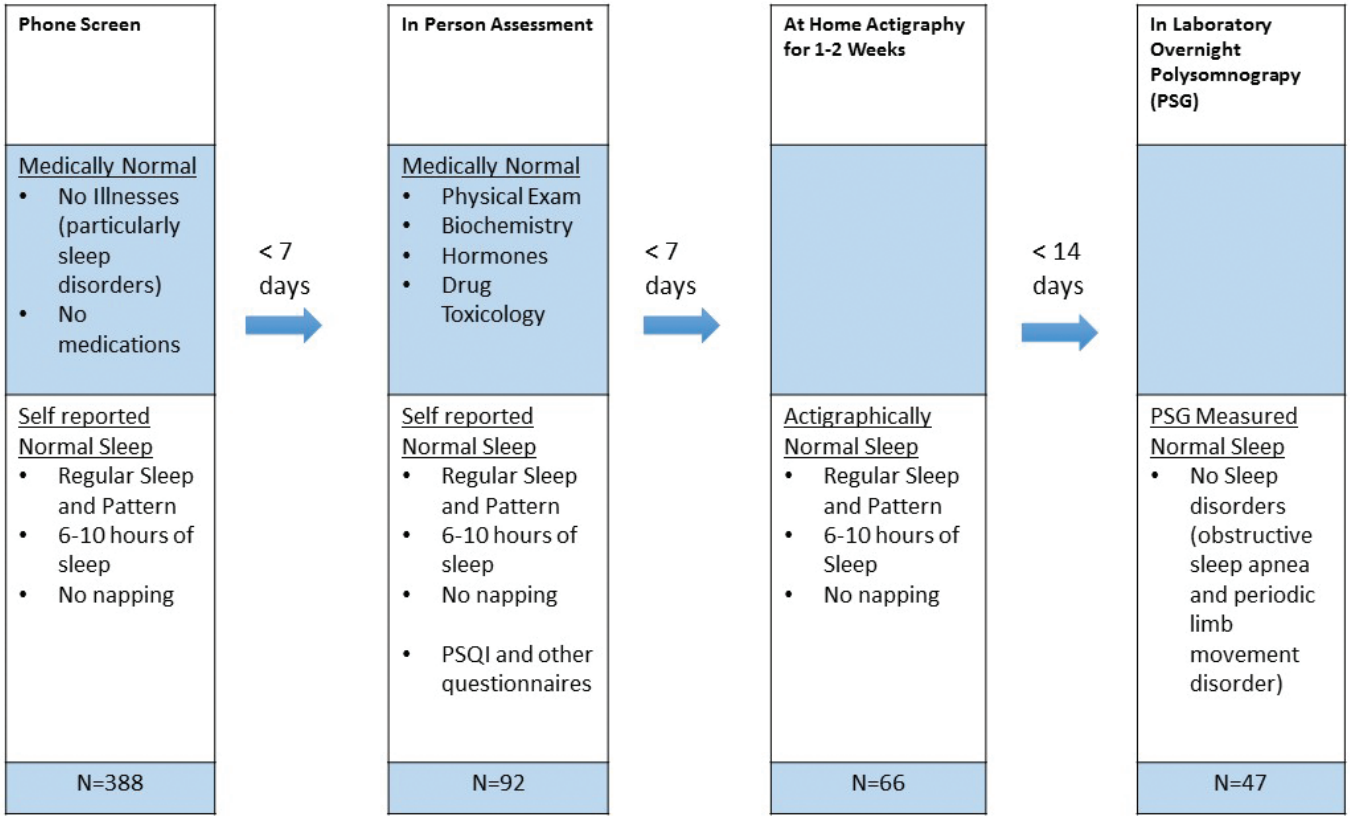
Respondents to public advertisement contacted study staff by phone and if still interested were invited for on-site screening, during which time a licensed medical practitioner obtained a history and performed a physical examination. The examination included a detailed andrological assessment including measurement of testicular volumes with the assistance of a Prader orchidometer and a digital rectal examination if the participant was older than 40 years. Testicular measurements were performed by two physicians (KP and WZ) under the supervision of an experienced andrologist (PYL), and agreement in measurements were periodically reviewed. A 12-lead electrocardiogram was obtained to confirm sinus rhythm. Blood was collected in the early morning (before 9:00 AM) in the fasting state for later measurement of total testosterone, free testosterone, luteinizing hormone (LH), FSH, thyroid stimulating hormone, cortisol, and prolactin. Hematological, renal, and metabolic diseases were screened for by complete blood count, comprehensive metabolic panel, lipids, and hemoglobin A1c. Illicit drug use was excluded by a urine drug screen. Depression, mood disorders, and erectile dysfunction were excluded by the Patient Health Questionnaire-9, Profile of Mood States questionnaire, Depression Anxiety Stress Scales, and the International Index of Erectile Function. Sleep quality and duration were determined by the Functional Outcome of Sleep Questionnaire, Epworth Sleepiness Scale, Pittsburgh Sleep Quality Index, and at-home actigraphy. Sleep architecture was determined, and sleep disorders excluded, by an in-laboratory polysomnography.

Participants who were normal and healthy by clinical and biochemical assessment (including blood hormones), and who remained interested, then underwent at home actigraphy for at least 1 week, in combination with an actigraphy log to document habitual sleep.[23] Those who demonstrated regular sleep patterns and no napping by actigraphy were then invited for overnight in-laboratory polysomnography to exclude sleep disorders (including obstructive sleep apnea (OSA) and periodic limb movement disorder). See **Figure 1** for flow diagram.

Inclusion Criteria

Eligible participants were men age 22 to 45 years, who met the following entry criteria: (1) BMI 20 to 28 kg/m^2 with stable weight over the previous 6 weeks; (2) physically and psychologically healthy (ie, no clinical disorders and /or illness); (3) no current medical or drug treatment; (4) no clinically significant abnormalities in blood and urine, and free of traces of

Figure 1—Flow diagram of typical screening process.



drugs; (5) no history of psychiatric illness; (6) no history of drug or alcohol abuse; (7) not a current smoker; (8) no endocrine disorders.

Exclusion Criteria

Participants were excluded from the study if they had any of the following: (1) unable or unwilling to provide Institutional Review Board-approved informed consent; (2) history of brain injury or of learning disability; (3) anemia (hematocrit < 38%); (4) blood donation in previous 8 weeks; (5) travel across time zones within 1 month of entering study; (6) sleep or circadian disorder; (7) shift work within 3 months of entering study; (8) concurrent participation in another research study.

Self-Reported Sleep Duration and Quality

Self-reported sleep duration and quality was determined from the Pittsburgh Sleep Quality Index.[24] Specifically, this instrument records recalled usual sleep, usual bedtime, and usual waketime during the past month. Usual sleep patterns are defined as the patterns that occurred on most days in the past month and does not separate weekday and weekend sleep.

Wrist Actigraphy

Men were instructed to wear the Actiwatch spectrum activity monitor (Philips Respironics, Murrysville, Pennsylvania, United States) on the nondominant wrist for at least 7 consecutive days (and up to 14 days) in conjunction with an actigraphy log, which is the recommended practice.[23] This is a wrist-worn device that detects acceleration (ie, movement), to a sensitivity of 0.025 G at a sampling rate of 32 Hz. Light was sensed in three visible color bands, and events could be marked within the device's solid state memory to compare against an actigraphy log of sleep and wake times, and times of Actiwatch removal (eg, while showering). Data were edited and analyzed using proprietary Actiware 5 software (Philips Respironics).

Polysomnography

Eligible participants were admitted to the sleep laboratory at 8:00 PM after dinner, and in-laboratory polysomnography was performed in a sound-attenuated, light- and temperature-controlled room. Participants were asked to go to bed and lights were switched off at 10:00 PM. They were awakened at 8:00 AM the next day if still asleep at that time. Electroencephalographic, electrooculographic, electromyographic, and respiratory recordings were obtained. Sleep stages (wake, N1, N2, N3, R), arousals, apneas, and hypopneas were scored by standard criteria, using contemporaneous American Academy of Sleep Medicine criteria.[25]

Reproductive Hormone Measurement

Blood samples were processed by centrifuge, separated, and stored at −20°C until assay. Serum FSH and LH were determined by immunochemiluminometric assay on a Siemens Centaur platform, analytic sensitivity were 0.7 mIU/mL and 0.2 mIU/mL, respectively. Serum total testosterone level was determined by liquid chromatography tandem mass

Table 1—Baseline characteristics.

	All Participants (n = 92)	Participants with Actigraphy (n = 66)	Participants with PSG (n = 47)
Demographics			
Age (years)	32.78 (6.24)	32.80 (6.29)	32.40 (6.77)
Weight (kg)	79.79 (11.5)	79.64 (10.53)	77.90 (10.06)
BMI (kg/m^2)	24.66 (6.07)	25.02 (5.23)	25.35 (2.97)
Summed testicular volume (mL)	49.31 (12.11)	48.49 (10.92)	48.77 (10.08)
Race (%)			
Asian	20	20	20
Pacific Islander	5	5	5
African American	30	25	20
Caucasian	40	40	50
Other	10	10	5
Ethnicity (%)			
Hispanic/Latino	30	35	35
Non-Hispanic	55	55	55
Other	15	10	10
Tobacco smoking (%)			
Never	80	80	80
Former	20	20	20
Alcohol (gram/day) (%)			
None	55	60	55
0–5	30	35	40
5–10	10	10	5
> 10	5	0	0
Sleep Duration			
Self-report (hours)	8.26 (1.29)	8.28 (1.28)	8.28 (1.09)
Actigraphy (hours)	7.97 (1.17)	7.97 (1.17)	8.05 (1.31)
PSG			
Sleep duration (hours)	7.39 (0.98)	7.46 (0.94)	7.39 (0.98)
Sleep efficiency (%)	86.81 (7.55)	86.93 (7.65)	86.81 (7.55)
REM sleep (hours)	1.60 (0.51)	1.62 (0.50)	1.60 (0.51)
Stage R sleep (%)	21.47 (5.42)	21.64 (5.47)	21.47 (5.42)
Stage N1 sleep (%)	7.77 (3.10)	7.93 (3.06)	7.77 (3.10)
Stage N2 sleep (%)	61.53 (8.46)	61.29 (8.56)	61.53 (8.46)
Stage N3 sleep (%)	9.38 (6.36)	9.29 (6.49)	9.38 (6.36)
Total arousal index (events/h)	3.59 (2.20)	3.59 (2.24)	3.59 (2.20)
Reproductive Hormone Levels			
Serum FSH (mIU/mL)	4.32 (2.55)	4.30 (2.37)	4.31 (2.43)
Serum LH (mIU/mL)	4.40 (1.69)	4.24 (1.5)	4.22 (1.48)
Serum total testosterone (ng/dL)	522.24 (149.82)	517.67 (150.66)	553.47 (140.94)
Serum-free testosterone (pg/mL)	95.00 (31.57)	92.37 (29.75)	100.68 (26.17)

Values are presented as mean (standard deviation) or % to nearest 5%.

spectrometry, and analytic sensitivity was 1 ng/dL. Free testosterone level was measured by tracer equilibrium dialysis. All coefficients of variation were ≤ 10%.

Statistical Analysis

This was an exploratory analysis of screening data using a prespecified hypothesis that sleep duration and sleep architecture could be associated with andrological parameters including testis volume and reproductive hormones.

Descriptive statistics, presented as mean ± standard deviation, were used to characterize the cohort. The strength and statistical significance of linear relationships among sleep parameters, hormone levels, and testicular volumes were assessed by Pearson correlation. Polynomial regression was conducted to test for a specific U-shaped relationship between sleep duration and testicular volume because this analysis was suggested *a priori* from the literature. Unadjusted models and models adjusted for BMI and age are presented, because these factors are known to be related to sleep and reproductive hormone concentrations. Data were resampled 10,000 and 100,000 times with replacement to nonparametrically confirm Pearson correlation and polynomial regression. Only data from bootstrapping 10,000 times are presented because results from 100,000 times resampling were congruent. Significance was

Table 2—Significant Pearson correlations among reproductive and sleep parameters.

		Model 1		Model 2	
		Before Resampling	After Resampling*	Before Resampling	After Resampling*
Testis Volume and Actigraphic Sleep Duration	*r*	.31	.39	.38	.39
	P	.046	.039	.020	.013
FSH and Actigraphic Sleep Duration	*r*	−.30	−.30	−.33	−.34
	P	.035	.030	.046	.017
FSH and Testis Volume	*r*	−.39	−.38	−.38	−.36
	P	.0030	.0042	.018	.0093
REM Sleep (minutes) and FSH	*r*	.44	.45	.43	.44
	P	.0060	.0042	.0086	.0066

Model 1: Pearson correlation, model 2: Pearson partial correlation, adjusted for age and BMI. * = median point estimate obtained after resampling with replacement 10,000 times.

Table 3—Polynomial regression of summed testicular volume and sleep duration.

			Model 1		Model 2	
			Before Resampling	After Resampling*	Before Resampling	After Resampling*
Testis Volume and Actigraphic Sleep Duration	Linear term	Coefficient	20.42	18.26	21.68	19.39
		P	.026	.043	.015	.032
	Quadratic term	Coefficient	−1.03	−.92	−1.08	−.95
		P	.049	.068	.034	.056

Model 1: polynomial regression, model 2: polynomial regression, adjusted for age and BMI. * = median point estimate obtained after resampling with replacement 10,000 times.

construed at two-tailed alpha = .05. Statistical analysis was performed using SAS statistical package version 9.3, and procs corr, glm, surveyselect, and univariate (SAS Institute, Cary, North Carolina, United States).

RESULTS

Study Participants

A total of 388 participants were telephone screened. Unmedicated individuals with normal sleeping patterns and without medical illnesses, particularly sleep disorders, were invited for in-person assessment. A total of 92 participants supplied written informed consent, and had no illnesses by clinical and biochemical criteria. Of these, 66 participants completed at least 1 week of actigraphy and 47 underwent in-laboratory polysomnography; see **Table 1**. Individuals with any medical illnesses (including hormonal or sleep disorders) were excluded from these analyses. Based on these demographics, those who underwent actigraphy or polysomnography appear to be representative of the entire group of 92 men. Very few men smoked cigarettes or drank alcohol.

Cross-Sectional Relationships

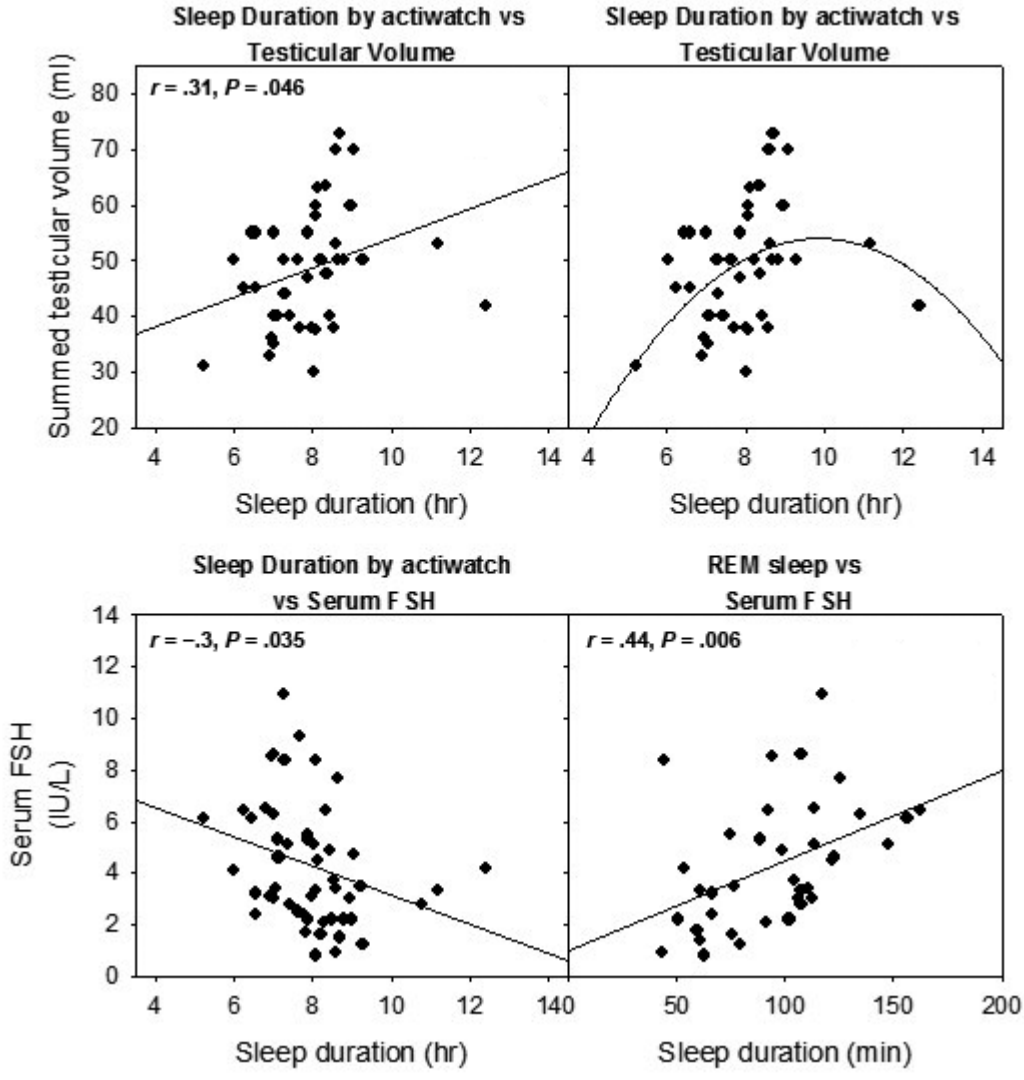
As expected, significant correlations between age and FSH (r = .023, P = .05), age and testosterone (r = −.31, P = .008), and BMI and testosterone (r = −.27, P = .02) were disclosed. Significant pairwise linear associations among reproductive parameters (summed testis volume, LH, FSH, testosterone), sleep duration (by self-report, actigraphy), and sleep architecture (sleep stages) are shown by Pearson correlation in **Table 2**. In brief, significant correlations between sleep duration (measured by actigraphy) and summed testis volume (r = .31, P = .046), sleep duration and FSH (r = −.30, P = .035), and rapid eye movement sleep and FSH (r = .44, P = .006) were disclosed; see **Figure 1**. The findings remained statistically significant after resampling (r = .39, P = .039; r −.30, P = .030; and r = .45, P = .004, respectively), and after adjustment for age and BMI: see **Table 2**. Sleep duration determined by self-report was not significantly associated with any of these parameters (data not shown). Sleep duration and architecture was not associated with total and free testosterone, or with LH (data not shown).

Polynomial regression with a linear and a quadratic term was undertaken to explore a U-shaped relationship between testis volume and sleep duration: see **Table 3** and **Figure 2**, upper right panel. The linear coefficient ranged from 18.26 to 21.68 before and after resampling, and with or without adjustment for age and BMI, and was statistically different from zero (P values ranged from .015 to .043) indicating that the addition of a quadratic term had little effect on the linear relationship: **Table 3**. This is congruent with findings from the Pearson correlational analyses. In contrast, the quadratic term was −1.03 and −1.08, and significantly different from zero without and with adjustment for age and BMI, respectively. After resampling, the statistical significance of these findings was not confirmed (P = .068 and P = .056, respectively).

DISCUSSION

Our main finding is that sleep duration is linearly, and also possibly quadratically, related with testis volume. We show this in

Figure 2—Scatterplots of sleep duration with testis volume (upper left and upper right), sleep duration with serum FSH (lower left), and REM sleep duration with serum FSH (lower right).



Linear and quadratic regression lines are shown.

a cohort of healthy young men who were participating in an unrelated mechanistic trial, and not overtly interested in their reproductive potential. We reasoned that such a cohort would complement cohorts where semen analysis was the main variable of interest, because studies that require semen collection are known to cause marked selection bias.[18] Previous studies linking sleep duration with testis volume are not available, although others have shown that self-reported sleep duration is related to semen parameters.[21] Testicular volumes measured by Prader orchidometer remain the foundation of the standard andrological examination, and such measurements have long been accepted as important clinical markers of male fertility that correlate positively with sperm count.[26] More recent studies have confirmed this positive correlation between testicular volumes and semen analysis, using modern ultrasound equipment.[27,28] The use of testicular ultrasound would have increased the precision of the measurements, reduced the standard deviation, and thereby increased the likelihood of unveiling significant correlations. However, we show significant correlations with a less precise method, which suggests that our findings are robust.

An earlier study showed inverse-U shaped relationships between sleep duration and semen parameters and concluded that semen volume and total sperm count fell with sleep durations less than or equal to 6.5 hours or more than 9 hours.[21] Our analyses by polynomial regression show that the highest testicular volumes occurred with a sleep duration of approximately 9.5 hours. However, our analyses, although significant with and without adjustment for age and BMI, were not confirmed by our resampling procedure, which was implemented to remove the effects of extreme values and to provide model-free verification of the foregoing parametric analyses. Accordingly, these data should be interpreted as being suggestive, not conclusive, of an inverse U-shaped relationship between sleep duration and testicular size. Future studies using more precise methods to measure sleep duration or testicular volumes, or in a larger cohort, would be required to determine the ideal sleep duration at which the largest testicular volumes are observed.

We also show that serum FSH is inversely related to testicular volume. This is a surprising finding because the FSH receptor is expressed exclusively on testicular Sertoli cells, and a direct, rather than an inverse, relationship might have been predicted. However, an inverse relationship between FSH and testicular volume has been shown many times previously in different cohorts.[26–28] This inverse relationship suggests that FSH acts as a barometer of testicular function through negative feedback.[29] Such a hypothesis might also explain the inverse relationship between sleep duration and FSH that we discovered for the first time, but the cross-sectional nature of the relationship requires replication in another cohort because no relationship between sleep duration and FSH was reported in an earlier study.[21]

Our study, and an earlier cross-sectional study,[21] did not show any relationship between sleep duration with total or free testosterone. Our study in particular used gold standard methods to measure total and free testosterone. However, interventional studies where sleep is restricted causes a reduction in testosterone concentrations in young men.[14,15] The reasons for this discrepancy could include the marked reduction in sleep (from 10 hours to 5 hours sleep opportunity each night), and the relatively acute, rather than chronic, nature of the intervention. In-laboratory sleep changes may also have a different effect compared with in-the-field changes, because multiple factors including the order of interventions, can be strictly controlled. Additionally, we assume that our measurements reflect "usual" (or chronic) sleep patterns, and recognize that the sampling period influences the reliability of this assessment. For example, sampling for 1 week (as occurred by actigraphy), and 1 month (as occurred by recalled self-reported sleep), is more likely to capture chronic sleep patterns reliably than from a single night of polysomnography. However, polysomnography is the only method to determine sleep architecture.

Sleep architecture was not associated with testicular volumes. A preliminary new finding is that rapid eye movement (REM) sleep duration is positively associated with serum FSH. This finding is not entirely unexpected because peak testosterone concentrations occur during REM sleep, and alterations in REM sleep due to OSA or age have been associated with lower testosterone concentrations.[16] Earlier studies have also shown that LH, but not FSH, secretion is associated with REM sleep.[30] Importantly, previous studies[16,30] have linked sleep architecture with LH or testosterone by showing concordance within an individual of two events: an increase in hormone concentrations indicating recent pulsatile release, and sleep stage. Our analytical method is different, and shows a correlation between hormone concentrations and the duration of a specific sleep stage. Such correlations have not been previously reported, and would therefore require replication. A limitation of this and all cross-sectional studies is that causality and the direction of the association cannot be determined. A possible explanation could be that greater REM sleep might increase FSH, promote spermatogenesis, and increase testicular volumes. Such a hypothesis would be compatible with the known physiology of the male gonadal axis, and provide a testable mechanism to explain why increased sleep duration could increase testicular volume.

Strengths of this study include the actual measurement of sleep duration by actigraphy at home, and of sleep architecture by in-laboratory polysomnography. The lack of association with self-reported sleep duration emphasizes that such assessments are less precise, thereby requiring larger cohorts to unveil significant associations. Our study, although and perhaps because it was smaller, allowed for deeper phenotyping of sleep and reproductive function. Future interventional studies manipulating sleep duration or sleep architecture in the longer term will be required to confirm these preliminary findings.

ABBREVIATIONS

BMI, body mass index
DNA, deoxyribonucleic acid
FSH, follicle stimulating hormone
HPG, hypothalamic-pituitary-gonadal
LH, luteinizing hormone
OSA, obstructive sleep apnea
REM, rapid eye movement
UCLA, University of California – Los Angeles

REFERENCES

1. Banks S, Van Dongen HP, Maislin G, Dinges DF. Neurobehavioral dynamics following chronic sleep restriction: dose-response effects of one night for recovery. *Sleep.* 2010;33(8):1013–1026.
2. Mitler MM, Carskadon MA, Czeisler CA, Dement WC, Dinges DF, Graeber RC. Catastrophes, sleep, and public policy: consensus report. *Sleep.* 1988;11(1):100–109.
3. Van Dongen HP, Maislin G, Mullington JM, Dinges DF. The cumulative cost of additional wakefulness: dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. *Sleep.* 2003;26(2):117–126.
4. Banks S, Dinges DF. Behavioral and physiological consequences of sleep restriction. *J Clin Sleep Med.* 2007;3(5):519–528.
5. Lockley SW, Cronin JW, Evans EE, et al. Effect of reducing interns' weekly work hours on sleep and attentional failures. *N Engl J Med.* 2004;351(18):1829–1837.
6. Basner M, Dinges DF. Dubious bargain: trading sleep for Leno and Letterman. *Sleep.* 2009;32(6):747–752.
7. Killick R, Banks S, Liu PY. Implications of Sleep Restriction and Recovery on Metabolic Outcomes. *J Clin Endocrinol Metab.* 2012;97(11):3876–3890.
8. Khan MS, Aouad R. The effects of insomnia and sleep loss on cardiovascular disease. *Sleep Med Clin.* 2017;12(2):167–177.
9. Killick R, Hoyos CM, Melehan KL, Dungan GC 2nd, Poh J, Liu PY. Metabolic and hormonal effects of 'catch-up' sleep in men with chronic, repetitive, lifestyle-driven sleep restriction. *Clin Endocrinol (Oxf).* 2015;83(4):498–507.
10. Nedeltcheva AV, Kilkus JM, Imperial J, Schoeller DA, Penev PD. Insufficient sleep undermines dietary efforts to reduce adiposity. *Ann Intern Med.* 2010;153(7):435–441.
11. Spaeth AM, Dinges DF, Goel N. Effects of experimental sleep restriction on weight gain, caloric intake, and meal timing in healthy adults. *Sleep.* 2013;36(7):981–990.
12. Meerlo P, Sgoifo A, Suchecki D. Restricted and disrupted sleep: effects on autonomic function, neuroendocrine stress systems and stress responsivity. *Sleep Med Rev.* 2008;12(3):197–210.
13. Nedeltcheva AV, Kilkus JM, Imperial J, Kasza K, Schoeller DA, Penev PD. Sleep curtailment is accompanied by increased intake of calories from snacks. *Am J Clin Nutr.* 2009;89(1):126–133.

14. Leproult R, Van Cauter E. Effect of 1 week of sleep restriction on testosterone levels in young healthy men. *JAMA.* 2011;305(21):2173–2174.
15. Reynolds AC, Dorrian J, Liu PY, et al. Impact of five nights of sleep restriction on glucose metabolism, leptin and testosterone in young adult men. *PLoS One.* 2012;7(7):e41218.
16. Andersen ML, Tufik S. The effects of testosterone on sleep and sleep-disordered breathing in men: its bidirectional interaction with erectile function. *Sleep Med Rev.* 2008;12(5):365–379.
17. Deng N, Kohn TP, Lipshultz LI, Pastuszak AW. The relationship between shift work and men's health. *Sex Med Rev.* 2018;6(3):446–456.
18. Muller A, De La Rochebrochard E, Labbe-Decleves C, et al. Selection bias in semen studies due to self-selection of volunteers. *Hum Reprod.* 2004;19(12):2838–2844.
19. Vigano P, Chiaffarino F, Bonzi V, et al. Sleep disturbances and semen quality in an Italian cross sectional study. *Basic Clin Androl.* 2017;27:16.
20. Jensen TK, Andersson AM, Skakkebaek NE, et al. Association of sleep disturbances with reduced semen quality: a cross-sectional study among 953 healthy young Danish men. *Am J Epidemiol.* 2013;177(10):1027–1037.
21. Chen Q, Yang H, Zhou N, et al. Inverse U-shaped association between sleep duration and semen quality: longitudinal observational study (MARHCS) in Chongqing, China. *Sleep.* 2016;39(1):79–86.
22. Wang X, Chen Q, Zou P, et al. Sleep duration is associated with sperm chromatin integrity among young men in Chongqing, China. *J Sleep Res.* 2018;27(4):e12615.
23. Ancoli-Israel S, Martin JL, Blackwell T, et al. The SBSM guide to actigraphy monitoring: clinical and research applications. *Behav Sleep Med.* 2015;13 Suppl 1:S4-S38.
24. Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res.* 1989;28(2):193–213.
25. Rechtschaffen A, Kales A. *A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects.* Bethesda, MD: National Institute for Neurological Disease and Blindness; 1968.
26. Aribarg A, Kenkeerati W, Vorapaiboonsak V, Leepipatpaiboon S, Farley TM. Testicular volume, semen profile and serum hormone levels in fertile Thai males. *Int J Androl.* 1986;9(3):170–180.
27. Bahk JY, Jung JH, Jin LM, Min SK. Cut-off value of testes volume in young adults and correlation among testes volume, body mass index, hormonal level, and seminal profiles. *Urology.* 2010;75(6):1318–1323.
28. Hart RJ, Doherty DA, McLachlan RI, et al. Testicular function in a birth cohort of young men. *Hum Reprod.* 2015;30(12):2713–2724.
29. Liu PY, Veldhuis JD. The hypothalamo-pituitary unit, testis and male accessory organs. In: Strauss JF, Barbieri RL, eds. *Yen and Jaffe's Reproductive Endocrinology: Physiology, Pathophysiology and Clinical Management.* 8th ed. Philadelphia, PA: WB Saunders; 2018:285–300.
30. Rubin RT, Gouin PR, Kales A, Odell WD. Luteinizing hormone, follicle stimulating hormone, and growth hormone secretion in normal adult men during sleep and dreaming. *Psychosom Med.* 1973;35(4):309–321.

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