Obstructive sleep apnea is not an independent determinant of testosterone in men

Brigette Marie Clarke[1,2], Andrew D Vincent[3], Sean Martin[2,3], Robert Adams[2,4], Sarah Appleton[2,3,4], Andrew Vakulin[4,5], David Jesudason[1,2,6] and **Gary Allen Wittert[1,2,3]**

[1]Department of Endocrinology and Metabolism, Royal Adelaide Hospital, Adelaide, South Australia, Australia, [2]School of Medicine, The University of Adelaide, Adelaide, South Australia, Australia, [3]Freemason Foundation Centre for Men's Health, University of Adelaide, Adelaide, South Australia, Australia, [4]Adelaide Institute for Sleep Health: A Flinders Centre of Research Excellence, College of Medicine and Public Health, Flinders University, Bedford Park, South Australia, Australia, [5]NeuroSleep – NHMRC Centre of Research Excellence, Woolcock Institute of Medical Research, University of Sydney, Sydney, New South Wales, Australia, and [6]Department of Endocrinology and Diabetes, Queen Elizabeth Hospital, Woodville, South Australia, Australia

Correspondence should be addressed to G A Wittert
Email
gary.wittert@adelaide.edu.au

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Abstract

Objective: Obstructive sleep apnea (OSA) is generally considered to lower serum testosterone concentration in men, although data supporting this as a direct effect are limited. The aim of this study was to determine the relationship between the presence and severity of OSA and testosterone in a community-based cohort of men aged over 40 years.
Design and methods: Anthropometry, polysomnography and biomedical information were collected from enrolled, consenting men from the prospective, longitudinal MAILES study cohort. Fasting morning blood samples (n = 1869) were drawn between 2010 and 2012 for measurement of testosterone using liquid chromatography mass spectrometry. Home polysomnography was completed in 861 men between 2010 and 2012. The final analysis sample consisted of 623 men aged 41–86 years. The effect of OSA on testosterone were analyzed using linear regression models controlling for potential confounders (age, BMI and sex hormone binding globulin (SHBG)).
Results: The mean (s.d.) cohort characteristics were: age 59.0 (10.2) years, testosterone 16.8 (5.3) nmol/L, SHBG 32.9 (13.1) nmol/L, BMI 28.6 (4.2) kg/m^2 and apnoea hypopnoea index (AHI) 14.9 (13.7). OSA was present in 51.5%. There was an inverse relationship between AHI and testosterone ($P = 0.01$), which was lost after covariate adjustment.
Conclusions: These data suggest that obesity, rather than OSA *per se*, determine testosterone concentration. This accords with the graded effect of weight loss, but limited effect of continuous positive airway pressure to increase testosterone, and highlights the importance of managing obesity in men with low testosterone concentration, particularly in the context of OSA.

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Introduction

Obstructive sleep apnea (OSA) is characterised by the recurrent interruption of breathing during sleep due to a collapse of the upper airways. Recent data from different countries reveal it to be a common disorder, with a reported prevalence around 50% in middle-aged and older men (1, 2). Although not an exclusively obesity-related condition, the prevalence of OSA rises with increasing obesity. In patients being evaluated for bariatric surgery, 71% of individuals with a BMI between 35–40 kg/m^2 were diagnosed with OSA on polysomnography, with the figure rising to 95% among those with class 3 obesity and a BMI >60 kg/m^2 (3). These findings were supported by a recent

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systematic review that found rising BMI to be a factor associated with an increase in OSA prevalence (4).

An inverse relationship between the presence of OSA and serum testosterone concentration in men has been reported in some (5, 6, 7, 8) but not all studies (9, 10, 11). Interpretation of many of these studies has been hampered by observational study design, small sample sizes and limited or absent covariates in the data analyses (5, 6, 7, 8). The largest study cohort studying this association detected a relationship between low testosterone concentration and OSA; however, this association became non-significant after adjustment for either BMI or waist circumference (9).

Given the discrepant data and still widely held clinical view that OSA causes low testosterone levels, we examined the relationship between the presence and severity of OSA and serum testosterone concentration in a comprehensively characterized community dwelling cohort of middle-aged and elderly men, approximately half of whom were randomly invited to undergo a home sleep study (12).

Subjects and methods

Study participants and protocol

The Men Androgen Inflammation Lifestyle Environment and Stress (MAILES) Study, as has previously been described (12), includes randomly selected men from the community, aged 35 years or more at enrolment. The study was approved by the Human Research Ethics Committees of the Royal Adelaide Hospital (approval number: 020305) and North West Adelaide Health Service (approval number: 2010054). All participants provided written informed consent after full explanation of the purpose and nature of the study. Data for analysis in the current study were collected from follow-up biomedical assessments, including fasting blood samples completed between 2007 and 2010 (time point codes M2, M3) and sleep assessments (M4) completed between September 2010 and February 2012.

A computer-assisted telephone interview was completed by MAILES study participants (n=1,629) to identify men with a prior diagnosis of OSA. Subjects reporting 'No' when asked 'Have you ever been diagnosed with OSA with a sleep study?' were invited to undergo a sleep study. Overall, 1087 of 1445 without a previous OSA diagnosis (75.2%) initially agreed to participate (12). From this group, a randomly selected sample (n=861) underwent polysomnography. A total of 238 men were subsequently excluded from the data analysis due to known hypothalamic-pituitary-gonadal (HPG) disease (n=43), pre-existing use of medications known to affect testosterone concentration, SHBG or sleep (n=76), presence of active malignancy (n=20) or missing primary measurement values (BMI, AHI or testosterone) (n=99). The final analysis group consisted of 623 men, aged 41 to 86 years. The methods of population selection for the analysis are outlined in Fig. 1.

Anthropometry

Anthropometric measures and current medications were recorded at the time of sleep study completion. Weight, height and waist circumference were recorded to the nearest 0.1 kg and 0.1 cm, respectively, according to methods as previously described (13). BMI in kilograms per metre squared was calculated according to routine methodology. Overweight and obesity were defined by the standard BMI thresholds 25 and 30 kg/m^2, respectively.

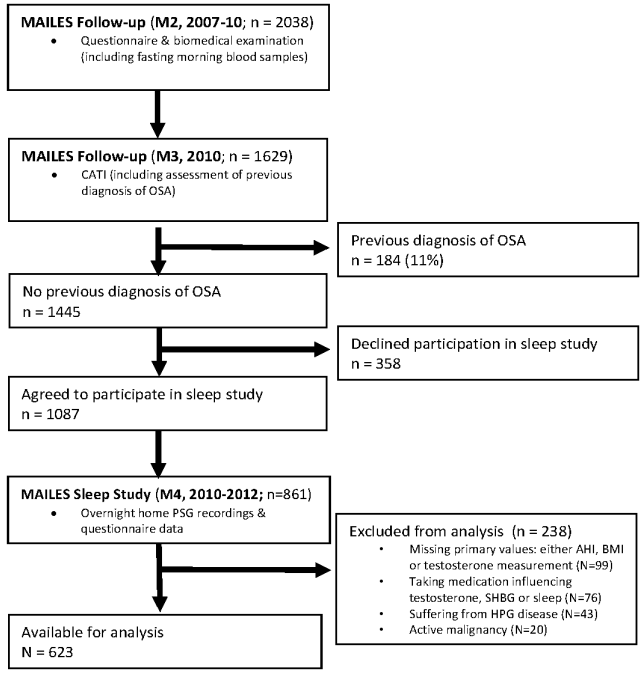

Figure 1

Participant flow chart for study analysis cohort. MAILES, men androgen inflammation lifestyle environment and stress study; CATI, computer assisted telephone interview; OSA, obstructive sleep apnoea; PSG, polysomnography; AHI, apnea hypopnea index; BMI, body mass index; SHBG, sex hormone binding globulin; HPG, hypothalamic pituitary gonadal.

Polysomnography

Participants were visited in their homes by trained staff to complete 8-channel in-home unattended polysomnography (Embletta X100, Embla Systems, Thornton, CO, USA) for measurement of EEG, electrooculogram, electromyogram, nasal pressure, thoracic and abdominal effort, oximetry and body position.

All home polysomnography reports were scored manually by a single experienced sleep technician according to the 2007 American Academy of Sleep Medicine criteria (14). Hypopneas were defined as a greater than 50% reduction in nasal pressure or in both thoracic and abdominal excursions, in conjunction with a ≥3% oxygen desaturation or arousal on EEG. An apnea hypopnea index (AHI) ≥10 per h was used to define the presence of OSA, with severity based on the International Classification of Sleep Disorders (ICSD-2) and classified as follows: mild: AHI 10–19; moderate: 20–29 and severe: ≥30 per h. The rationale for selecting these thresholds in our cohort has been previously described (15) and was based on an AHI cut off of five events/h, as used to define sleep-disordered breathing in the Wisconsin Sleep Cohort Study (16), having been determined to be approximately equivalent to an AHI of ten events/h using the alternate American Academy criteria (17). The total sleep time with oxygen desaturation below 90% (TST90) and oxygen desaturation index (ODI), describing the average number of oxygen desaturation events ≥3% per h, were extracted from oximetry data.

Assays

Blood plasma samples were collected by venepuncture in the morning following an overnight fast and stored at −80°C. Total testosterone was assayed by API-5000 triple-quadruple mass spectrometer (Applied Biosystems/MDS SCIEX) (18). The inter-assay coefficients of variation (CV) for the testosterone assay were 10.2% at 0.43 nmol/L, 11.1% at 1.66 nmol/L and 4% at 8.17 nmol/L. Sex hormone binding globulin (SHBG) and glycated haemoglobin (HbA1c) were measured using two-site chemiluminescent immunoassay and HPLC, respectively, in a NATA certified laboratory (SA Pathology, Adelaide, Australia).

Statistical analysis

Associations between baseline covariates and measured testosterone concentrations were assessed using Jonckheere's trend tests. Baseline covariates included general demographics (age, marital status and years of shift work), average consumption habits (alcohol, caffeine and smoking), measures of adiposity (BMI and waist circumference), metabolic morbidities (diabetes and triglycerides), endocrine (SHGB) and polysomnography measures (AHI, arousal index, TST90 and ODI). For these analyses subjects were divided by testosterone concentration quartiles (Q1: ≤13.1, Q2: 13.1–16.3, Q3: 16.3–20.2 and Q4: >20.2).

To evaluate the effect of OSA on testosterone concentration, linear regression analyses were constructed for each of the sleep parameters AHI, ODI, TST90 and arousal index. For each linear regression model, covariate adjustment included log SHBG (model 1), secondly for a combination of log SHBG, BMI and study arm (model 2) and finally all three of these factors plus age (model 3). In each of these models, the measures of OSA included were as linear continuous predictors, with total testosterone being log transformed. Examination of residual distributions ensured that assumptions concerning error distributions were not unduly violated. For each model coefficent described, we report the standardized estimate, 95% CI and *P*-value.

Each of the multiply adjusted models (model 3) were extended using restricted cubic splines with four degrees of freedom. Log-likelihood ratio tests of the nested linear continuous models and the non-linear models were used to assess the presence of non-linear associations between OSA measures and total testosterone. To present non-linear estimates of the final models (model 3), the OSA continuous measures were replaced with these measures divided into quartiles. The exception in this model being AHI, for which standard thresholds based on OSA severity categories (no OSA: AHI ≤ 10; mild OSA: 10 < AHI ≤ 20; Moderate: 20 < AHI ≤ 30 and Severe AHI: > 30) are presented.

As data collection was sequential rather than from a single time point, post-hoc stability analyses were undertaken in order to evaluate the assumption of stability of both total testosterone concentration and OSA within individual subjects over the study period. Correlations in testosterone concentrations between time points M1 and M2 and BMI measurements from M2 and M4 were evaluated. A subsequent subgroup sensitivity analysis was completed to determine the effect that variation within these parameters may have had on the primary outcome in men with minimal variation in testosterone. In all analyses significance is set at 0.05 (two-sided). Statistical analyses were conducted using R version 3.5.0.

Results

The mean (s.d.) age of the 623 men analyzed was 59 (10) years, with an average (s.d.) BMI of 28.2 (4.2) kg/m^2 (Range: 17.2–46.7 kg/m^2). Testosterone concentration ranged from 4.5 to 38.5 nmol/L, with a mean (s.d.) of 16.8 (5.3) nmol/L. The proportion of individuals with testosterone concentration measured below the thresholds of 6.0 mmol/L, 8.0 mmol/L and 10.0 mmol/L were 0.3%, 2.4% and 8.0%, respectively. The prevalence of OSA of any severity was 51%. The breakdown by OSA severity category was as follows: mild: 26%, moderate: 14% and severe: 11%.

The distribution of demographic, lifestyle, comorbidities, hormonal, anthropomorphic and sleep parameters according to measured total testosterone quartiles are provided in Table 1. There were strong associations between testosterone levels and both measures of adiposity, the presence of either diabetes or hypertriglyceridemia, SHBG, TST90 (all $P<0.0001$) and ODI ($P=0.0002$). A weak negative association was apparent between total testosterone levels and AHI ($P=0.04$).

In the linear regression models of log testosterone, after adjustment for SHBG there were negative associations with AHI, ODI (both $P=0.01$) and TST90 ($P=0.0008$), but not arousal index ($P=0.08$). After additional adjustment

Table 1 Patient characteristics by total testosterone quartiles.

	All	Q1	Q2	Q3	Q4	
	n = 623	*n* = 157	*n* = 157	*n* = 153	*n* = 156	***P*-value**
Cohort						0.008
NWAHS	262 (42%)	60 (38%)	55 (35%)	68 (44%)	79 (51%)	
FAMAS	361 (58%)	97 (62%)	102 (65%)	85 (56%)	77 (49%)	
Demographics						
Age (M4)	59 (10.2)	61.3 (9.8)	57.2 (9.8)	59.2 (9.7)	58.5 (11.3)	0.08
Marital Status (M4)						0.24
Partner	502 (81%)	131 (83%)	126 (80%)	125 (82%)	120 (77%)	
Single	120 (19%)	26 (17%)	31 (20%)	28 (18%)	35 (23%)	
Shift work, years (M3)						0.08
None	302 (49%)	67 (44%)	74 (47%)	81 (54%)	80 (51%)	
less than 3 years	105 (17%)	22 (14%)	35 (22%)	23 (15%)	25 (16%)	
3 or more years	211 (34%)	65 (42%)	48 (31%)	47 (31%)	51 (33%)	
Lifestyle (M2)						
Alcohol, StD/day	1.7 (3.7)	1.7 (5.5)	1.9 (3.1)	1.5 (2.4)	1.6 (3.1)	0.32
Coffee, cups/day	1.8 (1.6)	1.7 (1.5)	1.8 (1.5)	1.8 (1.8)	1.9 (1.6)	0.66
Smoking history						0.37
Never	248 (40%)	64 (41%)	58 (37%)	64 (42%)	62 (40%)	
Past	270 (44%)	80 (51%)	65 (42%)	61 (40%)	64 (42%)	
Current	101 (16%)	13 (8%)	33 (21%)	27 (18%)	28 (18%)	
Adiposity (M4)						
BMI	28.6 (4.2)	30.5 (4.3)	29 (4.2)	28 (3.6)	27 (3.9)	<0.0001
Waist circumference (cm)	102 (11.7)	106.6 (11)	102.8 (11.8)	101.2 (10.8)	97.5 (11.6)	<0.0001
Metabolic Morbidities						
Diabetes (M2)						<0.0001
No diabetes	471 (77%)	93 (61%)	120 (77%)	124 (83%)	134 (87%)	
Diabetes	141 (23%)	60 (39%)	36 (23%)	25 (17%)	20 (13%)	
High triglycerides (M2)						<0.0001
No, TG ≤1.7 mmol/L	397 (64%)	77 (49%)	106 (68%)	94 (61%)	120 (77%)	
Yes, TG >1.7 mmol/L	226 (36%)	80 (51%)	51 (32%)	59 (39%)	36 (23%)	
Endocrine						
SHBG (M2)	32.9 (13.1)	23.6 (8.4)	30 (9.6)	34.4 (10.8)	43.9 (13.8)	<0.0001
Polysomnography (M4)						
AHI (1/h)	14.9 (13.7)	17.2 (15.5)	14.6 (11.6)	14.1 (14.5)	13.8 (12.6)	0.04
Arousal Index (1/h)	18.1 (7.8)	19.2 (8.8)	17.5 (7.5)	17.9 (7.8)	17.7 (7.1)	0.39
TST90 (min)	16.2 (40.6)	21.4 (45.9)	18.2 (50.9)	16 (34.9)	9.3 (25.1)	<0.0001
ODI (1/h)	12.2 (12.5)	14.8 (14.7)	11.7 (9.6)	11.6 (13.6)	10.5 (11.2)	0.0002

Testosterone quartile divisions were as follows: Q1: ≤13.1, Q2: 13.1–16.3, Q3: 16.3–20.2, Q4: >20.2 nmol/L. Time points for data collection are annotated by M2, M3 and M4.

AHI, apnea hypopnea index; FAMAS, Florey Adelaide Male Aging Study cohort; NWAHS, North West Adelaide Health Study cohort; ODI, oxygen desaturation index; SHBG, sex hormone binding globulin; StD, standard drinks; TG, triglycerides; TST90, total sleep time with oxygen saturation below 90%.

for BMI and study (Florey Adelaide Male Aging Study (FAMAS) vs North West Adelaide Health Study (NWAHS)), there were no detectable linear associations between testosterone and either AHI or ODI, though the association between testosterone and TST90 remained weakly significant. No detectable linear associations between testosterone and any of the four OSA measures remained after further adjustment for age (Fig. 2 and Table 2). In these analyses, BMI and age were both strongly negatively associated with log testosterone, while SHBG was strongly positively associated (all $P<0.0001$, Supplementary Table 1, see section on supplementary materials given at the end of this article).

Extending these multivariable models with restricted cubic splines and comparing linear vs non-linear models using log-likelihood ratio tests indicated a weak non-linear association with AHI ($P=0.04$). There was no evidence for non-linear associations with either ODI ($P=0.17$), TST90 ($P=0.99$) or arousal index ($P=0.92$). In the model with non-linear AHI, 54.6% of the variation of log testosterone was explained, as compared to 53.8% that is explained by the four covariates alone (age, BMI, log SHBG and study). Replacing continuous AHI with the four-level discretised version (none, mild, moderate vs severe) indicated an inverted U-shape with log-transformed total testosterone higher in men with mild ($P=0.04$) or moderate ($P=0.03$) OSA as compared to men with negligble OSA (Supplementary Table 2).

The post-hoc stability analyses demonstrated that BMI remained very stable overtime (correlation, 0.95), though there was some variability in total testosterone (correlation 0.72) (Supplementary Fig. 1). However, restriction of the cohort to include only men in whom changes of less than 25% in total testosterone were observed ($n=466$), the associations between total testosterone and OSA measures were almost unchanged from the analyses in the full cohort, though widening of CIs is noted, in keeping with the smaller sample size (Supplementary Table 3).

Discussion

OSA is a common disorder, with an overall prevalence of more than 50% found in our study population of community dwelling men with no known history of OSA. This rate is similar to those reported in other populations of middle-aged and older men in recent years (1, 2). It appears that OSA remains significantly under-diagnosed in the community, evident by only 11% of our population screened for sleep study participation reporting a history of diagnosed OSA.

The main findings from our results suggest that OSA is not an independent determinant of serum testosterone concentration in community dwelling middle-aged and older men. Though there was a linear association between lower measured total testosterone concentration and more severe sleep disordered breathing as measured by both AHI and ODI, the association was lost with adjustment for BMI. Supplementary Table 1 reports the parameter estimates for the AHI M3 model (Table 2) in full and confirms there is no association between testosterone and AHI after adjustment for confounding by age and BMI. This model assumes linearity, and under this assumption there is no evidence of differences in testosterone levels with mild to moderate OSA. Increased total duration of oxygen desaturation, as measured by the TST90, was also

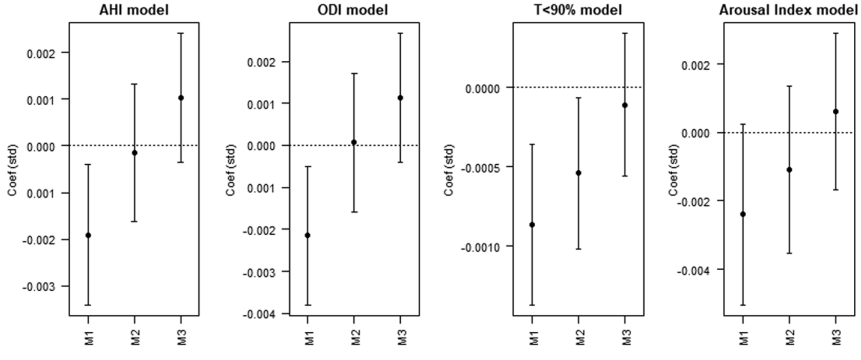

Figure 2
Effect of OSA parameters on testosterone concentration, after adjustment for covariates. The linear regression model estimates and 95% CIs for the effect of different OSA parameters on (log) testosterone concentration, after adjustment for covariates are represented. Model 1: adjustment for log SHBG. Model 2: adjustment for log SHBG, BMI and study arm. Model 3: adjustment for log SHBG, BMI, study arm and age. AHI, apnea hypopnea index; ODI, oxygen desaturation index; TST90, total sleep time with oxygen saturation below 90%.

Table 2 Linear regressions of log total testosterone on AHI, ODI, TST90 and arousal index.

	Model 1		Model 2		Model 3	
	Coef (95%CI)	*P*-value	Coef (95%CI)	*P*-value	Coef (95%CI)	*P*-value
AHI	−0.026 (−0.047, −0.0055)	0.01	−0.0019 (−0.022, 0.018)	0.85	0.014 (−0.0047, 0.033)	0.14
ODI	−0.027 (−0.048, −0.0063)	0.01	0.00083 (−0.02, 0.021)	0.94	0.014 (−0.0049, 0.033)	0.15
TST90	−0.035 (−0.056, −0.015)	0.0008	−0.022 (−0.041, −0.0026)	0.03	−0.0045 (−0.023, 0.014)	0.63
Arousals	−0.019 (−0.039, 0.0019)	0.08	−0.0085 (−0.028, 0.011)	0.39	0.0047 (−0.013, 0.023)	0.61

For each measure of obstructive sleep apnea, three models are constructed adjusting for (model 1) log SHBG, (model 2) log SHBG, BMI and study (FAMAS vs NWAHS) and (model 3) log SHBG, age, BMI and study. Standardized coefficients are reported.
AHI, apnea hypopnea index; ODI, oxygen desaturation index; TST90, total sleep time with oxygen saturation below 90%.

associated with lower testosterone concentration; and though the relationship remained borderline significant after adjustment for BMI, the association was again lost after adjustment for age.

Several past observational studies have reported outcomes contrary to our results, finding a negative relationship between testosterone concentration and the presence of OSA that is independent of BMI. However, all of these studies have been limited by small study populations, with cohorts of less than 100 subjects (5, 6, 7, 8, 10, 11). Other limitations include failure to clearly account for other factors that may influence testosterone (5), failure to adjust for the effect of BMI on testosterone when evaluating the relationship with OSA (6) and a lack of objective evaluation of OSA in all patients studied (8). It is also worth noting that though the two small studies by Luboshitzky (10, 11) found persistence of the relationship between lower testosterone and the categorical presence of OSA, the authors concluded that the primary cause for altered gonadal function in this population was due to the effects of obesity and aging, though sleep fragmentation and hypoxia may also contribute. We have reported results from a large sample of community dwelling middle-aged and older men, with outcomes similar to the findings by Barrett-Connor's study of more than 1300 elderly community dwelling men (9); There is an inverse relationship between testosterone and polysomnography measures of OSA including AHI, though these associations are attenuated after adjustment for BMI. In comparison to Barrett-Connor's cohort, our patient population was on average 15 years younger (59 years compared with 73 years) and had proportionally fewer men with a low testosterone concentration below 8.7 nmol/L (250 ng/dL) (4% compared with 9%). Notably, the mean BMI across each of our testosterone quartiles was higher than in Barrett-Connor's cohort, though a similar trend of rising BMI with lower testosterone concentration was still observed.

Our data are also supported by evidence showing that testosterone concentration is not improved by treatment of OSA with continuous positive airway pressure (CPAP), irrespective of treatment duration (19, 20, 21, 22, 23, 24, 25). Only a single study has reported an increase in total testosterone after 3 months of nasal CPAP treatment, used in 43 men with severe OSA (26). However, in this report there was no change in measured free testosterone due to a rise in SHBG in conjunction with testosterone rise during the intervention. The outcome in this study was also not adjusted for the change in body mass over the treatment period, with a mean weight loss of 1.4 kg reported during the intervention which reached borderline significance ($P=0.06$). Placebo-controlled evaluation of the effect of CPAP on testosterone concentration has been evaluated in only a single study; though more severe OSA correlated with lower testosterone concentrations at baseline, 1 month of active nasal CPAP treatment as compared to sham CPAP did not result in a significant rise in the measured testosterone concentration (27). A recent meta-analysis of this topic also concluded that, in men with OSA, CPAP has no influence on testosterone concentration (28). The three published studies excluded from the meta-analysis due to insufficient or missing key data, all still reported findings in support of this conclusion (19, 25, 29). By contrast, improvement in testosterone concentration has been consistently demonstrated in response to weight loss, with the magnitude of improvement in T proportional to the degree of weight loss achieved (30). As far as we can determine, there is no evidence to support a converse hypothesis that OSA is more common in hypogonadal men, in the absence of concurrent obesity.

A strength of our study is the inclusion of a large number of subjects with baseline characteristics representative of the broader community. We have evaluated sleep disordered breathing using a validated and reliable diagnostic method in all participants and utilised a variety of different objective polysomnography parameters, including AHI, ODI, TST90 and arousals in the analyses. Though we have selectively employed BMI as the measure of adiposity in our study for statistical evaluation, there was a very high degree of positive correlation

between all adiposity measures recorded (results not shown), such that it is unlikely that substituting BMI for an alternative parameter of adiposity would significantly alter the OSA-testosterone associations found. We have also previously reported an analysis of self-selection bias, which did not find any significant differences in relation to obesity or sleep symptoms between those who did and did not participate in the sleep study (31).

The main limitation of our study is its observational design, meaning that associations may be drawn from the data, though this is insufficient to prove causality of BMI in mediating the effect of OSA on total testosterone concentration. A further limitation is the stepwise collection of data at different time points; as the timing of assessments was not identical, the data is not a true cross-sectional analysis from a single time point. For transparency, the timing of data collection has been indicated in the relevant tables by the codes M1, M2, M3 and M4, respectively. As testosterone concentration was not remeasured at the time of the sleep study, it is not possible to definitively exclude a change in measured testosterone between the time of testosterone measurement used in the analysis (M2) and the time of the sleep study (M4), confounding the relationship between these parameters. To address this issue within the limitations of the available data, we performed post-hoc stability analyses of testosterone measurements and BMI. From these analyses, we conclude that the high level of stability of BMI between time point M2 and M4 supports that it is a reasonable assumption that the measures of OSA magnitude would also be stable over this same period. Testosterone levels were relatively stable between M1 and M2 and the time interval between M2 and M4 was significantly shorter (median 20 months, IQR 5 months, compared with 5 years), thus it is also reasonable to assume that testosterone measurements would have similar or greater stability over the period of interest. Furthermore, on restriction of the primary analysis to only those individuals whom showed minimal variability in measured testosterone, the result of the primary analysis remains essentially unchanged. This provides evidence supporting the assumption that the OSA-testosterone associations in the overall cohort are unaffected by the difference in assessment times (M2 for testosterone, M4 for sleep parameters).

We acknowledge that our study design excluded individuals with pre-existing obstructive sleep apnoea from the analysis. It is possible that these individuals had more severe OSA to have come to clinical attention. In such an instance, their exclusion from analysis may have resulted in a bias towards the detection of milder OSA, obscuring the relationship with testosterone concentration. However, a pre-existing diagnosis of OSA was uncommon in the screened population, particularly when compared to the diagnosis rates following sleep study completion, and despite the exclusion those with a pre-existing diagnosis, moderate or severe OSA was still detected in half of all individuals who met the OSA diagnostic criteria following sleep study. In combination, this seems to support the proposition that OSA is under-diagnosed in the community and less likely that our study design resulted in a skew towards the detection of mild OSA only. The inclusion of individuals with pre-diagnosed OSA would also result in the incorporation of a proportion of individuals treated for OSA, though the evidence, as discussed, indicating that the treatment of OSA with CPAP does not improve testosterone concentration independent of change in weight. With respect to the results obtained, it is also important to acknowledge that the CIs of the direct OSA effect, as measured by AHI, on testosterone after adjustment for covariates, remain large, and therefore could be consistent with any of three different outcomes, that there is no effect, a positive effect or a negative effect of OSA on testosterone concentration.

Overall the findings from our study lend further support to the argument that low serum testosterone concentrations, in the context of obesity, are not the consequence of comorbid OSA and rather reflect the effect of obesity. From a clinical standpoint, treatment of OSA with CPAP cannot be expected to lead to an improvement in testosterone concentration though, in contrast, weight loss can increase testosterone (30) and improve objective measures of OSA (32, 33). Taken together, these findings highlight the importance of addressing obesity in men with OSA, particularly if testosterone is decreased, irrespective of whether CPAP is instituted or not.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/EJE-19-0978.

Declaration of interest

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