Eur Respir J 2011; 38: 1349–1354
DOI: 10.1183/09031936.00022111

Self-reported sleep apnoea and mortality in patients from the Swedish Obese Subjects study

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ABSTRACT: Sleep apnoea is associated with increased mortality in sleep clinic and community population groups. It is unclear whether a clinical report of sleep apnoea results in additional mortality risk in patients with severe obesity.

The Swedish Obese Subjects (SOS) study is a nonrandomised controlled trial of bariatric surgery *versus* conventional treatment for the treatment of severe obesity and its complications (mean ± SD body mass index 41 ± 5 kg·m^{-2}). The presence or absence of sleep apnoea (witnessed pauses in breathing) was determined by self-reporting at baseline in 3,953 patients who were observed for 54,236 person-yrs (mean 13.5 maximum 21.0 yrs).

Sleep apnoea was reported by 934 (23.6%) patients at baseline and was a significant univariate predictor of mortality (hazard ratio (95% CI) 1.74 (1.40–2.18)). In a range of multivariate models of mortality risk, controlling for ⩽16 other potential confounders and established mortality risk factors, sleep apnoea remained a significant prognostic factor (fully adjusted model 1.29 (1.01–1.65)).

Self-reported sleep apnoea is an independent prognostic marker of all-cause mortality in obese patients.

KEYWORDS: Mortality, obesity, sleep apnoea

There is increasing evidence that sleep apnoea is a risk factor for mortality independent of obesity. This has been shown both in clinical settings [1–5] and, more recently, in three community-based cohorts [6–8]. In addition, bariatric surgery is an effective treatment for sleep apnoea [9].

Severe obesity (body mass index (BMI) >37 kg·m^{-2}) is strongly associated with mortality [10, 11]. One of the mechanisms might be sleep apnoea, which is very common in severe obesity and causes impaired cardiovascular function [7, 8, 12, 13], and also impairs psycho-social health [14]. However, it is unclear whether sleep apnoea still confers a higher mortality risk in patients, who all have severe obesity. In addition, there remain lingering doubts about the possible role of visceral obesity being the real cause of at least some of the mortality attributed to obstructive sleep apnoea (OSA) [6, 15]. Studying the OSA–mortality association in people who are all severely obese should help clarify both whether this effect can be seen in the severely obese and whether the population-wide effects of sleep apnoea are in addition to the other established effects of obesity on health.

In the Swedish Obese Subjects (SOS) study, bariatric surgery was associated with a reduced overall mortality compared with conventional treatment in matched, obese controls (hazard ratio 0.71) [11]. Patients in the SOS study have now been followed for ⩽22 yrs and are well characterised for health risk factors [11, 16–18]. Our aim here was to investigate whether self-reported sleep apnoea is independently associated with increased mortality. An additional question posed here is whether remission of apnoea at 2 yrs in patients originally reporting sleep apnoea at baseline is predictive of lower mortality compared with patients in whom that apnoea persists at 2 yrs.

METHODS

The SOS study is a prospective, controlled intervention trial of bariatric surgery *versus* conventional treatment for the treatment of severe obesity and its complications. The study design and primary findings are described in detail elsewhere [11, 16–18]. Briefly, 2,010 obese patients (BMI >34 kg·m^{-2} for males and >38 kg·m^{-2} for females, aged 37–60 yrs at baseline) in the surgically treated group received one of the following three surgical procedures: gastric bypass, gastric banding or

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Received:
Feb 06 2011
Accepted after revision:
May 01 2011
First published online:
May 26 2011

European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003

vertical-banded gastroplasty [19]. An additional 2,037 patients received nonsurgical treatment for obesity, which was non-standardised and was handled according the prevailing custom in the unit where the patient was enrolled. Anti-obesity drugs were not available in Sweden until 1998. The primary outcome of this trial was mortality during a mean 11-yr follow-up [11].

Randomisation to gastric surgery was considered to be unethical in 1987 by six out of the seven relevant institutional review boards due to the high mortality associated with these procedures at that time. Gastric surgery patients were, however, matched by a computer algorithm [16] with control patients. The following variables were considered when constructing the computer program to run the matching algorithm: age, sex, weight, height, waist and hip circumferences, systolic pressure, serum cholesterol, serum triglyceride levels, smoking status, diabetes, menopause, four psycho-social variables with mortality associations, and two treatment preference variables indicative of personality traits. Exclusion criteria have been listed in detail [17]; however, patients were not excluded for hypertension, lipid disturbance, diabetes, history of myocardial infarction or stroke, or for any sleep disorder or sleep disturbance.

Examinations

Patients were recruited from 480 primary health care centres in Sweden. Standard application forms were sent to 11,453 subjects between September 1987 and November 2000. Of these, 8,966 patients met age and height–weight requirements. Information was provided about the surgical and medical treatments and patients were asked for their preference on treatment. Of the 7,593 patients who returned these questionnaires, 6,905 completed a registry examination.

Patients who became candidates for surgical intervention also underwent a surgical examination. These took place, on average, 8 months after the registry examination and 5 months before surgery.

Matched controls were selected by computer algorithm 8 weeks before surgery, and both the surgical candidate and control attended separate examinations 4 weeks before the surgical intervention and thus the start date for the trial. Subsequent examination occurred at 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0 and 10.0 yrs after surgery for both of the matched patient groups.

Assessments

Anthropometry, biochemical variables and blood pressure were measured at baseline, and at 2 and 10 yrs. Anthropometric measurements were obtained as described elsewhere [16, 17], blood samples were taken in the morning after a 10–12-h fast and were analysed in the accredited Central Laboratory of the Sahlgrenska University Hospital, Gothenburg, Sweden (accredited according to European Standard 45001; www.european-accreditation.org). Blood pressure was ascertained *via* a sphygmomanometer placed on the right arm after 15 min of supine rest.

Criteria for health and disease

Diabetes was defined as a fasting blood glucose level of $\geqslant$6.1 mmol·L^{-1} or a patient report of using a glucose-lowering agent. Hypertension was defined as a systolic blood pressure of $\geqslant$140 mmHg and/or a diastolic blood pressure $\geqslant$90 mmHg, or treatment with antihypertensive medication. A baseline questionnaire included questions about previous myocardial infarction, stroke and cancer.

In the SOS study, five questions about sleep apnoea were asked. The patients were asked if they had a regular home partner and if the partner had observed pauses in breathing during sleep. They also answered questions about daytime sleepiness, irresistible napping, and loud and disruptive snoring. The last three questions were to be answered on a five-point scale: never, rarely, sometimes, often and very often.

In these analyses, sleep apnoea was a binary variable assessed by asking all patients: ''Has anyone told you that you have brief breathing pauses during your sleep?'' (translated from Swedish).

Ascertainment of mortality and vitality

The Swedish Population Register and Address Register (SPAR) is cross-matched with the SOS database using social security numbers once a year on November 1. In our analyses, SPAR was cross-checked until November 1, 2008.

Data analyses

Baseline characteristics were investigated for their association with sleep apnoea using the Chi-squared, unpaired t-test or

TABLE 1 Baseline characteristics of males and females with and without apnoea at baseline

	Sleep apnoea	No sleep apnoea	p-value
Subjects n	934	3019	
Age yrs	48.1±6.0	47.9±6.2	0.54
Females	460 (49.3)	2349 (77.8)	**<0.001**
Surgery	493 (52.8)	1471 (48.7)	**0.03**
BMI kg·m^{-2}	41.3±4.8	41.2±4.7	0.55
Weight kg	122.7±18.1	116.4±16.1	**<0.001**
Weight loss at 2 yrs kg	-16.4±19.3	-14.7±18.4	**0.053#**
Waist/hip ratio	1.01±0.07	0.98±0.08	**<0.001**
Waist circumference cm	125.8±11.3	122.1±11.4	**<0.001**
Sagittal diameter cm	29.1±3.9	27.8±3.6	**<0.001**
Average blood pressure mmHg	116.3±14.0	114.0±13.7	**<0.001**
Total cholesterol mmol·L^{-1}	5.8±1.1	5.7±1.1	**0.02**
HDL cholesterol mmol·L^{-1}	1.13±0.27	1.21±0.29	**<0.001**
Triglycerides mmol·L^{-1}	2.0 (1.5–2.8)	1.75 (1.29–2.40)	**<0.001#**
Glucose mmol·L^{-1}	4.8 (4.3–5.7)	4.7 (4.2–5.4)	**<0.001#**
Insulin mU·L^{-1}	19.2 (13.5–27.4)	16.3 (11.6–23.4)	**<0.001#**
Diabetes	189 (20.2)	467 (15.5)	**<0.001**
History of stroke	14 (1.5)	23 (0.8)	**0.04**
History of CVD	38 (4.1)	53 (1.8)	**<0.001**
History of cancer	16 (1.7)	28 (0.9)	**0.046**
Smokers	260 (27.8)	660 (21.8)	**<0.001**

Data are presented as mean±SD, n (%) or median (interquartile range), unless otherwise indicated. BMI: body mass index; HDL: high-density lipoprotein; CVD: cardiovascular disease. Values in bold were considered to be statistically significant. #: Wilcoxon test was used when the data were either visually non-normal or skewed; otherwise, unpaired t-tests were used.

TABLE 2 Univariate baseline risk factors for mortality

Baseline risk factor	HR (95% CI)	p-value
Age yrs per decade	2.13 (1.79–2.54)	**<0.001**
Sex		
Female	0.52 (0.42–0.64)	**<0.001**
Male	1.00 (ref.)	
BMI per 10 kg·m^{-2}	1.29 (1.05–1.60)	**0.02**
Weight per 10 kg	1.14 (1.07–1.21)	**<0.001**
Waist/hip ratio	1.70 (1.48–1.96)	**<0.001**
Waist circumference per 10 cm	1.34 (1.23–1.46)	**<0.001**
Sagittal diameter per 1 cm	1.09 (1.06–1.12)	**<0.001**
Total cholesterol per 1 mmol·L	1.21 (1.10–1.32)	**<0.001**
HDL cholesterol per 1 mmol·L	1.24 (0.85–1.79)	0.26
Triglycerides per mmol·L	1.13 (1.09–1.17)	**<0.001**
Fasting glucose per mmol·L	1.17 (1.13–1.21)	**<0.001**
Insulin per 10 mU·L	1.14 (1.09–1.19)	**<0.001**
Diabetes at baseline yes *versus* no	2.20 (1.75–2.78)	**<0.001**
History of stroke at baseline yes *versus* no	2.36 (1.05–5.29)	**0.04**
History of cardiovascular disease at baseline yes *versus* no	3.66 (2.42–5.55)	**<0.001**
History of cancer at baseline yes *versus* no	1.90 (0.90–4.01)	**0.09**
Current smoker *versus* nonsmoker or ex-smoker	2.07 (1.67–2.56)	**<0.001**

Data are derived from univariate Cox models based on information gathered at baseline pooled across the surgery and control groups. Values in bold are considered to be statistically significant. HR: hazard ratio; BMI: body mass index; HDL: high-density lipoprotein; ref.: reference category.

Wilcoxon tests where appropriate. Univariate associations between baseline characteristics and mortality were investigated with Kaplan–Meier estimates and log-rank tests, and with univariate Cox proportional hazards models.

Multivariate models for mortality were built using Cox regression models, and confirmed by best-subset variable selection. The following variables were forced *a priori* into the models because of known associations with OSA or mortality: age, sex, obesity, smoking status, blood pressure, total cholesterol, high-density lipoprotein (HDL) cholesterol and glucose. In addition, other risk factors were examined for independent association with mortality when they exhibited some evidence of a univariate association with either mortality or with sleep apnoea at statistical significance level of $p=0.05$. Schoenfeld and Martingale residuals were used to confirm the proportional hazards and linearity assumptions, respectively.

We further evaluated whether bariatric surgery modified the association between OSA and mortality. This was performed by including an interaction term between sleep apnoea and treatment group in our main models. In addition, Cox models were used to evaluate whether regression of sleep apnoea from baseline to the 2-yr follow-up was associated with better survival than continued report of sleep apnoea after 2 yrs. Analyses were undertaken by N.S. Marshall using SAS (v 9.2; SAS Institute Inc., Cary, NC, USA).

RESULTS

A total of 4,047 patients were enrolled in the study (2,010 in the surgical arm and 2,037 in the control arm). Information about apnoea status at baseline was supplied by 3,953 (97.7%) subjects.

Baseline characteristics for the pooled control and surgical intervention groups across sleep apnoea categories are described in table 1. Differences between the two groups are described elsewhere [11, 18]. The mean observation time was 13.9 yrs (maximum 21.0 yrs) in those without sleep apnoea and 13.2 yrs (maximum 21.0 yrs) in the sleep apnoea group. There were 237

TABLE 3 Association of sleep apnoea with mortality

Sleep apnoea status	Unadjusted HR (95% CI)	Partially adjusted HR (95% CI)#	Fully adjusted HR (95% CI)¶
Sleep apnoea	1.74 (1.40–2.18)	1.30 (1.02–1.67)	1.29 (1.01–1.65)
No sleep apnoea	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)

The partially adjusted model was built only from those variables that were statistically significant in the full model. HR: hazard ratio; ref.: reference category. #: adjusted for baseline age, sex, treatment group (surgical *versus* control), waist/hip ratio, sagittal diameter, smoking status (current *versus* never- or ex-smoker), high-density lipoprotein cholesterol, glucose, and baseline history of cardiovascular disease (yes *versus* no); ¶: additionally adjusted for baseline history of stroke (yes *versus* no), diabetes (yes *versus* no), triglycerides, mean blood pressure, insulin, history of cancer (yes *versus* no) and total cholesterol.

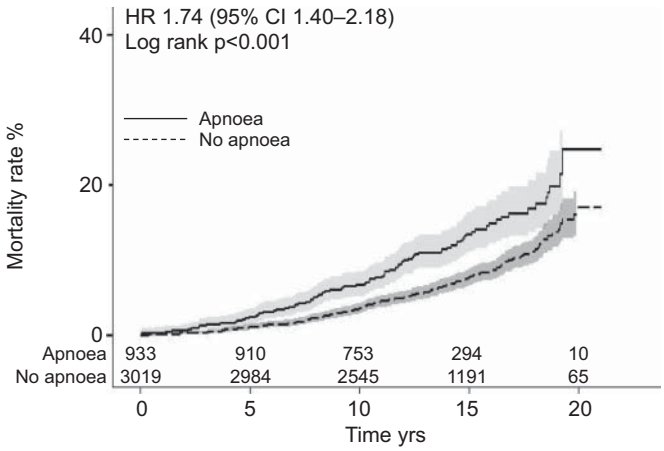

FIGURE 1. Univariate association between the presence or absence of sleep apnoea reported at baseline and 21-yr mortality in the Swedish Obese Subjects study pooled across both surgical intervention and control groups. Numbers across the bottom of the graph indicate the numbers of patients being observed at each 5-yr time-point. HR: hazard ratio.

deaths observed in those without sleep apnoea (raw mortality 7.9%) and 117 (12.5%) in those with sleep apnoea.

Univariate mortality risk factors, other than apnoea status, are detailed in table 2. Self-reported sleep apnoea was associated with excess mortality at both a univariate level and in subsequent multivariate proportional hazards models (table 3). The significant univariate association between apnoea and mortality is further demonstrated in a Kaplan–Meier plot (fig. 1). We also ran models where all deaths within the first 2 yrs were excluded and these were also statistically significant.

Several definitions of blood pressure were evaluated, including mean arterial pressure, but average blood pressure ($0.5 \times$ systolic $+0.5 \times$ diastolic) gave the best fit to observed mortality. The best fit for body habitus to mortality was the combined variation in sagittal diameter and waist/hip ratio. We also tested BMI and neck circumference as linear and categorical variables.

We attempted to test whether bariatric surgery might mitigate the OSA–mortality association by stratifying by treatment group. Sleep apnoea did elevate mortality risk in the control group (partially adjusted HR 1.41 (95% CI 1.01–1.97) and fully adjusted HR 1.36 (0.96–1.91)). But this elevation was not as evident in the surgical group (partially adjusted HR 1.17 (0.82–1.69) and fully adjusted HR 1.14 (0.79–1.63); table 4). We attempted to verify whether this apparent difference was significant but, in the full model (table 3), the introduction of an interaction between treatment group and sleep apnoea was not statistically significant.

Secondary subgroup analyses

In people with sleep apnoea at baseline who were alive at 2 yrs and reported their sleep apnoea status (349 females and 330 males), there was a significant survival advantage in those females whose sleep apnoea had regressed (n=203; p=0.04) (fig. 2). This univariate association in females was not significant after adjustment for age. Males whose sleep apnoea had regressed at 2 yrs did not have a greater survival advantage as compared with those without remission (n=202; p=0.5)(fig. 3).

DISCUSSION

Self-reported sleep apnoea appears to be an independent prognostic marker of all-cause mortality in patients in the SOS study. This confirms previous observations in both population-based cohorts and in cardiovascular and sleep clinic cohorts that sleep apnoea is a mortality risk factor [8, 15]. Thus, even amongst the severely obese, patient reports of sleep apnoea are not incidental.

Bariatric surgery in severely obese patients has benefits that extend beyond the correction of apnoea [11, 16, 18, 20]; our findings could also have implied that patients with sleep apnoea might represent an important subgroup, like diabetics [21], where bariatric surgery is especially effective [22]. Our direct statistical testing of this hypothesis, however, was not significant.

The mortality risk associated with sleep apnoea in the SOS study was lower (HR 1.29) than the risk associated with sleep apnoea in the general community (HR >2.0) [6–8]. It is possible that the lower estimate here could be explained by a misclassification of patients' apnoea status caused by inaccurate self-reports. SHARKEY *et al.* [23], for instance, found that self-reported apnoeas in females presenting for bariatric surgery did correlate with sleep apnoea ascertained *via* an overnight sleep study, but with notable misclassification of people with OSA saying they

TABLE 4 Mortality risk associated with sleep apnoea in the surgical and the control groups separately

Sleep apnoea status	Unadjusted HR (95% CI)	Partially adjusted HR (95% CI)#	Fully adjusted HR (95% CI)¶
Control			
Sleep apnoea	1.87 (1.38–2.54)	1.41 (1.01–1.97)	1.36 (0.96–1.91)
No sleep apnoea	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Surgical			
Sleep apnoea	1.64 (1.19–2.27)	1.17 (0.82–1.69)	1.14 (0.79–1.63)
No sleep apnoea	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)

HR: hazard ratio; ref.: reference category. #: adjusted for baseline age, sex, waist/hip ratio, sagittal diameter, smoking status (current *versus* never- or ex-smoker), high-density lipoprotein cholesterol, glucose, history of cardiovascular disease (yes *versus* no); ¶: additionally adjusted for baseline history of stroke (yes *versus* no), diabetes (yes *versus* no), triglycerides, mean blood pressure, insulin, history of cancer (yes *versus* no), and total cholesterol.

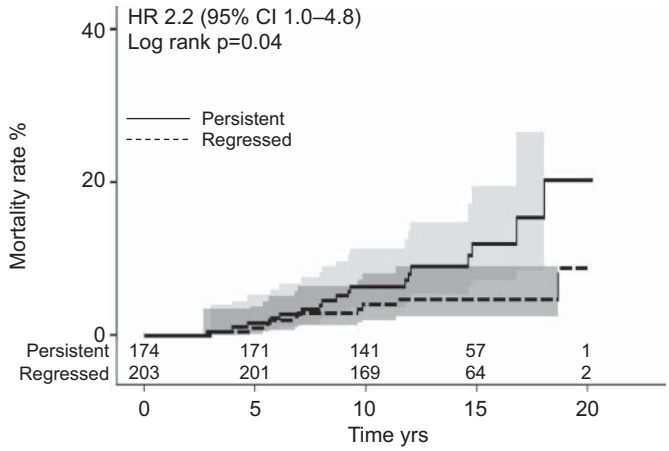

FIGURE 2. Univariate mortality rates in female patients with sleep apnoea at baseline who reported that their sleep apnoea had either persisted or regressed at 2 yrs. Numbers across the bottom of the graph indicate the numbers of patients being observed at each 5-yr time-point. HR: hazard ratio.

did not have the condition. However, our small HR may also be an indication that the risk attributable to sleep apnoea decreases as obesity and associated risk factors worsen. It has also been suggested that some of the mortality risk associated with sleep apnoea might be attributable to the residual confounding effects on the metabolism of visceral obesity [15]. The severe obesity in the SOS study coupled with our specific control of central obesity markers (sagittal diameter and waist/hip ratio) should have controlled for some of this potential residual confounding. Previous studies have indicated that sleep apnoea may not be a mortality risk for females in the same way it is for males [8]. The predominantly female make-up of the SOS cohort (~70%) may thus partially explain our relatively lower than expected magnitude of risk.

Excess weight is the major modifiable risk factor for sleep apnoea [24, 25]. In community-based cohorts, incident sleep apnoea is more often observed in those gaining weight than

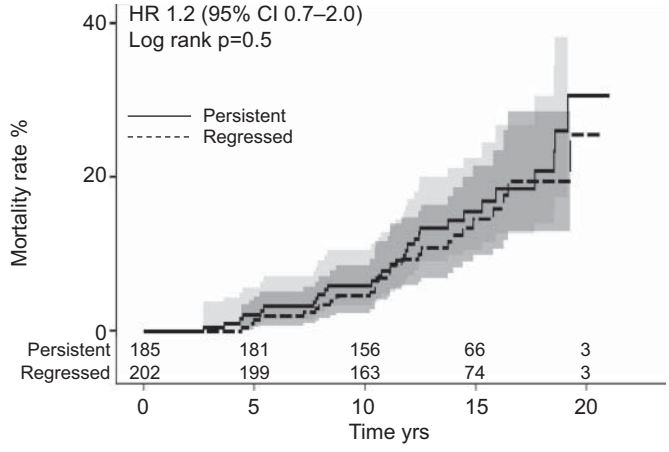

FIGURE 3. Univariate mortality rates in male patients with sleep apnoea at baseline who reported that their sleep apnoea had either persisted or regressed at 2 yrs. Numbers across the bottom of the graph indicate the numbers of patients being observed at each 5-yr time-point. HR: hazard ratio.

those with stable weight [26–28]. Obesity reduction in OSA patients reduces sleep apnoea severity, whether weight loss is achieved *via* pharmacotherapy [29], diet [30–32] or surgery [20]. As a result of this, the relative weakness of the mortality association, in addition to the already-mentioned misclassification problem, may also be explained by the success of the surgical interventions in reducing body mass. We tested this hypothesis by stratifying by treatment group across all our models. In the parsimonious model, sleep apnoea was an independent predictor of mortality in the control group (HR 1.4; $p=0.04$) but not in the surgical group (HR 1.2; $p=0.4$)(table 4). This indirectly suggested that the marked weight loss caused by bariatric surgery resulted in subsequent regression of sleep apnoea [24], a phenomenon which we have already demonstrated in this cohort [9]. We also analysed whether the regression of sleep apnoea at 2 yrs was associated with greater survival in those with sleep apnoea at baseline. Apnoea regression was associated with significantly greater survival compared with persistent sleep apnoea in females, but not in males ($p=0.04$ and $p=0.5$ for females and males, respectively). However, in females, this association was not significant after controlling for age ($p=0.09$). Combined with the lack of a population-based cohort that has definitively linked sleep apnoea to female mortality [6–8], these secondary analyses in a relatively smaller number of patients should be interpreted with caution, given the likelihood of misclassification. However, the SOS cohort suggests that treating sleep apnoea in severely obese females may extend life expectancy. Sleep apnoea is poorly studied in females and thus our observation may present a valuable clinical trial target.

There are a number of strengths and limitations in using the SOS cohort to study sleep apnoea and mortality risk. The patients were severely obese at baseline and therefore had a high prior likelihood of having sleep apnoea. Due to the successful intervention (weight loss surgery) in this study, we were able to observe both a cohort of people with high and stable body mass (the control group) alongside an equally well-characterised cohort of people who have lost substantial body mass (the surgical group). The female predominance of the cohort may be important, as is the ascertainment of sleep apnoea through self-reports. The self-report of sleep apnoea *via* reported breathing pauses during sleep is unlikely to be sensitive to the presence of sleep apnoea. For instance, a recent study of female bariatric patients indicated that self-reported apnoea was ~58% sensitive and 88% specific to detecting at least mild OSA, with 93% of patients reporting witnessed apnoeas actually testing positive for sleep apnoea on an overnight sleep study (true positive rate) [23]. We therefore suspect that, in the SOS cohort, there is a substantial proportion of the apnoea-negative group who really did have sleep apnoea. Previous studies have used self-reporting of sleep apnoea or snoring and also found, for instance, an increased mortality risk in sleepy snorers [33]. Nevertheless, the interventional SOS cohort contains almost 4,000 severely obese patients followed for $\leqslant$22 yrs and is, from this perspective, not currently matched anywhere else in the sleep literature.

Data from the SOS study confirm that the higher mortality observed in people with sleep apnoea both in the general community [6–8] and in cohorts of sleep apnoea patients [1–5] is also present in patients with severe obesity. Although the

magnitude of this added risk appears attenuated when compared with these previous reports, self-reported sleep apnoea in severely obese patients does provide additional information about mortality risk.

SUPPORT STATEMENT

The Swedish Obese Subjects study was supported by grants from Hoffman-La Roche, AstraZeneca, Cederroth, Ethicon, Sanofi-Adventis and the Swedish Medical Research Council (to L. Sjöström), and NHMRC grants 352483, 457-94 and 264598 to RR. Grunstein.

STATEMENT OF INTEREST

Statements of interest for C.D. Sjöström, L.M.S. Carlsson and for the study itself can be found at www.erj.ersjournals.com/site/misc/statements.xhtml

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