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Title: **Self-reported sleep apnoea and mortality in patients from The Swedish Obese Subjects Study.**

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Abstract

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

Methods: The Swedish Obese Subjects (SOS) Study is a non-randomized controlled trial of bariatric surgery versus conventional treatment for the treatment of severe obesity and its complications (mean BMI 41±5 kg/m^2). The presence or absence of sleep apnoea (witnessed pauses in breathing) was determined by self-report at baseline in 3953 patients who were observed for 54,236 person-years (Mean=13.5 max=21.0 years).

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

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

Introduction

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 (BMI > 37) 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 impairs psycho-social health.[14] However, it is unclear whether sleep apnoea still confers 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 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 Subject (SOS) study bariatric surgery is associated with a reduced overall mortality compared to conventional treatment in matched, obese controls (hazard ratio=0.71).[11] Patients in the SOS study have now been followed for up to 22 years and are well characterised for health risk factors.[11, 16-18] Our aim now is to investigate whether self-reported sleep apnoea is independently associated with increased mortality. An additional question is whether in patients reporting sleep apnoea at baseline is remission of that apnea at 2 years predictive of lower mortality than apnea that persists at 2 years?

METHODS

The Swedish Obese Subjects (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, 2010 obese patients (BMI>34 kg/m^2 for men and BMI>38 kg/m^2 for women, aged 37-60 years at baseline) in the surgically treated group received one of the following three surgical procedures: gastric bypass, gastric banding or vertical banded gastroplasty.[19] The remaining 2037 patients received

nonsurgical treatment for obesity, which was non-standardized 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 year follow-up.[11]

Randomisation to gastric surgery was considered to be unethical in 1987 by 6 of the 7 relevant institutional review boards due to the high mortality associated with these procedures at that time. They were however matched by 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 psychosocial 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, nor for any sleep disorder/disturbance.

Examinations

Patients were recruited from 480 primary health care centres in Sweden. Standard application forms were sent to 11453 subjects between September 1987 and November 2000. Of these, 8966 patients met age and height-to-weight requirements. Information was provided about the surgical and medical treatments and patients were asked for their preference on treatment. Of the 7593 patients who returned these questionnaires, 6905 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 years after surgery for both of the matched patient groups.

Assessments

Anthropometry, biochemical variables and blood pressure were measured at baseline, 2 and 10 years. Anthropometric measurements were obtained as described elsewhere, blood samples were taken in the morning after a 10-12 hour fast and were analysed in the accredited Central Laboratory of the Sahlgrenska University Hospital (Accredited according to European norm 45001) blood pressure was ascertained via a sphygmomanometer placed on the right arm of after 15 minutes of supine rest.

Criteria for health and disease

Diabetes was defined as a fasting blood glucose level of ≥6.1 mmol/l or a patient report of using a glucose lowering agent. Hypertension was defined as a systolic blood pressure of ≥140 and/or a diastolic blood pressure ≥90, or treatment with antihypertensive medication. A baseline questionnaire included questions about previous myocardial infarction, stroke and cancer.

In the SOS study 5 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 3 questions were to be answered with a 5 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 the 1st of November. In these analyses SPAR was cross-checked until the 1st of November 2008

Data Analyses

Baseline characteristics were investigated for their association with sleep apnoea using chi-square, t-test or 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 a priori forced into the models because of known associations with OSA or mortality: age, gender, 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 0.05. Schoenfeld and Martingale residuals were used to confirm the proportional hazards and linearity assumptions, respectively.

We further evaluated whether the bariatric surgery modifies the association between OSA and mortality. This was done by including an interaction term between sleep apnea and treatment group in our main models. In addition, Cox models were used to evaluate if regression of sleep apnoea from baseline to the 2-year follow-up was associated with better survival than continued report of sleep apnoea after 2 years. Analyses were undertaken by the first author using SAS (v 9.2; SAS institute NC, USA).

RESULTS

A total of 4047 patients were enrolled in the study (2010 in the surgical arm and 2037 in the control arm). Information about apnoea status at baseline was supplied by 3953 subjects (97.7%)

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 years (max 21.0 years) in those without sleep apnoea and 13.2 years (max 21.0 years) in the sleep apnoea group. There were 237 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 (Figure 1). We also ran models where all deaths within the first two years 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*Systolic+0.5*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 sleep apnoea-mortality association by stratifying by treatment group. Sleep apnoea did elevate mortality risk in the control group (Partially adjusted HR=1.41 (1.01, 1.97); 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); Fully adjusted HR=1.14 (0.79, 1.63), see Table 4). We attempted to verify whether this apparent difference was significant

but in the full model (as presented in Table 3) when an interaction between treatment group and sleep apnoea was introduced it was not statistically significant.

Secondary subgroup analyses

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

DISCUSSION

Self-reported sleep apnoea appears to be an independent prognostic marker of all-cause mortality in patients in the Swedish Obese Subjects 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] However, our findings might have also implied that patients with sleep apnoea might represent an important sub-group, like diabetics,[21] where bariatric surgery is especially effective.[22] However, our direct statistical testing of this hypothesis 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 (Hazard ratios above 2.0).[6-8] It is possible that the lower estimate here could be explained by a miss-classification of patients' apnoea status caused by inaccurate self-reports. Sharkey and colleagues, for instance, found that self-reported apnoeas in women presenting for bariatric surgery did correlate with sleep apnoea ascertained via an overnight sleep study, but with notable misclassification of people with objective

sleep apnoea saying they did not have the condition.[23] However, our small hazard ratio 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 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-to-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 as it is for males.[8] The predominantly female make-up of the SOS cohort (ca. 70%) may thus partially explain our relatively lower magnitude of risk than expected.

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 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] Because 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 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, see also Table 4). This indirectly suggested that the marked weight loss caused by bariatric surgery resulted in subsequent regression of sleep apnoea[24]; a phenomenon we have already demonstrated in this cohort.[9] We also analysed whether the regression of sleep apnoea at 2 years was associated with greater survival in those with sleep apnoea at baseline. Apnoea regression was associated with significantly greater survival compared to persistent sleep apnoea in women, but not in men (p=0.04 and p=0.5 for each gender, respectively). However, in women 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 women may extend life expectancy. Sleep

apnoea is poorly studied in women 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. Because of the successful intervention in this study (weight loss surgery) we can 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 about 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] Because of this we 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-report of sleep apnoea or snoring and also found increased mortality risk in sleepy snorers, for instance.[33] Nevertheless, the interventional SOS cohort contains almost 4000 severely obese patients followed for up to 22 years and is from this perspective not currently matched anywhere in the sleep literature.

Data from the Swedish Obese Subjects study confirms that the higher mortality observed in people with sleep apnoea in the general community[6-8] and in cohorts of sleep apnoea patients[1-5] is also present in patients with severe obesity. Although, compared with these previous reports the magnitude of this added risk appears attenuated, self-reported sleep apnoea in severely obese patients does provide additional information about mortality risk.

Table 1: Baseline characteristics of men and women with and without apnoea at baseline.

	Sleep Apnoea Mean (SD)	**Not Sleep Apnoea Mean (SD)**	**Test for difference**
Number (n)	934	3019	
Age in years	48.1 (6.0)	47.9 (6.2)	0.54
Female %, (n cases)	49.3 (460)	77.8 (2349)	**<0.001**
Surgery %, (n cases)	52.8 (493)	48.7 (1471)	**0.03**
Body Mass Index (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 (kg) at 2 years	-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)	5.8 (1.1)	5.7 (1.1)	**0.02**
HDL Cholesterol (mmol/l)	1.13 (0.27)	1.21 (0.29)	**<0.001**
Triglycerides (mmol/l) median and IQR	2.0 (1.5, 2.8)	1.75 (1.29, 2.40)	**<0.001†**
Glucose (mmol/l)	4.8 (4.3, 5.7)	4.7 (4.2, 5.4)	**<0.001†**

median and IQR			
Insulin (mU/l) median (IQR)	19.2 (13.5, 27.4)	16.3 (11.6, 23.4)	**<0.001†**
Diabetes %, (n cases)	20.2 (189)	15.5 (467)	**<0.001**
History of Stroke %, (n cases)	1.5 (14)	0.8 (23)	**0.04**
History of CVD %, (n cases)	4.1 (38)	1.8 (53)	**<0.001**
History of Cancer %, (n cases)	1.7 (16)	0.9 (28)	**0.046**
Smokers %, (n cases)	27.8 (260)	21.8 (660)	**<0.001**

†Used Wilcoxon test when either the data were visually non-normal or skewed. Independent samples t-tests used otherwise. IQR= Interquartile range.

Table 2: Univariate Baseline Risk Factors for Mortality

Baseline Risk Factor	**Unit of measure**	**Hazard Ratio (95% CL)**	**p value**
Age	Per Decade	2.13 (1.79, 2.54)	**<0.001**
Gender	Female Male	0.52 (0.42, 0.64) 1.00 (REF)	**<0.001**
Body Mass Index	Per 10 BMI units	1.29 (1.05, 1.60)	**0.02**
Weight	Per 10 kilograms	1.14(1.07, 1.21)	**<0.001**
Waist: Hip Ratio	Per 0.1 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**
High Density Lipoprotein 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 (1.087, 1.190)	**<0.001**
Diabetes at baseline	Yes vs. No	2.20 (1.75, 2.78)	**<0.001**

History of Stroke at baseline	Yes vs. No	2.36 (1.05, 5.29)	**0.04**
History of Cardiovascular Disease at baseline	Yes vs. No	3.66 (2.42, 5.55)	**<0.001**
History of Cancer at baseline	Yes vs. No	1.90 (0.90, 4.01)	**0.09**
Smoking	Current vs. Non/Ex.	2.07 (1.67, 2.56)	**<0.001**

Figures are derived from univariate Cox models based on information gathered at baseline pooled across the surgery and control groups. REF= Reference category, CL= Confidence Limits.

Table 3: Association of sleep apnoea with mortality.

Sleep apnoea Status	Unadjusted Hazard ratio (95% CL)	Partially Adjusted Hazard Ratio (95% CL)†	Fully Adjusted Hazard Ratio (95% CL)‡
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. †Adjusted for baseline age, gender, treatment group (surgical vs. control), Waist hip ratio, Sagittal diameter, smoking status (current, vs. Never/Former), high density lipoprotein cholesterol, glucose, baseline history of cardiovascular disease (Yes vs. No). ‡ Additionally adjusted for baseline history of stroke (Yes vs. No), diabetes (Yes vs. No), triglycerides, mean blood pressure, insulin, history of cancer (Yes vs. No) and total cholesterol.

Table 4: Mortality risk associated with Sleep Apnoea in the Surgical and the Control groups separately

Group	Sleep apnoea Status	Unadjusted Hazard ratio (95% CL)	Partially Adjusted Hazard Ratio (95% CL)†	Fully Adjusted Hazard Ratio (95% CL)‡
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)

†Adjusted for baseline Age, gender, Waist: hip ratio, Sagittal diameter, smoking status (current, vs. Never/Former), high density lipoprotein cholesterol, glucose, history of cardiovascular disease (Yes vs. No). ‡ Additionally adjusted for baseline history of stroke (Yes vs. No), diabetes (Yes vs. No), triglycerides, mean blood pressure, insulin, history of cancer (Yes vs. No) and total cholesterol.

Figure 1 Legend: Univariate association between the presence (solid line) or absence (dashed line) of sleep apnoea reported at baseline and 21-year mortality in the Swedish Obese Subjects Study pooled across both surgery and control groups. Figures across the bottom of the graph indicate the numbers of patients being observed at each 5-year time point.

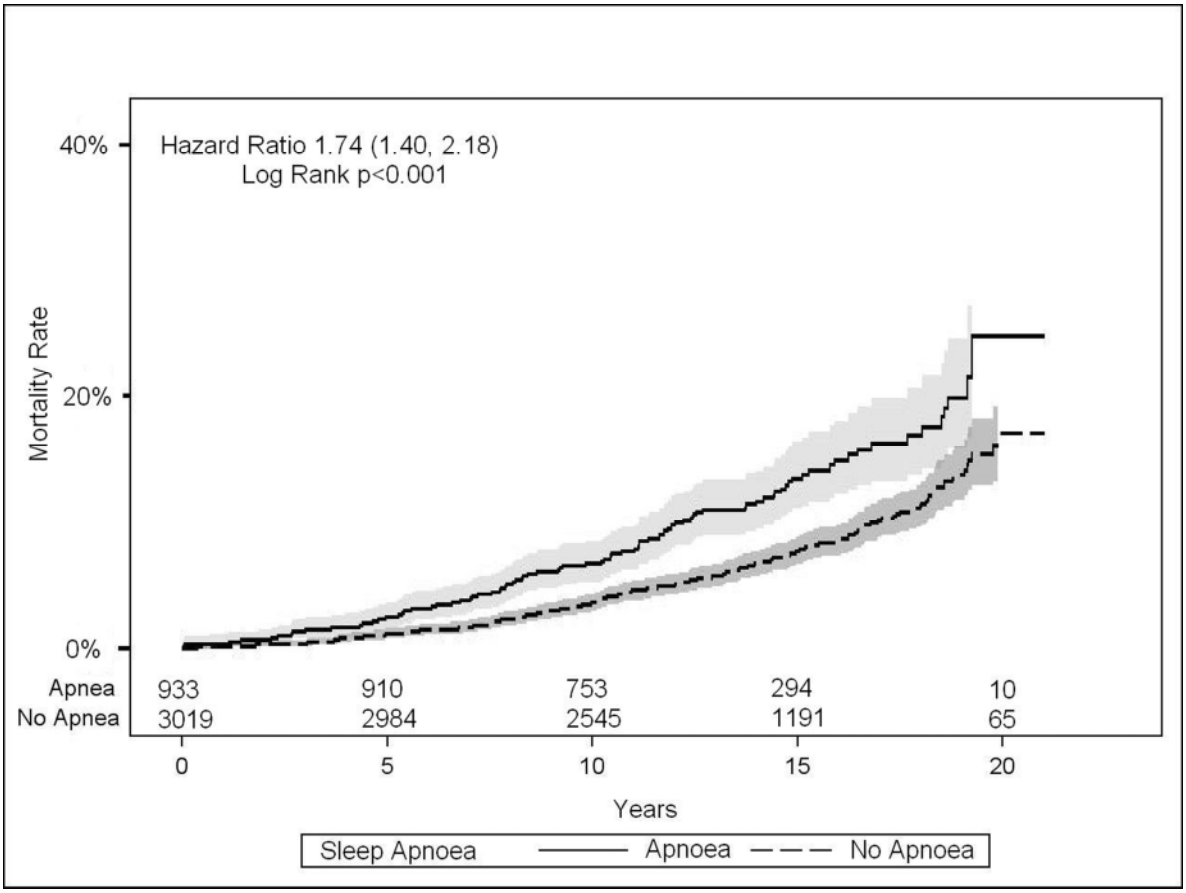


Figure 2 Legend: Univariate mortality rates in female patients with sleep apnea at baseline who reported that their sleep apnoea had either persisted (solid line) or regressed (dashed line) at 2 years. Figures across the bottom of the graph indicate the numbers of patients being observed at each 5-year time point.

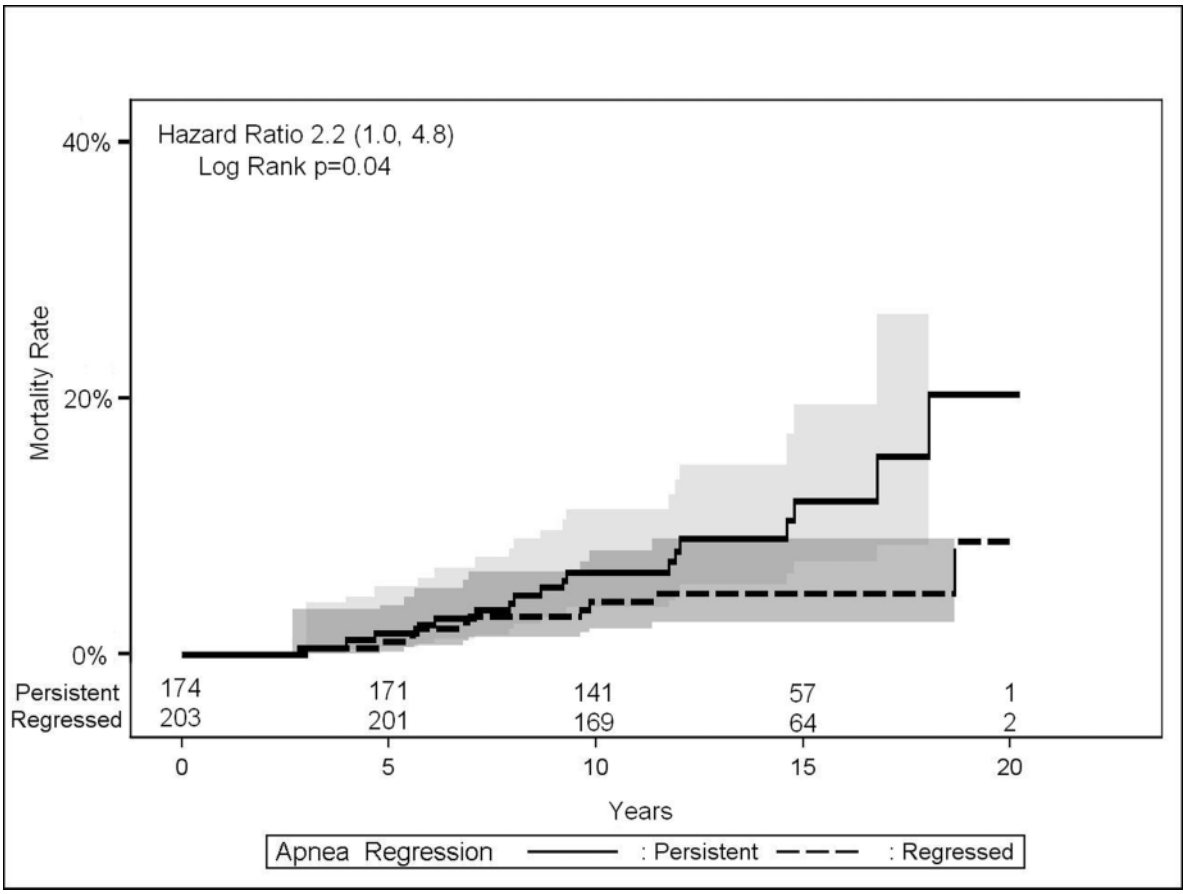
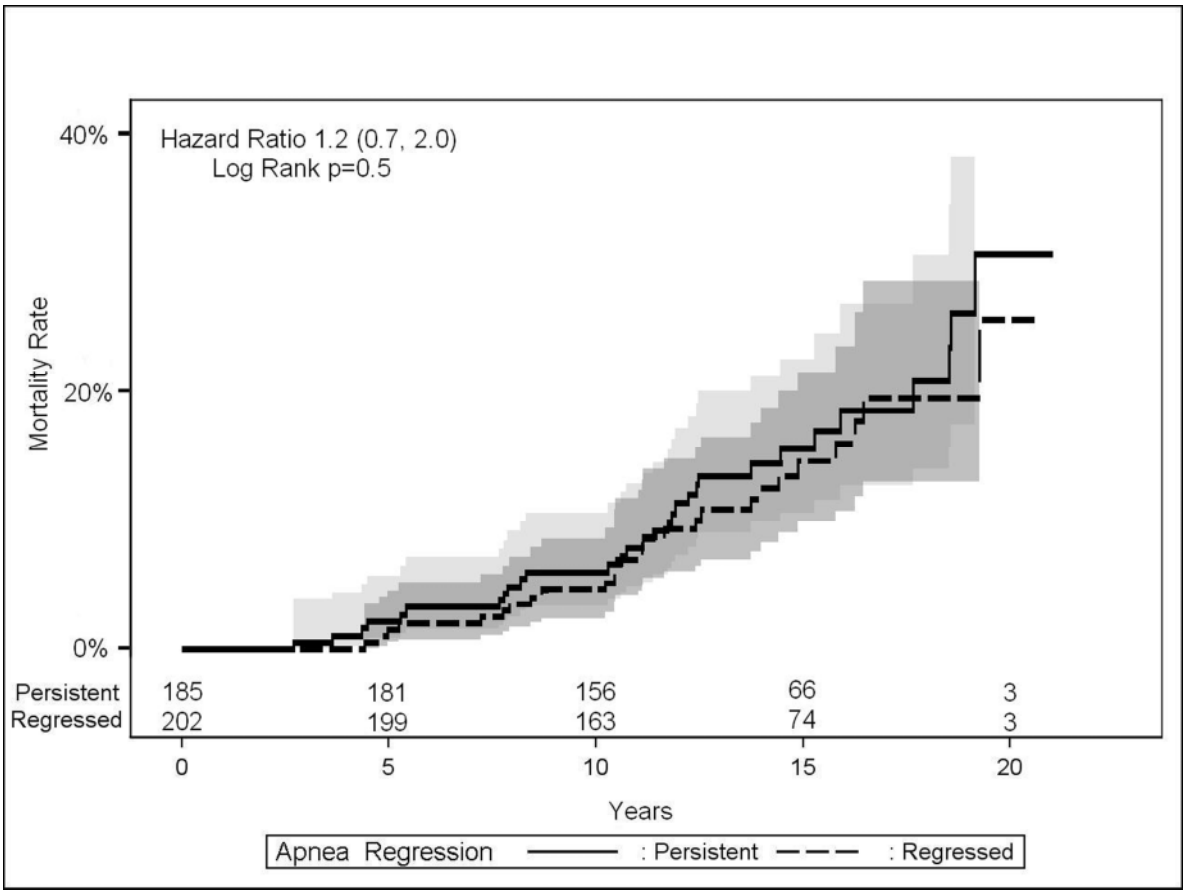


Figure 3 Legend: Univariate mortality rates in male patients with sleep apnea at baseline who reported that their sleep apnoea had either persisted (solid line) or regressed (dashed line) at 2 years. Figures across the bottom of the graph indicate the numbers of patients being observed at each 5-year time point.


Hazard Ratio 1.2 (0.7, 2.0)
Log Rank p=0.5
40%
20%
0%
Mortality Rate
Persistent 185 181 156 66 3
Regressed 202 199 163 74 3
0
5
10
15
20
Years
Apnea Regression : Persistent : Regressed

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