Progression and Regression of Sleep-Disordered Breathing With Changes in Weight

The Sleep Heart Health Study

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Background: The relationship of weight changes to the incidence, progression, and remission of sleep-disordered breathing (SDB) is not well defined. This study aims to determine the relationship between change in weight and progression or remission of SDB by polysomnography.

Methods: We performed a longitudinal cohort study of the cardiovascular consequences of sleep apnea in diverse US communities. Sleep apnea and polysomnographic indicators of SDB were assessed 5 years apart.

Results: A total of 2968 men and women (mean age, 62 years) participated in the study. Men were more likely to have an increase in Respiratory Disturbance Index (RDI) with a given increase in weight than were women, and this was not explained by differences in starting weight, waist circumference, age, or ethnicity. In a linear regression analysis, both men and women had a greater increase in RDI with weight gain than a decrease in RDI with weight loss. In a categorical analysis of larger degrees of change, this sex difference was also evident. Associations were similar in diverse ethnic groups. However, SDB progressed over time, even in those with stable weight.

Conclusion: Modest changes in weight were related to an increase or decrease in SDB, and this association was stronger in men than in women.

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SLEEP-DISORDERED BREATHING (SDB) is strongly associated with level of obesity.1 Weight gain is linked to development of sleep apnea in small series or case reports.2,3 One large study of the natural history of SDB in a large cohort of middle-aged men and women noted a 6-fold increase in the odds of developing moderate to severe SDB with a 10% weight gain throughout 4 years.4 In the Cleveland Family Study, the effect of weight gain was strongest in older men.5 These studies support the idea that the prevention of weight gain could be effective in the prevention of SDB.

A few small uncontrolled clinical trials of diet or surgery in extremely obese people have reported significant improvements in SDB.6-11 In the community, men and women with SDB are less obese, and often their conditions are undiagnosed. Prevention or treatment of SDB in community populations may differ from that reported at extremes of SDB and weight. Whether the relationships between weight gain and weight loss and the progression or remission in SDB are consistent in more diverse populations is uncertain. In this article, we describe the natural history of changes in SDB with weight change in the Sleep Heart Health Study (SHHS), a large multiethnic cohort of middle-aged and older men and women sampled from cohorts across the United States (a full list of the SHHS investigators and institutions can be found at http://www.jhuccp.com/shhs).

METHODS

The SHHS is a multicenter, longitudinal cohort study designed to determine the cardiovascular consequences and the natural history of SDB. The study included an assessment of weight and SDB in 2968 participants at 2 examinations approximately 5 years apart. Details of the design, protocol, and quality control procedures have been previously reported.12-14 Between 1995 and 1998, 6441 men and women were enrolled from among 11 145 participants approached in the Atherosclerosis Risk in Communities Study, Cardiovascular Health Study, Framingham Heart Study, Strong Heart Study, New York Hypertension Cohorts, Tucson Epidemiologic Study of Airways Obstructive Diseases, and the Health and Environment Study. Participants were 40 years or older at enrollment, and snorers were oversampled to increase the number of partici-
pants with SDB at baseline. The only exclusion criteria related to technical difficulties in performing unattended home polysomnography (PSG), such as tracheostomy, ongoing treatment with oxygen, or positive pressure therapy. The study protocol was approved by the institutional review board of each participating center.

Of the 6441 participants with baseline PSG, 3295 (51%) had follow-up PSG, and another 1019 (16%) had a home visit without PSG. Four hundred ninety-five (8%) were dead, 119 (2%) were too sick to participate, and 1513 (23%) refused follow-up or could not be reached. Complete weight and PSG data were available for 2968 participants. Data from all 215 participants who had follow-up PSG from the New York center were excluded because they did not meet quality standards for the follow-up examination, and 112 were missing key covariate data such as weight. Those who did not have follow-up PSG were approximately 2 years older on average than those who had subsequent PSG (P < .001) and more likely to be white (P < .001). For each PSG examination, participants completed a brief sleep habits questionnaire, medical history, assessment of current medication use, and blood pressure and anthropometric measurements.1,2

Overnight PSG was performed using a portable system (PS-2 System; Compumedics Limited, Abbotsford, Victoria, Australia), using methods previously detailed.3 Apnea was defined as a complete or almost complete cessation of airflow (at least <25% of baseline), as measured by the amplitude of the thermocouple signal, lasting 10 seconds or more. Hypopnea was identified when the amplitude of a measure of flow or volume fell to less than 70% of the amplitude of baseline breathing for 10 seconds or more but did not meet criteria for apnea. The Respiratory Disturbance Index (RDI) was defined as the number of events per hour, where an event was categorized into 5 levels: increase in RDI of more than 15 events per hour, increase in RDI of 5 to 15 events per hour, stable RDI (change of 0 to 4.9), decrease in RDI of 5 to 15 events per hour, and decrease in RDI of more than 15 events per hour. Incidence and remission were also defined as a change in RDI from a normal range (<5 events per hour) to abnormal (≥15 events per hour) and vice versa, respectively.

Multiple linear regression was used to determine the effect of weight change on RDI change, adjusting for age, baseline weight, weight change squared, the mean of baseline and follow-up RDI, and sex. Multiple linear regression was also used to test for sex–by–weight change interaction. The square of weight change, and a spline term at weight change of 0 were included to look for nonlinearity in the relationship between weight change and RDI change. After sex stratification, the quadratic term created a better model fit than the cubic weight change and spline at weight change of 0. Regression diagnostics were performed to test model assumptions and assess for adequacy of fit. The averages of the baseline and follow-up RDI were used to avoid bias due to regression to the mean.3 Additional multiple linear regression models explored the effect of controlling for race and other measures of body habitus, including BMI, neck circumference, and waist-hip circumference ratio, and tested for interactions among weight change and age, sex, ethnicity, and starting weight in the associations with change in RDI. Because of significant sex interactions, all subsequent models were stratified by sex. The χ² test was used to assess differences between weight change categories in the distribution of RDI change categories and in incidence of remission and progression of RDI.

Multiple linear regression and the χ² test were performed again using change in BMI and change in neck circumference as alternative measures of weight change. Sex-stratified multinomial logistic regression was used to determine the effect of weight change categories on RDI change using stable weight and stable RDI as the reference groups, with age, race, baseline weight, and the average of baseline and follow-up RDI as covariates. The statistical significance (2-tailed; P < .05) of the multiple linear regression coefficients was assessed by t tests, and the coefficients in the multinomial logistic regression were determined by the Wald χ² statistic.4 Models were reassessed, excluding data with high outlier influence scores, with no substantial change in results.

Statistical analyses were conducted using SAS statistical software, version 8.01 (SAS Institute Inc, Cary, NC), except for the multinomial logistic regressions, which were conducted using Stata statistical software, version 7.0 (Stata Corp, College Station, Tex).

RESULTS

The participants were on average moderately overweight and middle-aged to older (Table 1). Average weight change was small during the 5-year follow-up, but approximately 5% of both men and women either gained or lost more than 10 kg during the 5-year follow-up. The RDI increased by a mean ± SD of 3.4 ± 12.4 in men and 2.2 ± 9.0 in women.

The proportions of men and women with increases or decreases in RDI are shown for each category of percentage of weight gain or loss in Figure 1. Relative to stable-weight individuals, both men and women with weight gain were more likely to have increases rather than decreases in the RDI, and men were more likely to have increases in RDI than women. Proportions with a decrease in the RDI were less than proportions with increases in RDI but were highest in men and women with weight loss. Compared with those with stable weight, the groups with weight loss had a more frequent increase and decrease in RDI. This figure suggests that regardless of weight change, the RDI was more likely to increase over time in men than women but that this was influenced by changes in weight. The incidence rate of an RDI of 15 events per hour or more among those with a baseline RDI of fewer than 5 events per hour was 11.1% in men vs 4.9% in women, whereas the remission rate for going from an RDI of more than 15
Weight change category, %

-10-kg gain 4.6 5.8
5-10-kg gain 10.4 13.0
Stable 69.5 64.2
5-10-kg loss 10.3 11.9
>10-kg loss 4.2 5.2
BMI change, mean (SD)* 0.5 (2.3) 0.6 (2.7)
Neck circumference change, mean (SD), cm* 0.0 (2.5) 0.2 (2.3)
Baseline RDI, median (IQR)† 6.3 (2.2-14.0) 2.8 (0.8-7.6)
Follow-up RDI, median (IQR)‡ 8.3 (3.3-17.9) 4.7 (1.5-10.4)
RDI change, mean (SD)* 3.4 (12.4) 2.2 (9.0)
>15 Events per hour increase, % 12.2 6.2
5-15 Events per hour increase, % 18.6 15.4
Stable, % 54.6 69.5
5-15 Events per hour decrease, % 11.4 7.0
>15 Events per hour decrease, % 3.3 1.9
Incidence rate, %§ 11.1 4.9
Remission rate, %§ 7.0 8.0

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); IQR, interquartile range; RDI, Respiratory Disturbance Index.

*Follow-up minus baseline.
†Median RDI reported owing to a positively skewed RDI distribution.
‡RDI increase from fewer than 5 events per hour to 15 events per hour or more. Percentage shown is of participants with a baseline RDI higher than 15 events per hour. Percentage shown is of participants with a baseline RDI of less than 5 events per hour.
§RDI decrease from 15 events per hour or more to less than 5 events per hour.

To quantify the degree to which the absolute change in RDI was related to a given change in weight, multiple linear regression models of the effect of weight change on change in RDI were examined with and without adjustment. Interactions between weight change and sex, ethnicity, age, and baseline weight were examined. Of note, the interaction between sex and weight change was statistically significant (P = .002), indicating that the effect of weight change on RDI was not homogeneous for men and women (Figure 2). In addition, the statistically significant quadratic weight change term (weight change squared, P < .001) indicated that the relationship between weight change and change in RDI was not linear, showing that RDI increased more with weight gain than it decreased with weight loss. After adjusting for age, neck circumference, BMI, ethnicity, and waist-hip ratio, the sex interaction and the nonlinear association with weight gain remained statistically significant. Because women were more likely to have a lower baseline RDI and may not have been able to decrease the RDI further, these models were further stratified by starting RDI to determine whether a floor effect explained the lower slope in women. Although RDI tended to increase as weight increased and decrease as weight decreased, this effect was much stronger at a higher RDI and remained much stronger in men than in women when this floor effect was removed. The quadratic weight change term was not statistically significant in the models stratified by baseline RDI greater than 15, indicating that much of the nonlinearity was due to a floor effect, whereby those with a low RDI at base-
line had no opportunity for a further RDI decrease. Additional potential interactions between weight change and ethnicity and age were explored and were not statistically significant. A statistically significant weight change by baseline weight interaction was found in men (P < .001) but not women (P = .95), suggesting that RDI increases were greater for a given weight gain in men who were already overweight or obese. Further stratification by ethnicity did not suggest any clear differences in these relationships in African American, Hispanic, American Indian, Asian, or white participants.

To show the risk of developing clinically relevant changes in the degree of SDB, we examined transitions in changing the RDI by a moderate (5-15 events per hour) to a large (> 15 events per hour) extent compared with no change (within 5 RDI units) (Table 2). Increases were considered evidence of progression and decreases evidence of regression of SDB. Each level of change was examined in sex-stratified multinomial logistic regression to determine the odds of progression and regression at each level of weight change. Results based on crude rates were similar to those with adjustment for baseline weight, average of baseline and follow-up RDI, age, and ethnicity. In the adjusted models, the men who gained at least 10 kg had 5.21 (95% confidence interval, 2.35-11.53) times the odds of having a large (> 15 events per hour) increase in the RDI, whereas those with more modest weight gains had about 3 times the odds of having a large increase in the RDI. Men with weight loss also tended to have a higher likelihood of increasing the RDI compared with those with stable weight, but the odds ratios were generally not significantly greater than 1. The risk of a more moderate 5 to 15 times increase in the RDI tended to be higher in men at both levels of weight gain, but this was significant only in the moderate–weight gain group. Consistent with the linear model, the odds for moderate to high levels of increase in the RDI were lower in the women than the men with similar degrees of weight gain. Nevertheless, women with a weight gain of 10 kg or more had approximately a 2.5-fold higher odds of moderate or high increases in RDI than stable-weight women. This was statistically significant only for a moderate increase in

![Figure 2. Change in Respiratory Disturbance Index (RDI) by change in weight.](image)

<table>
<thead>
<tr>
<th>Weight Change Group</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Participants</td>
<td>Adjusted OR (95% CI)*</td>
</tr>
<tr>
<td>Progression, RDI &gt; 15 increase vs stable RDI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss &gt; 10 kg</td>
<td>26</td>
<td>0.98 (0.29-3.28)</td>
</tr>
<tr>
<td>Loss, 5-10 kg</td>
<td>85</td>
<td>0.91 (0.43-1.93)</td>
</tr>
<tr>
<td>Stable weight</td>
<td>642</td>
<td>1.00†</td>
</tr>
<tr>
<td>Gain, 5-10 kg</td>
<td>99</td>
<td>2.97 (1.66-5.32)</td>
</tr>
<tr>
<td>Gain &gt; 10 kg</td>
<td>44</td>
<td>5.21 (2.35-11.53)</td>
</tr>
<tr>
<td>Progression, RDI &gt; 5-15 increase vs stable RDI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss &gt; 10 kg</td>
<td>33</td>
<td>1.57 (0.70-3.51)</td>
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<tr>
<td>Loss, 5-10 kg</td>
<td>97</td>
<td>1.14 (0.67-1.94)</td>
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<tr>
<td>Stable weight</td>
<td>710</td>
<td>1.00†</td>
</tr>
<tr>
<td>Gain, 5-10 kg</td>
<td>105</td>
<td>1.83 (1.14-2.95)</td>
</tr>
<tr>
<td>Gain &gt; 10 kg</td>
<td>37</td>
<td>1.83 (0.87-3.85)</td>
</tr>
<tr>
<td>Progression, RDI &gt; 15 decrease vs stable RDI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss &gt; 10 kg</td>
<td>35</td>
<td>2.85 (1.28-6.31)</td>
</tr>
<tr>
<td>Loss, 5-10 kg</td>
<td>95</td>
<td>1.61 (0.91-2.84)</td>
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<tr>
<td>Stable weight</td>
<td>647</td>
<td>1.00†</td>
</tr>
<tr>
<td>Gain, 5-10 kg</td>
<td>83</td>
<td>1.21 (0.63-2.29)</td>
</tr>
<tr>
<td>Gain &gt; 10 kg</td>
<td>26</td>
<td>0.68 (0.19-2.10)</td>
</tr>
<tr>
<td>Progression, RDI &gt; 5-15 decrease vs stable RDI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss &gt; 10 kg</td>
<td>28</td>
<td>5.40 (1.69-17.25)</td>
</tr>
<tr>
<td>Loss, 5-10 kg</td>
<td>88</td>
<td>2.23 (0.84-5.91)</td>
</tr>
<tr>
<td>Stable weight</td>
<td>572</td>
<td>1.00†</td>
</tr>
<tr>
<td>Gain, 5-10 kg</td>
<td>73</td>
<td>1.28 (0.40-4.07)</td>
</tr>
<tr>
<td>Gain &gt; 10 kg</td>
<td>24</td>
<td>0.78 (0.09-6.37)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; OR, odds ratio; RDI, Respiratory Disturbance Index.
*Adjusted for age, race, baseline weight, and average RDI.
†Indicates referent.
the RDI but similar in pattern to the model of continuous change.

Regression of SDB was noted to follow a pattern similar to the linear model in that women with weight loss were less likely to show a decline in RDI than were men with weight loss. With weight loss of 10 kg or more, men had approximately 3 times the odds of reducing the RDI by 15 units compared with weight-stable men. Weight loss of as little as 5 to 10 kg tended to be associated with a greater than 2-fold greater odds of a 15-unit or greater reduction in the RDI compared with weight stability in men. The odds for a lesser degree (5-15 RDI units) of regression were also significantly related to weight loss of more than 10 kg in the men. Women with weight loss had a tendency to reduce the RDI, but generally the odds of reductions in RDI with weight loss were not significantly different from 1. Men and women with weight gain did not show regression in the RDI.

The addition of baseline neck circumference and baseline waist-hip ratio covariates had little effect on the results. Also, because of the tendency for those with weight loss to have changes in the RDI in both directions, either an increase or a decrease in RDI, we considered the possibility that weight loss might reflect the long-term health conditions associated with SDB, including myocardial infarction, stroke, congestive heart failure, or diabetes. However, with adjustment the odds ratios were essentially unchanged and remained nonsignificant, although slightly greater than 1. Analysis of change in BMI and neck circumference yielded similar results in that the associations were stronger in men than in women.

Finally, Figure 3 illustrates the proportion of persons with a normal RDI of less than 5 events per hour of sleep who converted to an abnormal or high RDI of greater than 15 events per hour in each weight change group. Consistent with the other approaches to analysis, the rate of new or incident cases of high RDI was related to weight gain in men. Although not statistically significant in women, a similar pattern was observed. Small numbers of these events precluded multivariate analyses.

In a diverse cohort of middle-aged and older men and women, we found important differences between men and women in the relationship between weight change and progression or regression in SDB. This sex difference was not explained by a higher neck circumference or waist-hip ratio in men. This finding supports previous cross-sectional reports that SDB is more closely related to weight in men than in women, who tend to develop SDB only at much higher levels of obesity than do men.1,22 Potentially, weight control efforts might have a greater impact on SDB in men than in women. We also noted a tendency for an acceleration of worsening in RDI with more extreme weight gain, especially in men who were already overweight or obese. This finding suggests that attempts to avoid continued weight gain in those who have already gained weight would be highly beneficial. Additionally, we found that weight loss was associated with less regression of the RDI than was weight gain with progression, especially in the women, and this was only partially explained by a lower prevalence of SDB. Nevertheless, modest weight loss would be expected to reduce the degree of SDB in the community. Although statistical power was limited, the findings were consistent across a diverse range of ethnic groups.

The sex difference in the association between weight change and RDI change was consistent whether the changes were examined on a continuous basis or categorically and for conversion from low to high level of RDI. Previous population studies1,22 have reported that the cross-sectional association between obesity and SDB is high in both men and women, yet women tend to have a lower RDI at every level of BMI when compared with men of the same BMI. In the Wisconsin Sleep Cohort Study, sex differences in the association between weight gain and increased SDB were not statistically significant. In contrast, the Cleveland Family Study found a similar sex difference in both incidence and progression of SDB in relation to weight gain.5,23 Because women with SDB have a much higher BMI than men with a similar RDI,26 it would follow that women have to gain more weight to have a similar increase in RDI. The higher risk of SDB in men might be explained by their tendency to a higher proportion of central body fat, including both visceral fat and upper body fat. Potentially, more specific imaging methods of body habitus might explain the sex differences.24

The longitudinal associations are consistent with a causal association between obesity and SDB, yet the direction of causality could be in either or both directions. Several studies25-26 have examined the effect of treatment of SDB on weight loss and fat distribution and suggest that the correction of SDB increases the likelihood of weight loss and lowers visceral fat and leptin levels. Conceivably, SDB develops with weight gain but could promote further weight gain because of the high stress and lower daytime energy level associated with chronically disrupted sleep.27

In the longitudinal component of the SHHS, subsequent PSG was obtained on only 51% of participants. This could potentially bias the estimate of the longitudinal associations if the associations differed in those who dropped.
out or died. A higher rate of adverse health events in those who dropped out or died might confound the associations in ways that are difficult to predict and result in apparently different associations. However, the association of weight loss with RDI change was not confounded by the occurrence of interim cardiovascular disease events, the most common health event in the cohort and known to be associated with secondary SDB. The SHHS cohort was not intended to be a representative population but was constructed by recruiting volunteers from several larger studies, with oversampling of snorers from the younger cohorts. This later strategy enhanced the statistical power for the primary goal of determining risk of cardiovascular disease without altering internal study validity.13

Other important limitations of this study include the small number of people with large changes in weight or RDI and biological variability in PSG recordings. Although our total sample was large, only 5% experienced a large increase in RDI and 5% a large decrease in weight, so the findings cannot be extrapolated to large changes in weight. The night-to-night variability of RDI also limits the power to demonstrate significant associations between weight change and change in RDI.17

The observation that it is more difficult to improve sleep apnea by decreasing weight than to make sleep apnea worse by gaining weight should not be construed to reduce the emphasis on weight control for the prevention or treatment of SDB. In addition, the importance of obesity as a risk factor for SDB in women should not be minimized. Although women appear to have a different pattern and natural history of SDB than men,20 their conditions are still far more often underrecognized and underdiagnosed relative to men. Obesity remains the major risk factor for SDB in both men and women.1

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