Sleep-Disordered Breathing and Cardiovascular Disease: Epidemiologic Evidence for a Relationship

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INTRODUCTION

SEVERAL EPIDEMIOLOGY STUDIES OF SLEEP-DISORDERED BREATHING (SDB) AND CARDIOVASCULAR DISEASE (CVD) have been conducted over the past decade, and others are now underway. The collective results of the published findings do suggest an association of SDB and CVD, but some of the findings are weak and there are inconsistencies. The lack of strong, consistent findings, in fact, was cited in a recent review as the reason for concluding that evidence for an association of SDB and CVD was lacking.[1] However, it is important to determine if, in the framework of the etiologic model of interest, inconsistencies can either be resolved or provide new insights. Using the following model (Figure 1) as a framework for assessing study strengths and weaknesses, selected prospective, case-control and cross sectional studies are reviewed here. In addition, preliminary cross-sectional data from the Wisconsin Sleep Cohort Study, an ongoing population-based study of the natural history of sleep disordered breathing, are presented.

As indicated by paths *(a)* through *(e)* in the model, nightly exposure to SDB for some period of time is proposed to be a direct cause of CVD *(a)*, an indirect cause of CVD by causing hypertension *(b)*, and a modifier of the effect of CVD on mortality *(c)*. Alternatively, SDB may be non-causally related to CVD due to confounding *(d)*, or it may be a consequence, rather than a cause of CVD *(e)*. Properly constructed prospective, case-control, and cross-sectional study designs all have the potential to address this model, with varying strengths and weaknesses. Common to all studies designs is the need to control (and not over-control) for confounding factors and to consider the effect time-period implicit in the study. Attention to study power and to the measurement accuracy of both SDB and CVD, and consideration of their durations (time from onset of the condition to initiation of the study) are also needed.

Prospective studies of SDB and CVD

In a prospective study, a large number of people with known SDB status are followed over the appropriate time interval to determine how baseline or change in SDB relates to incident (new) CVD and, worsening of CVD, mortality due to CVD. Although this is usually considered the design of choice for etiologic investigations, methodologic problems are possible. Specific to SDB and CVD, inadequate follow-up time could seriously compromise the validity of the study findings, but an effect period (i.e., "incubation period") for SDB to impact CVD has not been proposed. Furthermore, because SDB is a chronic condition that may remain undetected for a long time, unknown portions of the effect period will have already passed by the time SDB is measured on each individual at baseline. Another potential concern is loss of participants to follow-up. If drop out varies by the exposure-outcome subgroups, bias can result. For example, if, among those with developing CVD, those with SDB stay in the study but those without SDB drop out, overestimation of the association would result.

Four population-based prospective studies have been reported. Ancoli-Israel et. al.[2] investigated the mortality experience of a sample of 426 older adults (ages >65 years) that had been studied at baseline by in-home recording of breathing excursions. Follow-up, 8-10 years later, was excellent: mortality status was ascertained for all but four people. The proportions of cardiovascular deaths in people by respiratory distress index (RDI) was 35%, 59% and 54% for groups with RDI <15, 15-30, and >30 respectively. Survival analysis showed a significant difference in survival time ($p=.003$), with an average survival of 7.9 years for those with RDI >30 and 9.4 years for those with RDI <15. Stratification showed that gender was not a confounding factor. However, in a multiple regression model that included terms for age, gender, BMI, and history of CVD, RDI was not a significant predictor of mortality. Before considering this as a negative finding, note that as shown in figure 1, CVD would be intermediate in the causal pathway of SDB and CVD death, so it is not surprising that RDI lost significance when CVD was controlled for. The association of SDB and CVD mortality cannot be determined from this model, and it is not possible from the data given to determine how much the unadjusted results (which show a statistically significant difference) may be biased due to uncontrolled confounding from age and BMI. Given the strengths of this study design and the data collected, further

analyses of the existing data, without controlling for CVD history, would be very informative.

Three large, population-based Scandinavian studies have been conducted, using snoring as a surrogate for SDB and ascertaining CVD by hospital discharge and mortality records. In spite of similar methods, the studies yielded different results. Koskenvuo et. al.[3] surveyed 3847 male participants aged 40-69 years in the Finnish twin cohort on snoring status in 1981 and then ascertained CVD status with hospital discharge data and mortality records up to 1984. Among the men free of ischemic heart disease at the time of the survey (i.e., no history of angina or myocardial infarction), the odds ratio (95% C.I.) for new ischemic heart disease was 1.4 (1.15,1.71), for habitual and frequent snorers versus occasional and nonsnorers, independent of BMI, age, smoking, alcohol and hypertension. Note that by controlling for hypertension, if SDB causes CVD at least in part, through hypertension (illustrated in figure 1) the association between SDB and CVD would be underestimated. On the other hand, the positive association, in spite of controlling for hypertension, suggests that a direct effect of SDB on CVD may be operating.

In the second study, Jennum et. al.[4] studied 2937 men in the Copenhagen Male Study. Participants ages 54-74 years were surveyed on snoring and then followed for CVD outcomes through hospital and mortality records for up to 6 years. In this study, however, snoring was not related to CVD (relative risk=1.0, adjusted for confounding factors).

The disparity in results from the two Scandinavian studies with similar study methods and large, well-constructed samples is puzzling. The usual concern about inadequate length of follow-up can not explain the difference, because the Jennum et al study had the longer follow-up period. Jennum et. al.[4] suggest that an association may only be present in younger men, below the age range of the Copenhagen study. In support of this explanation, outcomes linked to SDB seen in middle-aged adults have not been found to be associated with SDB in samples of older people. In a recent survey of sleep disorders in older adults,

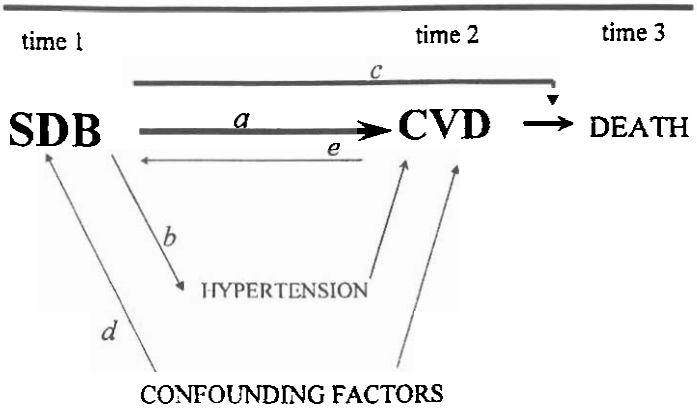

Figure 1—Etiologic model of sleep-disordered breathing (SDB) and cardiovascular disease (CVD)

Enright et. al.[5] found no correlation between snoring and outcomes that are associated with SDB (including hypertension) in middle-aged adults. It is also possible that other factors, such as genetics, may modify the effect of SDB on CVD development, and that these factors differ in the two Scandinavian samples. Alternatively, the conflicting findings may reflect measurement error. Snoring may be a poorer marker of SDB in the Copenhagen sample, compared to the Finnish sample, inaccurate measurement would bias findings toward "no association". It is also possible that SDB severity spectrum within the habitual snorer category differed in the two samples, with more severe SDB in the Finnish sample.

Most recently, Lindberg et al conducted a 10-year mortality follow-up of 3100 Swedish men who had been surveyed on snoring and sleepiness status[18]. Men with isolated snoring or sleepiness did not have an increased risk of mortality, compared to non snoring, non sleepy men. No excess mortality was associated with snoring for men who reported both snoring and sleepiness were more likely to have experienced cardiovascular mortality (relative risk=2.9, 95% confidence interval = 1.3, 6.7). There was no excess mortality associated with isolated snoring or sleepiness. These findings add further support to a greater effect of SDB on cardiovascular disease in younger men, and suggest that self-reported snoring alone may not identify a significant severity level of sleep-disordered breathing.

Three studies have been conducted in which incident CVD or CVD mortality in sleep clinic patients was ascertained some years after diagnosis.

In an early study, He et. al.[6] ascertained the vital status of 385 out of 706 sleep apnea patients. Conservatively treated patients (e.g., weight loss was advised) were found to have a significantly higher death rate than that of patients treated by tracheotomy. A serious limitation of the study was the large proportion of patients whose vital status was not found. Even a small bias in which surviving untreated patients, compared to treated patients, were less likely to be located for follow-up could account for the association.

However, similar findings were reported in a study with 99% follow-up. Partinen et. al. conducted a 5-year mortality follow-up[7] and a 7-year morbidity follow-up[8] on 200 sleep apnea patients. In the mortality follow-up study, the conservatively treated patients, compared to those treated by tracheotomy, had nearly 5 times the risk of cardiovascular or stroke-related death. In the morbidity follow-up study, the relative risk (95% C.I.) of new vascular disease for the untreated compared to treated group was 2.3 (1.5, 3.6). This study does provide support for a causal role of SDB in CVD disease and mortality, but it is important to recognize that it was conducted at a time when a large proportion of cases of SDB were quite severe and serious comorbidity was particularly high (probably due in part to

selection bias). Consequently, these findings may be less relevant to mild or moderate SDB, or be specific to the early clinic patient populations.

Case-Control Studies of SDB and CVD

For the case-control design, a group of people with CVD and a group without are selected. Ideally, the control group is selected from the same sampling base as the cases. If controls do differ on their underlying opportunity for exposure (e.g., controls selected from an active seniors club), a spurious association can result. After the sample is constructed, the "previous" occurrence (at baseline in figure 1) is determined. This aspect is obviously problematic: estimation of the duration of SDB may be nearly impossible. If onset of SDB in an individual is actually very recent, it may not have been possible to be a cause of the CVD, or, the CVD may have caused the SDB.

In the first case-control study, Hung et al[9] performed overnight polysomnography on 101 Australian myocardial infarction survivors and 53 volunteers from community clubs who served as heart disease-free controls. Both apnea index and snoring history were significantly associated with myocardial infarction, independent of BMI and other potential confounding factors. Men with an apnea index over 5 vs less than 5 were 23 times more likely to have had a myocardial infarction. The confidence interval for this very high odds ratio is wide (95% C.I.=4, 140) but even the low boundary indicates a substantial risk. Being a current snorer carried nearly as high a risk (odds ratio=11, 95% C.I.=3-40). A weakness of this and the following case-control studies is that the past SDB status (relevant to the development of CVD from exposure to SDB) is estimated by the current status. Perhaps even a more serious concern is that the source of the control group was very likely to be healthier than the general population and that the abnormally low levels of SDB and snoring in this group were responsible for the relationships.

A more conservative approach to construction of the control group was taken by D'Alessandro et. al.[10] in a case-control study of myocardial infarction and snoring history, conducted in Italy. For each case recruited from new hospital admissions for myocardial infarction (n=50), both a hospital control (the next acute illness hospital admission after each case's admission for myocardial infarction) and a community control randomly selected from the community census listing were used. Using both control groups together, the odds ratio, adjusted for confounders (including hypertension!), for snoring and myocardial infarction was 4.4 (95% C.I.=1. 1, 17.8). Although the same concern for the estimation of prior SDB holds, confidence in the findings is increased by the more appropriate control group.

More recently, Mooe et. al. studied coronary artery disease and SDB in 192 Swedish men[11] and in 152 women[12] using a case-control design. For both studies, cases were identified based on coronary angiographic evidence of coronary artery disease and controls were randomly selected from the population registry. All participants had an in-hospital sleep study. Both studies yielded positive findings: men and women with AHI in the upper quartile (>=5 for women, >=14 for men) versus those with lesser AHI were 4.5 and 4.1 times more likely to have coronary artery disease, respectively. Odds ratios, adjusted for BMI, smoking, diabetes, and hypertension were statistically significant at $p<.05$. The response rates for the comparison groups in both studies were excellent, reducing concern for a "healthy volunteer" bias, whereby response rates are higher among people with higher education, income, and better health. Although the Mooe et. al. studies[11,12] suffer from the same limitation in assuming that current SDB reflects the past status, concern is lessened because the cases had newly diagnosed coronary artery disease, reflecting perhaps less chance to cause SDB, compared to the more extreme pathophysiology of myocardial infarction.

Cross-Sectional Studies of SDB and CVD

In cross-sectional studies, the effect period is essentially ignored, and the current status of both SDB (of unknown

Table 1—Association of sleep-disordered breathing and prevalent cardiovascular disease, n=1206.

Model Terms	Odds Ration	p
Male	2.9	.002
Age/One Yr	1.2	.001
BMI	1.0	.20
AHI		
<2	(reference)	
2-5	1.2	.50
5-15	1.2	.62
15-30	1.5	.43
>30	3.0	.04

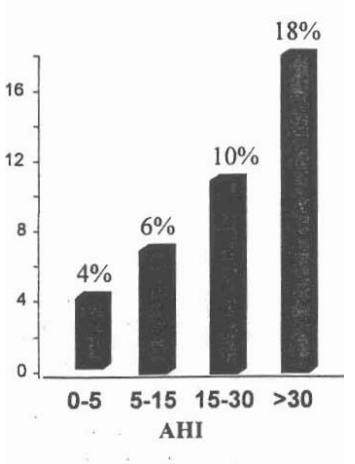

Figure 2—Prevalence of cardiovascular disease by apnea-hypopnea index (AHI) category in the Wisconsin Sleep Cohort Study, n= 1206

duration) and CVD are determined. In addition to obscuring the temporal order of the association, the design assumes people with SDB of different duration to be at equal risk for CVD. For example, persons with newly developed SDB in the sample do not have the opportunity for development of CVD as a result of SDB. This will contribute to an underestimation of the association. In addition, a cross-sectional sample represents "survivors". If SDB causes CVD and increased mortality, the remaining population that is sampled will lead to an underestimation of the association.

Schmidt-Nowara et. al.[13] investigated snoring and measured blood pressure in a population-based sample of 1206 Hispanic-Americans in New Mexico. In-home monitoring of breathing during sleep (using expired C02 detection) was conducted on a subset (n=275).[14] Positive odds ratios, adjusted for confounders, for both snoring and SDB indicated by an apnea index (number of apneic events per hour of sleep, AI) with CVD were reported. Loud snoring vs. not loud snoring was associated with a history of myocardial infarct (OR= 1.8, 95% confidence interval = 0.9, 3.6). AI = 10-19 and AI> 20 were related to history of ischemic heart disease;odds ratios (95% confidence intervals) were 2.3 (0.7, 7.7) and 4.1 (1.0, 16). Although these estimates are of marginal statistical significance, the age range of the sample (18->70 years, with a high proportion below age 40 years) may have precluded the sufficient number of CVD outcomes needed for adequate study power.

The association of SDB and CVD has been examined cross-sectionally using baseline data from the Wisconsin Sleep Cohort Study (n=1206), a prospective study of the natural history and outcomes of medically unrecognized SDB.[14] The cohort comprises middle-aged men and women who were employed by the state of Wisconsin in 1989 (see 16 for description of the study design). At 4-year intervals, participants in the cohort undergo in-laboratory overnight polysomnography and other tests, including several measurements of blood pressure Several other measures are taken, including weight, height, circumferences and extensive self-reported data on health history including doctor-diagnosed CVD, demographics, and life style are collected. SDB is indicated by the number of apneas and hypopneas per hour of sleep (AHI), with an apneic event defined as 10 seconds or more of no oral or nasal airflow and a hypopncic event defined as a reduction in breathing measured by calibrated respitrace accompanied by a 4% arterial blood oxygen desaturation. CVD was indicated by self-reported history of myocardial infarction, angina, and coronary artery disease. There were 60 cases of prevalent CVD; the distribution by apnea-hypopnea index categories is shown in figure 2. Multiple logistic regression, controlling for sex, age, and BMI, showed that people with an AHI >30 compared to those with AHI<2, were 3 times as likely to have a history of CVD (p<.04). At this time, findings are limited by the small number of people with CVD Study power as this relatively young cohort ages will permit more robust analyses in the future.

SUMMARY

Epidemiology studies of SDB and CVD to date do not provide a conclusive answer to the question of the degree to which SDB impacts CVD or mortality due to CVD. However, most of the studies seem to be consistent with a positive, but perhaps small, association. All the findings discussed or referred to in this review are likely to be biased to some degree. Bias can be both towards underestimation (e.g., from mismeasurment of SDB, and over-control for intermediate factors) and overestimation (e.g., from inadequate control of confounders and improper comparison groups), and the net magnitude of competing biases undoubtedly varies from study to study. Small associations were found in the prospective population-based studies. with one exception. The most obvious methodologic problem in these studies would be likely to result in underestimation of the associations. The case-control studies, in contrast, showed large associations, but serious biases in these studies would probably cause overestimation. Small associations of marginal statistical significance were reported from cross-sectional analyses; findings were limited by sample size.

Although each individual study to date could be (and has been) "dismissed" due to weaknesses, collectively they provide evidence that we cannot dismiss the hypothesis that SDB causes CVD. In many cases, the weak associations can be explained by problems that likely cause underestimation. In fact, finding any association with the limitations of most of the past studies is remarkable.

Perhaps most important, the findings to date, in conjunction with biologically plausible mechanisms have sparked the interest needed to initiate the large undertaking of a population-based prospective study. The Sleep Heart Health Study (SHHS)[15] is a large multicenter prospective study specifically designed to investigate the role of SDB in incident coronary heart disease, stroke, increased blood pressure, and allcause-mortality. A key feature of the study is that home polysomnography studies are performed on a sample of 6600 men and women, 40 years of age and older. drawn from the samples of other longitudinal studies. The new data collected by SHHS can then be linked to the large amount of data on cardiovascular risk factors available from the "parent" studies. All baseline polysomnography studies have now been completed. Cross-sectional analyses of SDB and CVD history are now being analyzed, and collection of outcome data for longitudinal analyses is underway. Results from SHHS and other studies in the near future should greatly increase our ability to assess the association of SDB and CVD.

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