Genetic and Environmental Influences in Sleep-Disordered Breathing in Older Male Twins

Dorit Carmelli PhD1; Ian M. Colrain PhD1,2; Gary E. Swan PhD1; Donald L. Bliwise PhD3

1SRI International, Menlo Park, CA; 2The University of Melbourne, Parkville, Victoria, Australia; 3Emory University Medical Center, Atlanta, GA

Study Objectives: To estimate the extent to which genetic factors contribute to the variation in several indices of sleep-disordered breathing in elderly male twins.

Design and Setting: A biometric genetic study based on data from unattended Edentrace recordings in a sample of elderly male twins.

Participants: 122 World War II male veteran twin pairs, including 68 monozygotic pairs aged 78.9 (± 2.7) years and 54 dizygotic pairs aged 78.4 (± 2.4) years.

Interventions: N/A.

Measurements and Results: The average (± SD) respiratory disturbance index for this sample was 17.2 ± 14.5, the average (± SD) oxygen desaturation index was 18.8 ± 16.4, and the average (± SD) minimum SaO2 level was 79.6 ± 8.1%. Intraclass twin-pair correlations for log-transformed respiratory disturbance index were 0.59 in monozygotic pairs and 0.36 in dizygotic pairs. For oxygen desaturation index, intraclass correlations were 0.44 in monozygotic pairs and 0.24 in dizygotic pairs. For minimum SaO2, intraclass correlations were 0.38 and 0.11, respectively. Maximum likelihood estimates of heritability with associated 95% confidence intervals were 37% [22%, 52%] for respiratory disturbance index, 36% [19%, 53%] for oxygen desaturation index, and 10% [0%, 30%] for minimum SaO2. Adjustments of sleep-disordered breathing measures for age, body mass index, and waist and neck circumference had minimal effect on estimates of heritability.

Conclusions: The present data indicate that sleep-disordered breathing, even in old age, is determined, in part, by genetic factors.

Key Words: sleep-disordered breathing, genetics, twins, epidemiology

Citation: Carmelli D; Colrain IM; Swan GE; Bliwise DL. Genetic and environmental influences in sleep-disordered breathing in older male twins. SLEEP 2004;27(5):917-22.

INTRODUCTION

THE EVALUATION OF CAUSE AND EFFECT IN COMORBIDITIES IN THE ELDERLY IS DIFFICULT. A genetically informative study, however, offers a simple route towards the dissection of the etiology of diseases such as sleep-disordered breathing (SDB) in the elderly. This is due to the fact that among monozygotic (MZ) twins, the occurrence of disease in one twin but not the co-twin must be due to individual (nonshared) environmental factors, whereas in dizygotic (DZ) twins, differences between discordant co-twins could be due to both genetic and nongenetic factors. Implicit in this inference is the assumption that genotype precedes phenotype in the pathway of causation even when the actual genetic determination of the traits studied is unknown. Previous studies of complex diseases such as asthma, Alzheimer’s disease, and osteoporosis have successfully applied the co-twin case-control methodology to dissect the underlying etiology of these diseases.1,7

The contribution of genetic influences to sleep apnea is suggested from several family studies.8-15 The data from these studies show strong familial influences in the development of SDB, with as much as 40% of the variance in SDB being due to factors not explained entirely by familial similarity in body mass index (BMI) or neck circumference.11

The largest population-based study of SDB symptoms in twins was conducted in Finland beginning in the early 1980s.16 Using information gathered from more than 6,000 male and female adult twin pairs, the authors of this study estimated that approximately half of the variation in self-reported symptoms of sleep apnea could be attributed to genetic factors. Another large study of sleep apnea symptoms in twins involved phone survey data. They reported that the proband-wise concordance rate for habitual snoring, was higher in MZ pairs than in DZ pairs, but the difference was not statistically significant. We have also reported that self-reported snoring has a greater within-pair correlation for MZ (0.24) than for DZ (0.09) twin pairs with an estimated heritability for snoring of 23% and that daytime sleepiness (Epworth Sleepiness Scale) showed within pair correlations of 0.39 for MZ and 0.21 for DZ twin pairs, with an estimated heritability of sleepiness of 38%.18

Recently, Kadotani et al20 reported an analysis of the association between the gene apolipoprotein (ApoE) ε4 and SDB in 791 middle-aged adults from the Wisconsin cohort. The probability of moderate-to-severe SDB (apnea-hypopnea index [AHI] ≥ 15) was significantly higher in participants with ApoE ε4, independent of age, sex, BMI, and ethnicity (12.0% vs 7.0%; P = .003). There was a significant increase in the likelihood of having SDB with the presence of 2 versus 1 ε4 allele, with the odds ratio of having an AHI of ≥ 15 being 2.1 for 1 allele and 3.9 for 2 alleles. Foley et al21 did not find this relationship in a sample of elderly Japanese (odds ratio of 0.77 for an AHI ≥ 15). Further analysis of the data comparing those with an AHI of > 30 to those with and AHI < 30, also failed to find an association with ApoE ε4 (odds ratio = 1.06 for AHI > 30). As indicated by the authors, the lack of consistency across the 2 studies points to the “need to address genetic associations across populations that vary by ethnicity and underlying risk factors.”21p1447

Palmer et al22 have recently published estimated heritability values for OSA and BMI in a paper investigating genetic linkage in a large family cohort. They reported heritability of 36.3% for...
AHI and 52.8% for BMI. After adjusting BMI for AHI, the BMI heritability was 42.9% (SE = 10.6%).

The objective of this investigation was to estimate the heritability of several physiologic indexes underlying manifestations of SDB, including the respiratory disturbance index (RDI), the oxygen desaturation index (O2DI), and the minimum SaO2. Subjects in the present study are a subset of community-living healthy male-male twin pairs from the World War II Twin Registry.

MATERIALS AND METHOD

Subjects

One hundred and twenty two pairs of male-male twin pairs, 68 MZ and 54 DZ, took part in the study. Mean ages were 78.9 (±2.7) years for the MZ twins and 78.4 (±2.4) for the DZ twins. Subjects were recruited from the NAS-NRC World War II Twin Registry of Caucasian males, where both twins served in the military. The methods used to construct this twin panel have been described in previous publications.

Zygosity determination was first made on the basis of physical similarities and then confirmed for more than half of the present sample by serologic assays. These methods of zygosity determination are estimated to be correct for approximately 95% of twin pairs.

Subjects were required not to have any severe medical illnesses. Physical and mental health were assessed by means of a medical history inventory. Twins participating in the present study were drawn from throughout California and the Southeastern United States. All subjects gave written informed consent to participate in the study after full explanation of the study aims and procedures.

Recruitment Procedures

A list of all living twins was obtained from the Medical Follow-up Agency of the NAS-NRC to identify a geographically representative sample of intact twin pairs suitable for participation in the study. In 1998, we sent a screening questionnaire to 300 pairs of twins (600 individual subjects) from this sample to determine the prevalence of SDB symptoms and twins’ interest in participation in an overnight sleep study. Overall, individuals’ return rate of the screening questionnaire was 51% including singleton pairs (i.e., twins whose brothers were deceased). Of the intact pairs who returned the questionnaire, 55% were MZ pairs and 45% were DZ pairs.

The mean age of the twins was 75.8 years (range 72-82 years). From twins’ responses to the screening questionnaire, we found that 3.8% were diagnosed to have sleep apnea, 8.6% reported loud snoring, and 2.4% had breathing difficulties during sleep. Of the twins contacted to participate in the home assessment, 45% (120 pairs) participated in the home assessments, 20% (53 pairs) refused to participate, 18% (48 pairs) were too ill to participate, 8% (21 pairs) were ineligible to participate, and 9% (24 pairs) were deceased. Due to the advanced age of this cohort, we experienced a higher number of twins who were too ill to participate or were deceased, compared to studies of younger individuals.

Respiratory and Cardiac Activity During Sleep

Subjects were monitored in their own homes with an Edentrace II Recording System (Malinckrodt, Hazelwood, MO). Breathing sounds, airflow, respiratory effort, SaO2, body position, and heart rate were recorded and used to derive measures of SDB severity. Standard disposable Edentrace sensors for airflow and pulse oximetry were used. SaO2 was measured using standard pulse oximetry hardware and software contained within the Edentrace II. The Edentrace II has been used widely in numerous epidemiologic studies recording respiration during sleep in the home setting. Validation studies reported by Redline et al and Emsellem et al noted high (above 90%) sensitivity and specificity and high correlations (above 0.95) between data collected with this system and data obtained using laboratory polysomnographic techniques.

Body-habitus measures were taken in a standardized manner by the technician studying each subject.

After downloading the data, a registered polysomnographic technologist, who was blind to all participants’ identifying information, manually edited the computerized scoring of all breathing events for the entire night on an event-by-event basis. SDB events were defined as follows: Apnea: airflow pause or absence of respiratory effort of at least 10 seconds from previous baseline, where baseline average excluded the lowest 7 of the last 10 breaths. Hypopnea: a fall in airflow amplitude of 50% below average amplitude for at least 10 seconds, accompanied by at least a 4% drop in SaO2. Desaturation: any fall in SaO2 below 90% or a drop of 4% or greater below baseline saturation.

On the basis of these definitions, the RDI was defined for each participant as the total number of apneas and hypopneas per hour of recording time. Additionally, we calculated an O2DI, defined as the number of desaturations per hour of total recording time, and noted the minimum SaO2 observed within the recording.

Statistical Analysis

Pearson Correlations

The relationships of obesity measures to SDB measures were evaluated using all available data (i.e., including both individuals of a pair). Because a bias can exist in making inference from a sample of nonindependent observations (i.e., twin pairs), we used bootstrap methods to derive empirical estimates of the standard errors of individual Pearson correlations. To accomplish this, we created 100 bootstrap data sets using the twins as genetically unrelated individuals.

Twin-pair Correlations

The comparison of MZ with DZ twin intraclass correlations provides an approximation of the genetic and environmental influences on the phenotypic variation of the particular trait examined (e.g., RDI). In general, a DZ twin correlation less than the MZ correlation is indicative of additive genetic influences, whereas a DZ correlation less than half the MZ correlation suggests genetic effects that operate nonadditively (i.e., dominant genetic effects or gene-gene interaction effects). The influence of the shared environment (those environmental experiences that are common to twins of a pair) is denoted by a DZ correlation greater than half the MZ correlation. Because dominant genetic influences will lower the DZ twin correlation, while shared environmental influences will increase the DZ correlation, the 2 effects are confounded, allowing the estimation of only 1 of these parameters. The effect of individual, nonshared environmental influences is indicated by an MZ correlation less than 1.0.
Correlations were calculated on the original and log transformed data.

Univariate Model Fitting

Whereas a comparison of the twin correlations can provide a broad picture of the causes of variation of the trait examined, structural equation-modeling procedures yield more precise estimates of genetic and environmental parameters. In addition, these procedures provide the opportunity for testing competing hypotheses underlying the causes of phenotypic variation. Theoretically, a model that includes additive genetic effects (A) fixes the genetic correlation between Twin 1 and Twin 2 to be unity in MZ twins and 0.50 in DZ twins. To include nonadditive genetic effects (D) in the model (as implied by a low DZ correlation), an additional parameter is required that specifies that dominance effects correlate 0.25 in DZ twins and 1.0 in MZ twins. In contrast, common shared environmental effects (C) specify a correlation of 1.0 for both MZ and DZ twin pairs. Because nonshared environmental influences (E) affect only 1 member of a pair, this correlation is assumed to be 0 for both zygosities. For the modeling procedures of the present study, the full model tested was either an ACE or an ADE model, as there were insufficient data to estimate both. The decision as to which model was estimated was based on the observed pattern of MZ-DZ correlations. If the DZ correlation was about half the MZ correlation, then we fitted the ACE model. On the other hand, if the DZ correlation was substantially less than half the MZ correlation, we fitted the ADE model. All models were fitted by maximum likelihood using the statistical program Mx^28(Virginia Commonwealth University, Richmond, VA). The adequacy of different models was evaluated by likelihood ratio χ^2 statistics and using Akaike information criteria, which specifies that the best fitting model is the model with the lowest Akaike information criteria value.

RESULTS

Table 1 presents descriptive statistics for MZ and DZ twins for age, obesity measures, substance use measures, and SDB measures including RDI, O2DI, and minimum SaO2. There were no significant differences between MZ and DZ twins on age, BMI, and SDB measures. We noticed that DZ twins reported drinking more and smoking more than MZ twins. Phenotypic correlations between SDB measures, age, obesity measures, and substance use are presented in Table 2. Small, but significant, correlations were observed between age and RDI and age and minimum SaO2. Larger correlations were observed between obesity measures and both RDI and O2DI, with the largest correlations being between minimum SaO2 and obesity measures. Of note, was the lack of association of RDI, O2DI and minimum SaO2 with smoking and alcohol use. Bootstrap resampling tests were performed to calculate the unbiased estimates of standard errors. Recalculation of the correlation between SDB measures and each obesity measure yielded the same pattern of results described in Table 2.

We observed that, in MZ twins, RDI was significantly and positively correlated with O2DI (r = 0.84, P < .001) and significantly negatively correlated with minimum SaO2 (r = -0.45, P < .001); O2DI was also significantly negatively correlated with minimum SaO2 (r = -0.60, P < .001). A similar pattern of correlations was apparent in the DZ twins, with RDI being significantly positively correlated with O2DI (r = 0.94, P < .001) and negatively correlated with minimum SaO2 (r = -0.39, P < .001). O2DI was significantly and negatively correlated with minimum SaO2 (r = -0.41, P < .001). Bootstrap resampling methods that account for the dependence of observations within twin pairs yielded the same pattern of results.

Intraclass twin correlations within MZ twins for log-transformed RDI were significant and exceeded the correlation within DZ twins, suggesting the presence of genetic effects. The RDI intraclass correlations were 0.59 in MZ twins and 0.27 in DZ twins, respectively. For O2DI, they were 0.44 in MZ pairs and 0.24 in DZ pairs. Twin correlations were smaller in magnitude for minimum SaO2, though greater in MZ twins than DZ twins (0.38 and 0.11, respectively).

Results from genetic model fitting are presented in Table 3 with larger P values indicating better model fit. For RDI, the ACE model fits the data well (χ^2 = 1.11, P = .78) The heritability estimate for RDI based on the full ACE model is 37% with a 95% confidence interval of 22% to 52%. We repeated this analy-
sis adjusting RDI for BMI and waist and neck circumference. Intraclass correlations for adjusted values of RDI were 0.60 in MZ pairs and 0.36 in DZ pairs. The heritability estimate of obesity-adjusted RDI values was not different than that for unadjusted values.

For O2DI, the full ACE model also fits the data ($\chi^2 = 1.93, P = .59$) with common environment (C) accounting for 11% of the total variance. The heritability estimate for O2DI based on the full ACE model is 36% with a 95% confidence interval of 19% to 53%.

For minimum SaO2, the DZ intraclass correlation is less than half the MZ correlation; therefore, the full model fitting these data is an ADE model. This model fits the data well ($\chi^2 = 3.83, P = .28$), with dominance effects (D) accounting for 27% of the total variance. When we tested the significance of the dominance effects by dropping the D parameter from the full ADE model, we observed no significant reduction in model fit ($\chi^2 = 0.21$). The heritability estimate for minimum SaO2 based on the full ADE model is 10% with a 95% confidence interval of 0% to 30%.

**DISCUSSION**

The use of the biometric model in an elderly population is particularly powerful in determining the extent to which genetic factors influence the observed level of SDB in this sample.14,29-32 While twin pairs have a shared intrauterine environment and are raised in the same family environment until late adolescence, some environmental divergence necessarily occurs with adulthood. The older the twins, the longer this period of “unshared” environmental influence, which would maximize potential environmental exposures that could be relevant to the etiology of SDB. For example, cumulative alcohol intake33 or lifetime exposure to tobacco,34 potential risk factors for SDB, have an impact that would be expected to be maximized in our design. On the other hand, in the presence of such shared and unique environmental influences, the impact of congenitally determined or developmentally salient factors (e.g., craniofacial structure35,36) relevant for SDB might be somewhat diminished in a study restricted to an elderly age group. Finally, other risk factors having both substantial genetic and environmental components (e.g., obesity) that may change across the life span (increased or decreased body weight in old age) may impact upon our elderly sample in ways that could either diminish or enhance these age-dependent risk factors in an elderly, relative to a younger, twin cohort. In this regard, specific components of this cohort other than age (e.g., geographic influences on body weight) may well have been the relevant features contributing to the observed partial variance effects.

To our knowledge, the present study is the first to provide estimates of heritability for continuous values of RDI, O2DI, and minimum SaO2 in a relatively large sample of elderly male twins. While each of these variables is a measure of SDB and are thus not orthogonal, they do index different aspects of apnea severity. RDI is a simple count of the number of events per hour of sleep, but provides no information as to the duration or impact of each event, thus a 10 second hypopnea with no O2 desaturation is counted the same as a 30 second apnea with a substantial desaturation. O2DI reflects a different count of events, and counts only those in which at least a moderate O2 desaturation occurs, but again does not distinguish between long and short events, or mild and severe desaturations. The minimum SaO2 desaturation value provides a clinically useful value of the worst case of desaturation across the night, but, as such, only provides information about the single most severe event. It should also be noted that the minimum SaO2 value could be more subject to technical error because it represents a limited time sampling of data. While the

**Table 3—Maximum Likelihood Model Comparisons**

<table>
<thead>
<tr>
<th>Model fitted</th>
<th>$a^2$</th>
<th>$c^2$ or $d^2$</th>
<th>$e^2$</th>
<th>$\chi^2$</th>
<th>df</th>
<th>$P$</th>
<th>AIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE</td>
<td>0.37</td>
<td>0.20</td>
<td>0.43</td>
<td>1.11</td>
<td>3</td>
<td>.78</td>
<td>-1.89</td>
</tr>
<tr>
<td>CE</td>
<td></td>
<td>0.49</td>
<td>0.51</td>
<td>3.13</td>
<td>4</td>
<td>.54</td>
<td>-0.87</td>
</tr>
<tr>
<td>AE</td>
<td>0.58</td>
<td></td>
<td>0.42</td>
<td>1.70</td>
<td>4</td>
<td>.79</td>
<td>-2.30</td>
</tr>
<tr>
<td>E</td>
<td></td>
<td></td>
<td>1.00</td>
<td>36.15</td>
<td>5</td>
<td>&lt;.001</td>
<td>31.15</td>
</tr>
<tr>
<td>ACE</td>
<td>0.36</td>
<td>0.11</td>
<td>0.53</td>
<td>1.93</td>
<td>3</td>
<td>.59</td>
<td>-4.07</td>
</tr>
<tr>
<td>CE</td>
<td></td>
<td>0.39</td>
<td>0.61</td>
<td>3.49</td>
<td>4</td>
<td>.48</td>
<td>-4.51</td>
</tr>
<tr>
<td>AE</td>
<td>0.49</td>
<td></td>
<td>0.51</td>
<td>2.11</td>
<td>4</td>
<td>.72</td>
<td>-5.89</td>
</tr>
<tr>
<td>E</td>
<td></td>
<td></td>
<td>1.00</td>
<td>22.53</td>
<td>5</td>
<td>&lt;.001</td>
<td>12.53</td>
</tr>
<tr>
<td>ADE</td>
<td>0.10</td>
<td>0.27</td>
<td>0.63</td>
<td>3.83</td>
<td>3</td>
<td>.28</td>
<td>-2.17</td>
</tr>
<tr>
<td>DE</td>
<td></td>
<td>0.27</td>
<td>0.73</td>
<td>6.03</td>
<td>4</td>
<td>.20</td>
<td>-1.97</td>
</tr>
<tr>
<td>AE</td>
<td>0.35</td>
<td></td>
<td>0.65</td>
<td>4.04</td>
<td>4</td>
<td>.40</td>
<td>-3.96</td>
</tr>
<tr>
<td>E</td>
<td></td>
<td></td>
<td>1.00</td>
<td>14.73</td>
<td>5</td>
<td>&lt;.001</td>
<td>4.73</td>
</tr>
</tbody>
</table>

Note: A, C, D and E refer to additive genetic, shared environmental, nonadditive genetic, and nonshared environmental influences, respectively. $a^2$, $c^2$, $d^2$ and $e^2$ are estimates of the proportion of additive genetic, shared environmental, nonadditive genetic, and nonshared environmental components of variance, respectively, calculated for the different structural equation models. Data were sufficient to calculate only 1 of the ACE or ADE models for each variable. $\chi^2$ represents the goodness-of-fit statistic, which is distributed as $\chi^2$. df indicates degrees of freedom. Model fits are summarized by the probability ($P$) and the Akaike information criteria (AIC) statistic. Models with lower values of AIC and higher values of $P$ indicate better fit, as the $P$ values represent the probability of the model fitting the data. RDI refers to respiratory disturbance index; O2DI, oxygen desaturation index.
3 measures are significantly intercorrelated, the data indicate that minimum SaO2, in particular, has substantial variance unaccounted for by either RDI or O2DI. RDI accounts for 20% of the minimum SaO2 variance in the MZ twin sample and 15% of the minimum SaO2 variance in the DZ sample. O2DI accounts for 36% of the minimum SaO2 variance in the MZ twin sample and 17% of the minimum SaO2 variance in the DZ sample.

Both twin samples displayed a range of values for each measure of SDB from those indicating the absence of pathology (RDI = 0.01, O2DI = 0.56, minimum SaO2 = 93%) to those indicating severe disease (RDI = 87, O2DI = 89, minimum SaO2 = 61%). Therefore, it is unlikely that the results are due to a bias from having either an unusually healthy or an unusually unhealthy population sample.

We observed that 37% of the variance in RDI and similarly 36% of the variance in O2DI could be attributed to genetic factors, with the remainder of the variance being due to nonshared individual environmental factors. The heritability of minimum SaO2 value was 10%. Further adjustment of each of these indices of SDB for BMI and waist and neck circumference had no effect on estimates of heritability. The 37% estimate for RDI is remarkably close to the estimated heritability of AHI of 36.3% reported by Palmer et al22 despite differences in the age and composition of the different subject populations.

In this study, home monitoring was used to quantify measures of SDB, and standardized questionnaires were used to assess sleep symptoms and exposures. Previous work has demonstrated that home monitoring can provide highly reproducible and accurate quantification of SDB in a diverse group of adults.26 Also, it appears unlikely that impaired sleep quality caused by the monitoring apparatus significantly influenced our estimates of SDB. Ascertainment bias is particularly important in genetic epidemiology studies. In this study, we achieved a high participation rate among the twins contacted; however, it is difficult to assess the potential impact of missing data caused by nonparticipation of twin pairs, as more severe cases were less likely to be seen.

The prevalence of SDB is known to increase with age,37 and in a population of older twins, the potential for unshared environmental influences, including risk factors, to dominate any genetic predisposition for sleep disordered breathing is maximized. However, the similarity in estimated heritability of RDI between the present data and those of Palmer et al22 indicates that the magnitude of genetic influence on SDB is as potent in an elderly twin population as it is when studying younger subjects in a family cohort.

REFERENCES


