Genetic and Environmental Influences on Insomnia, Daytime Sleepiness, and Obesity in Twins

Nathaniel F. Watson, MD; Jack Goldberg, PhD; Lester Arguelles, PhD; Dedra Buchwald, MD

Department of Neurology, University of Washington, Seattle, WA; Department of Epidemiology, University of Washington, Seattle and Vietnam Era Twin Registry, Seattle VA Medical Center, Seattle, WA; Epidemiology and Biostatistics Division, University of Illinois at Chicago, Chicago, IL; Department of Medicine, University of Washington, Seattle, WA

Study Objectives: To better understand the relationships of insomnia, sleepiness, and obesity.

Design: Classic twin study.


Patients or Participants: One thousand forty-two monozygotic and 828 dizygotic twin pairs participating in the University of Washington Twin Registry.

Interventions: None.

Measurements and Results: Twins were, on average, 32 years old; 61% were women, and 19.5% were obese, defined as a body mass index ≥ 28. Insomnia and sleepiness were endorsed by 19.3% and 3.7% of twins, respectively. Twin correlations were higher in monozygotic than dizygotic twins for insomnia (0.47 versus 0.15), sleepiness (0.37 versus 0.14), and obesity (0.82 versus 0.46). Heritability estimates were 57% for insomnia (p < .001; 95% confidence interval 47-63), 38% for sleepiness (p < .01; 95% confidence interval 16-46), and 73% for obesity (p < .001; 95% confidence interval 49-87). Multivariate genetic model fitting revealed that common additive genetic effects comprised 12.8% of the phenotypic correlation between insomnia and sleepiness (p < .01) and 10% of the phenotypic correlation between insomnia and obesity (p < .01). The phenotypic correlation between sleepiness and obesity was not due to common additive genetic effects.

Conclusions: Insomnia, sleepiness, and obesity are under strong genetic influence. Common genetic effects were observed between insomnia and both sleepiness and obesity, suggesting shared genetic contributions to these phenomena.

Keywords: Twins, genetics, insomnia, sleepiness, obesity

Citation: Watson NF; Goldberg J; Arguelles L et al. Genetic and environmental influences on insomnia, daytime sleepiness, and obesity in twins. SLEEP 2006;29(5):645-649.

INTRODUCTION

INSOMNIA AND SLEEPINESS ARE COMMON COMPLAINTS IN THE GENERAL POPULATION. APPROXIMATELY 40% OF INDIVIDUALS SUFFER FROM INSOMNIA AND SLEEPINESS EFFECTS UP TO 13% OF THE POPULATION. Both insomnia and sleepiness negatively impact daytime functioning, quality of life, and mental and physical health. Insomnia strains interpersonal relationships and impairs concentration and memory, and daytime sleepiness is associated with industrial and automobile accidents, increased morbidity and mortality, and poor quality of life. Moreover, individuals with poor self-reported health endorse insomnia or daytime sleepiness more often than do those with good or excellent health.

Insomnia and sleepiness also are frequent symptoms in sleep clinics. Some patients exhibit both symptoms simultaneously, such as those with obstructive sleep apnea or depression. Paradoxically, some patients with insomnia also experience sleepiness, and those with narcolepsy may display characteristics of sleep-onset and sleep-maintenance insomnia. Although both insomnia and sleepiness are genetically influenced, the extent of genetic overlap between these symptoms has not been examined. Furthermore, both insomnia and sleepiness are more common in obese than nonobese individuals, but the genetic relationship between obesity and these symptoms is unknown.

This study, therefore, examines the relative contributions of genetic and environmental influences on variation and covariation in the correlation of insomnia and sleepiness in a United States community-based sample of twins. In addition, because obesity is largely under genetic control, we explore the genetic overlap of obesity with both insomnia and sleepiness. In this analysis, we address these 3 questions: (1) What are the genetic and environmental contributions to self-reported insomnia and sleepiness? (2) Is the relationship between insomnia and sleepiness due to common genetic or common environmental influences? (3) Is the relationship of either insomnia or sleepiness with obesity due to common genetic or common environmental influences?

MATERIALS AND METHODS

Twin Registry: Construction and Recruitment

The University of Washington Twin Registry is a community-based sample of twin pairs constructed using data available from the Washington State Department of Licensing. In Washington, the driver’s license identification number is based on an applicant’s name and date of birth. Therefore, to avoid issuing duplicate license identification numbers, every new applicant is asked if she or he is a twin. We negotiated with the Department of Licensing to obtain access to their twin records beginning in 1999.

All twins 18 years of age or older were mailed a packet that included an introductory letter, a Registry brochure, a brief health and zygosity survey, and a postage-paid envelope. The survey also asked the index twin to inform her or his co-twin about the
Registry and to provide the co-twin’s contact information. A second packet was sent to twins who did not respond to the initial mailing, with corrected addresses as available. Telephone calls were made to twins who did not respond to the first mailing. Once the survey from the index twin was received, we mailed a Registry packet to his or her co-twin. Nonresponding co-twins were also followed-up by mail and telephone. The data-collection procedures have been approved by the University of Washington Institutional Review Board and the State of Washington Attorney General.

Measures

The date of birth and sex of the twin was obtained from the Department of Licensing records. Education level was obtained from self-report. Zygosity was determined using previously validated self-report methods that correctly assign zygosity at least 95% of the time.\textsuperscript{17,18} Insomnia and sleepiness were determined by response to the following 2 questions modified from a sleep assessment questionnaire:\textsuperscript{19} (1) How often do you have trouble falling asleep or staying asleep? (2) How often do you fall asleep during the day against your will? The possible responses were “never,” “sometimes,” “often,” or “always.” Responses of “often” or “always” were considered affirmative answers. Obesity was defined as a body mass index of 28 kg/m\textsuperscript{2} or greater, calculated from self-reported height and weight.

Statistical Analysis

Univariate Genetic Analysis

Initial analysis examined simple descriptive statistics for demographic characteristics and sleep and obesity measures. The genetic and nongenetic contribution to sleep and obesity were estimated with structural equation modeling.\textsuperscript{20} This approach captures the variability in sleep and obesity as a function of numerous genes and environmental factors, each with a relatively small effect. First, we estimated the within-pair twin correlation for each of the 3 outcome measures (insomnia, sleepiness, and obesity) separately in monozygotic and dizygotic pairs. Next, a model was fitted to the pattern in the twin correlations (or covariances) to estimate the component of phenotypic variance that is due to additive genetic (A), common environmental (C), and specific environmental (E) components. It is possible to estimate additive genetic effects because monozygotic twins share 100% of their genetic backgrounds and dizygotic twins share, on average, only 50%. Common environmental effects are environmental factors that are assumed to be shared 100% by both members of monozygotic and dizygotic pairs and reflect factors such as in utero exposures, socioeconomic class, and diet. Specific environmental effects reflect unique environmental exposures, for example, one twin having been in a motor vehicle accident and the other not.

Modeling began by including parameter estimates for the full ACE model and testing the goodness of fit using likelihood ratio \(\chi^2\) procedures. Reduced models were constructed by removing a specific parameter (usually A or C as E can rarely be excluded) and comparing the goodness of fit of the full and reduced models using a likelihood ratio test. We then compared 3 models: the full model (ACE), a model in which all variance was attributable to genetic and specific environmental factors (AE), and a model in which all variance was produced by common and specific environmental factors (CE). Parameters were removed from the model if its removal did not result in a significant degradation of the model’s fit. Best fitting models were evaluated using the Akaike Information Criteria to compare alternative nonnested models.\textsuperscript{21} From the final best fitting model, the proportions of variance attributable to latent variables A, C, and E were derived from the parameter estimates, along with the 95% confidence intervals. We also conducted separate univariate analyses in male and female same-sex twins; results in both men and women were similar, and we therefore present the results for all pairs combined.

Bivariate Genetic Analysis

To estimate the common genetic vulnerability to insomnia, sleepiness, and obesity, we used bivariate structural equation modeling. Three types of correlations in monozygotic and dizygotic pairs were calculated: phenotypic correlations examining the association of 2 traits within an individual, twin correlations for a single trait (sleepiness in twin 1 with sleepiness in twin 2), and cross-twin cross-trait correlations (i.e., sleepiness in twin 1 with obesity in twin 2). Larger monozygotic than dizygotic cross-twin cross-trait correlations are indicative of a common genetic influence on both phenotypes.

We conducted 3 separate bivariate analyses: insomnia and sleepiness, insomnia and obesity, and sleepiness and obesity. We used a bivariate model with a full Cholesky decomposition, which is the most general model form that permits any valid covariance structure. This model allowed us to decompose a phenotypic association between 2 different traits (e.g., sleepiness and obesity) into common and specific genetic effects. In a similar manner, the phenotypic correlation between 2 different traits can be decomposed into C and E components. Model fitting for the bivariate analysis followed a similar approach to that used in the univariate modeling. Likelihood ratio test \(\chi^2\) statistics compared various forms of reduced models that were constructed by removing model components.

RESULTS

Demographics and Prevalence

As shown in Table 1, the 2084 monozygotic and 1656 dizygotic twins enrolled in the Registry were, on average, 32 years old (range 18-90). Overall, 61% of twins were female and 86% were Caucasian; twins had a mean of 13.6 years of education. Among all pairs, 28% were male/male, 49% female/female, and 23% were opposite-sex pairs. Insomnia was endorsed by 19.3% and daytime sleepiness by 3.7%; 19.5% were obese.

Univariate Genetic Analysis

In the univariate analysis, the variation of each factor was partitioned into its genetic and environmental components. Twin polychoric correlations for insomnia, sleepiness, and obesity were presented in Table 2. Common environmental effects contributed little to these phenotypes. The within-pair correlations for insomnia, sleepiness, and obesity revealed that the monozygotic within-pair correlations (0.47, 0.37, 0.82) were greater than the corresponding dizygotic correlations (0.15, 0.14, 0.46), suggesting that genetic influences contributed to individual differences.
in self-reported insomnia, sleepiness, and obesity in these twins. For the most part, a significant relationship was observed between phenotypes within the same individual. Genetic commonality was supported by the fact that the cross-twin, cross-trait correlations were predominantly higher for monozygotic twins than for dizygotic twins (Table 3).

**Bivariate Genetic Analysis**

The bivariate analysis partitioned the covariation between factors into shared additive genetic components (A), shared common environmental components (C), and unique environmental components (E). The best fitting model in all cases included additive genetics and unique environment (AE). The bivariate analysis of the phenotypic correlation between insomnia, sleepiness, and obesity are represented in Table 4. In general, unique genetic effects outweighed common genetic effects for these traits. However, there were significant common additive genetic effects found between insomnia and sleepiness and insomnia and obesity. No effect of common environment was detected for any of the bivariate analyses.

**DISCUSSION**

In this study, we used a classic twin design to determine the extent to which individual differences in self-reported insomnia, sleepiness, and obesity were due to genetic or nongenetic (environmental) influences. Our results suggest a significant genetic influence on all 3 factors. The co-occurrence of insomnia and sleepiness and insomnia and obesity was largely due to common genetic factors. In contrast, the co-occurrence of sleepiness and obesity was not primarily due to common genetic influences, suggesting that either other genetic influences specific to sleepiness and obesity are involved or environmental influences predominate.

These results are consistent with previous twin studies demonstrating that genetic factors strongly influence insomnia. In a study of Australian volunteer twin pairs, genetic effects accounted for 32% to 36% of the variance in insomnia complaints, with no effect of common family environment. Likewise, in a study of male twins who were Vietnam-era veterans, genetic effects accounted for 28% of the variance in sleep-onset insomnia and 42% of the variance in sleep-maintenance insomnia, again, common family environment had no influence. Significant genetic effects on sleep quality and duration also have been observed in Finnish twins, but shared environmental factors (i.e., cohabitation) led to higher heritability estimates.

Our findings suggest a stronger genetic influence for insomnia than has been noted in previous reports, possibly reflecting the relatively young age of our cohort. In this regard, insomnia starting in childhood is under genetic control than insomnia occurring later in life. Indeed, 55% of patients with childhood-onset insomnia identified at least 1 family member with sleep difficulties, compared to 39% of patients with adult-onset insomnia. Other work has suggested a higher familial incidence among patients.
tients with insomnia starting in childhood, adolescence, or early adulthood (< 39 years of age) compared with those with onset in middle-age or late life. Thus, our youthful cohort may have been enriched with individuals suffering from childhood insomnia, which contributed to our high observed heritability.

Previous twin studies have demonstrated findings similar to the 38% heritability of sleepiness we observed. Using a single item, Heath et al derived a heritability estimate of 39% for daytime dozing in a volunteer twin registry. Others, using the Epworth Sleepiness Scale, have estimated the heritability of sleepiness at 38% in elderly male World War II veterans. In contrast, another study revealed a heritability estimate of 21% for waking up unrefreshed among Vietnam-era male twins, a finding possibly explained by the focus of the question more on sleep quality than on daytime sleepiness. It has been proposed that the heritability of sleepiness results from the genetic susceptibility for sleep-disordered breathing, a reasonable hypothesis in older men at high risk for having obstructive sleep apnea. Our sample, however, was young, included women, and had a relatively low rate of obesity, resulting in a low risk of having sleep apnea. This suggests that other heritable factors, such as sleep duration and subjective sleep quality, also contribute to the genetics of sleepiness.

The multivariate genetic analysis detected a significant phenotypic correlation between insomnia and both sleepiness and obesity, consistent with findings that insomnia is independently associated with these 2 factors. Yet, we observed no phenotypic correlation due to common additive genetic effects between sleepiness and obesity. This suggests that other genetic influences are contributing to sleepiness that are unrelated to the genetic factors influencing obesity. Examples of such influences include individual sleep need, circadian rhythms, and nocturnal timing of rapid eye movement sleep. This study has several limitations. First, as in all surveys, this study suffers from the biases associated with nonresponse. In addition, the preponderance of monozygotic and female twin pairs introduces another set of biases with unclear effects. Second, our analysis is based on the equal-environment assumption that monozygotic and dizygotic twin pairs experience the same non-genetic influences. A third set of concerns relates to measurement issues. We used only 2 self-reported items on sleep, which may not be accurate or sensitive enough to reveal genetic relationships. Furthermore, objective measures of insomnia such as sleep onset, offset, and duration, as documented by actigraphy, may not correlate with self-reported measures such as sleep diaries. Similarly, validated measures of subjective sleepiness often correlate poorly with objective measures of sleepiness such as the Multiple Sleep Latency Test. Lastly, body mass index was based on self-reported height and weight. Although a body mass index based on subjective anthropomorphic data may result in a biased calculation, validation studies suggest this bias is unlikely to affect conclusions about associations between body mass index and other health variables.

In summary, we found a high level of heritability for insomnia and obesity and a moderate level of heritability for sleepiness in a community-based sample of American twins. Genetic overlap was observed between insomnia and both sleepiness and obesity but not between sleepiness and obesity. Our heritability for insomnia was higher than previously reported and may be related to the youthful nature of our cohort and the relationship between age and onset of insomnia in childhood. Future twin studies should use objective measures of insomnia and sleepiness to confirm the heritability and genetic overlap of these conditions.

REFERENCES


SLEEP, Vol. 29, No. 5, 2006