HERITABILITY OF INSOMNIA SYMPTOMS IN YOUTH

Heritability of Insomnia Symptoms in Youth and Their Relationship to Depression and Anxiety

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Study Objectives: Insomnia is a highly prevalent sleep disorder yet little is known about the role of genetic factors in its pathophysiology. The aim of this study was to examine the relative contributions of genetic and environmental factors in explaining variability in insomnia symptoms.

Design: Traditional twin design.

Setting: Academic medical center.

Participants: 1412 twin pairs aged 8-16 years (48.8% MZ, 47.2% DZ, 4.0% indeterminate).

Interventions: None.

Measurements and Results: Ratings of insomnia symptoms, depression, and overanxious disorder were made by trained interviewers based on DSM-III-R criteria. ACE models were conducted using Mx statistical software. Insomnia symptoms were prevalent in this sample based both on parental (6.6%) and youth (19.5%) reports. The overall heritability of insomnia symptoms was modest (30.7%), with the remaining variance attributed to unique environmental effects. There was no evidence of sex differences in the prevalence of insomnia symptoms or in the contribution of genetic and environmental effects. In multivariate models, there was support for insomnia-specific unique environmental effects over and above overlapping effects with depression and overanxious disorder, but no evidence for insomnia-specific genetic effects.

Conclusions: Genetic factors play a modest role in the etiology of insomnia symptoms in 8-16 year-olds. These effects overlap with the genetics of depression and overanxious disorder. Further work is needed to determine which genes confer risk for all three disorders.

Keywords: Insomnia, genetics, twin study, depression, anxiety

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INTRODUCTION

Insomnia is a highly prevalent sleep disorder, affecting 10% of the U.S. population on a chronic basis and 30% episodically.1 There is a large body of research on pharmacologic and cognitive behavioral treatments for insomnia, but investigations of the underlying mechanisms are relatively sparse. In particular, studies of genetic factors are lacking. While the heritability of most psychiatric disorders has been studied for over 20 years, our understanding of the role of genetics in insomnia remains limited.

To date, several twin studies in adults have examined whether insomnia symptoms, broadly defined, are heritable traits. In one study, Heath and colleagues at the Australian Twin Registry collected sleep data from almost 4000 pairs of twins.2 The proportion of variance related to heritable factors (h²) was fairly consistent across questions ranging from sleep quality (h² = 32%) to “anxious insomnia” (h² = 36%). Subsequent studies generally yielded comparable estimates in the range of 20% to 40%,3,4 with the exception of one study that found a heritability of 64% for a single insomnia item.5 All of these studies were done with adults and relied on individual self-report items rather than validated measures. As a result, findings from these studies may reflect the more general concept of “sleep problems” rather than insomnia per se.

The lack of research in this area may reflect the traditional notion of insomnia as a symptom of another disorder rather than an independent clinical entity worthy of attention. For example, insomnia often occurs in conjunction with psychiatric disorders, most notably depression and generalized anxiety disorder, both of which have insomnia as a diagnostic criterion.6 As a criterion for each of these conditions, it is commonly felt that insomnia is simply a symptom (secondary to primary medical and/or psychiatric conditions). This said, it is now generally accepted within the sleep research community that insomnia can occur as an independent condition and that it is best construed as comorbid condition, one that has a bi-directional relationship with disorders such as depression and anxiety.7,8

There are a number of longitudinal studies demonstrating an increased risk of new-onset psychopathology over time in individuals with insomnia at baseline.9-11 In cases of remitted depression, insomnia often is a residual problem that confers increased risk for relapse.12,13 In cases where insomnia does resolve it often occurs as a prodromal symptom prior to relapse.14 Lastly, the neurobiology of sleep/wake regulation overlaps considerably with that for mood and anxiety, suggesting common mechanisms. These intricate interrelationships raise the question of the degree to which genetic effects are insomnia-specific vs. shared with these disorders. Several studies have now demonstrated that depression and generalized anxiety are different...
manifestations of the same genetic factors, and it is possible that insomnia is part of the same cluster.

While studies on the heritability of insomnia in children and adolescents are lacking, the literature provides evidence for genetic influences on more broadly defined sleep problems. For example, a recent longitudinal study by Gregory found that most of the variance in sleep problems could be explained by genetic and nonshared environmental influences at both 8 years (63% additive genetic factors, 32% nonshared environment) and at 10 years (66% genetic factors, 27% nonshared environment, 7% shared environment). There appears to be a genetic component to broadly defined sleep problems, but further studies are needed in different age groups to better understand how genetic and environmental influences interact to confer risk for insomnia over the course of development.

Thus, the primary goal of this study was to determine the broad heritability of insomnia symptoms based on clinical ratings in a large sample of twins aged 8-16. A second goal was to determine the extent to which any genetic effects are shared with depression and anxiety. It was hypothesized that there would be unique genetic effects specific to insomnia symptoms over and above those shared with depression and anxiety.

METHODS

The data for the present analysis were drawn from the Virginia Twin Study of Adolescent Behavioral Development (VT-SABD), a longitudinal sequential cohort study of twins aged 8 through 16. The current analyses focus on information from the first wave of data collection that consisted of 1412 families. Twin pairs were identified through the school system and participating private schools in the state of Virginia and then contacted by mail. Interested families were scheduled for detailed assessments of behavioral development and psychopathology. To maximize available sources of information, all interviews and questionnaires were completed by each child/adolescent as well as one or both parents or primary caregivers. Caregivers had to have been living with the youth for at least 6 months to be included.

Child and Adolescent Psychiatric Assessment

The primary assessment utilized the Child and Adolescent Psychiatric Assessment (CAPA), a semi-structured interview with separate parent and child/adolescent formats designed to assess a wide range of behavioral and psychological symptoms based on DSM-III-R. For the purposes of the current analysis, the modules for sleep problems, depression, and anxious affect and worries were utilized. The DSM-III-R criteria for insomnia are very similar to those in the DSM-IV-TR, and consist of (1) difficulty initiating or maintaining sleep, or non-restorative sleep; and (2) occurs ≥ 3 times per week for at least one month, and causes clinically significant distress or impairment. In the DSM-IV-TR the frequency criterion was dropped. In each area, the presence of symptoms over the past 3 months was ascertained, along with the frequency of occurrence, duration, and earliest age of onset (if symptoms were present).

A pair of trained interviewers was assigned to each family with each interviewer assessing one twin and one parent in the family and with the twin interviews always occurring first. The youth interviews and the interview from mothers (or fathers if mothers were not available) were used. All interviews were audio-taped throughout the study and rated by a team of monitors for fidelity. For all questions, a rating of 0 was used if it was determined that a symptom or disorder was not present. A rating of 2 indicated that the symptom or disorder was present at least at the minimum level of severity, and a rating of 3 that the symptom or disorder was present at a higher level of severity. A rating of 1 was discouraged because it indicated that the rater was not able to determine whether criteria were met, in which case the rater was supposed to continue to query the respondent until a determination could be made.

The sleep module of the CAPA interview includes a series of questions about the child’s/adolescent’s current sleep patterns, including whether the child has difficulty falling asleep or waking up too early in the morning, and then makes a clinical judgment of whether or not clinically significant insomnia symptoms are present. For these analyses, ratings of 2 and 3 were combined to create a dichotomous (yes/no) insomnia rating. For descriptive purposes, additional ratings of the timing of insomnia during the night (initial, middle, or late), and medication for insomnia were examined.

The CAPA also contains modules for DSM-III-R depression and overanxious disorder that were used for this study. For each disorder clinical ratings are made for the presence/absence of each of the criteria, allowing a determination to be made for whether the criteria are met. No sleep related criteria were used for either disorder. Youth and parent reports were combined using the standard “or” rule, in which a symptom is rated as present if it is endorsed by either the child or parent. For insomnia, univariate models were also computed for youth and parent reports separately. For overanxious disorder a dichotomous yes/no variable was computed based on whether criteria were met. Depression was rare in this cohort (1.3%), so subjects were dichotomized based on the presence or absence of ≥ 3 symptoms, with 3.4% meeting this threshold.

Zygosity

Zygosity was inferred using an algorithm that incorporates data from parental responses to a questionnaire and ratings of photographs, additional details of which have been published previously. Parental questions asked (1) how often the twins were mistaken for each other by strangers, (2) how similar the twins were, and (3) the perceived likelihood that the twins were identical. Photographs of the twins taken separately and together were scored by 2 independent raters as “definitely MZ,” “probably MZ,” “indeterminate,” “probably DZ,” or “definitely DZ.” In cases of disagreement the rating was assigned as indeterminate. The algorithm was validated in a subset of 231 twin pairs for whom zygosity was confirmed by typing for blood groups or DNA polymorphisms.

Data Analysis

Descriptive statistics for insomnia symptoms and correlations (tetrahoric for bivariate variables) with depression and overanxious disorder were computed. The correlations between insomnia symptoms and age, gender, and pubertal status, as determined by Tanner staging, were computed to explore the influence of development on insomnia reporting.
A series of twin models were conducted with the Mx statistical program for structural equation modeling. A full model was fit that allows for additive genetic (A), common environmental (C), and unique environmental (E) effects. This ACE model was then compared with models in which one or more of these effects were removed (AE, CE, and E), yielding a total of 4 models per analysis. The goal was to determine the model that provided the best combination of fit to the data and parsimony. Models were compared using likelihood ratio tests in which the negative log likelihood (-2LL) for a restricted model was subtracted from that for a more saturated model. The result follows a χ2 distribution with df equal to the difference in the number of parameters between the models. When the χ2 test yielded a P-value > 0.05 the restricted model was deemed to provide a fit that was not significantly worse than the more saturated model. Models that provided the best combination of parsimony and fit were characterized by the lowest values on the Akaike Information Criterion (AIC).

The first ACE model was applied to data on the presence or absence of insomnia symptoms. The second model allowed separate parameters for boys and girls to determine if there were gender differences in the relative contributions of genes and environment (i.e., sex-linked models). Separate models were then fit based on pubertal status. Lastly, a multivariate ACE model was fit to the data allowing for genetic and environmental effects for depression, anxiety, and insomnia symptoms based on a Cholesky decomposition. This method allows the model to contain multiple ACE factors up to the number of independent variables, in this case 3. In these analyses the "or" rule was used for insomnia symptoms. The first factor accounts for genetic and environmental contributions that are common to all 3 variables (depression, anxiety, and insomnia). The second factor and resulting model comparison determines whether there is second set of genetic and environmental contributions specific to the anxiety and insomnia. The third model comparison determines whether there is an "insomnia-specific" factor. This type of model favors allocation of variance to depression and anxiety as the first 2 variables in the model; this was intentionally done in order to determine the genetic variance that an insomnia-specific factor contributes over and above these shared influences. Figure 1A provides a diagram of the model. In Figure 1A, there are 3 factors representing depression, overanxious disorder, and insomnia. There are 3 additive genetic factors (A1-A3) and 3 unique environmental factors (E1-E3) specified. Note that common environmental factors were omitted from the figure for simplicity. The A1 and E1 factors influence all 3 phenotypes, whereas the A3 and E3 factors only influence insomnia and represent the unique effects for this phenotype. This approach extends previous studies in which a common factor accounted for both depression and anxiety, with insomnia the common factor in the current study. This analysis was also repeated with depression treated as the third factor, as depicted in Figure 1B. Univariate models for depression and overanxious disorder have been reported elsewhere.

RESULTS
A total of 1412 twin pairs participated, and the sample was split between males (46.3%) and females (53.7%). The mean age was 12.0 years (SD 2.6) with a range of 8-16. There were 689 monozygotic (MZ) twin pairs (48.8%), 666 dizygotic (DZ) twin pairs (47.2%), and 57 of indeterminate zygosity (4.0%). This last group was excluded from further analyses. Age and gender were not significantly correlated with any insomnia variables (all P > 0.05).

The prevalence of insomnia symptoms is shown in Table 1. The prevalence of insomnia symptoms in males and females was very similar at 18.3% and 20.5%, respectively. Parents consistently reported lower rates of insomnia symptoms (6.6%)
than their children (19.5%; Table 2). Parents and youth were in agreement about the presence or absence of insomnia symptoms 79.8% of the time. Discrepancies consisted almost entirely of youth reporting insomnia symptoms but parents not reporting any symptoms. The parent-youth correlations between symptoms counts for depression and overanxious disorder previously reported were low (r ranging from 0.12 to 0.29), suggesting that a discrepancy exists across disorders. The mean (SD) age of onset was 9.9 (3.4) years from youth reports and 9.0 (4.4) from parental reports. Depression was relatively rare in this cohort, with criteria met by only 1.3% of subjects and 3.4% of subjects having ≥3 symptoms. Overanxious disorder was more common, with 18.0% of subjects meeting criteria. The prevalence of insomnia symptoms in those with depression and/or overanxious disorder was 32.4% compared to 16.5% in those who did not meet criteria for either diagnosis. Table 3 displays the cross-twin cross-trait tetrachoric correlations among disorders. These correlations show the associations among traits within a twin pair for both MZ and DZ twins. For example, the correlation between MZ twin pairs for insomnia was 0.18, whereas for DZ twin pairs the correlation was 0.05, indicating a greater degree of concordance for MZ compared to DZ twins. On the other hand, the correlations between ratings of insomnia in MZ and DZ twin pairs were both 0.10, indicating a similar pattern of association regardless of zyosity.

For ratings of insomnia symptoms based on combined youth and parental reports, an AE model provided the best fit to the data ($\chi^2 (4) = 5.7, P = 0.2, AIC = −2.31$) with genetic effects accounting for 37.4% of the variance and unique environmental effects accounting for 62.6% of the variance. For ratings of insomnia symptoms based on youth reports, an AE model provided the best fit to the data ($\chi^2 (4) = 7.4, P = 0.11, AIC = −0.56$) with genetic effects accounting for 30.7% of the variance and unique environmental effects accounting for 69.3% of the variance. For ratings of insomnia symptoms based on parental reports, an AE model provided the best fit to the data ($\chi^2 (4) = 8.4, P = 0.08, AIC = 0.4$) with genetic effects accounting for 51.4% of the variance, and unique environmental effects accounting for 48.6% of the variance. There was no evidence for significant common environmental effects in any of these models. In sex-linked analyses, models were examined for all ACE effect combinations both with the effects for boys and girls constrained to be equal and with the effects allowed to differ. The model with the lowest AIC, both when using youth and parent ratings, was an AE model in which effects were constrained to be equal across gender. For youth ratings, the AE model yielded a $\chi^2(10) = 11.6$ (P = 0.31) and an AIC = −8.4. For parental ratings, the AE model yielded a $\chi^2(10) = 9.6$ (P = 0.31) and an AIC = −10.4. In analyses in which the sample was separated by pubertal status, an AE model provided the best fit for both pre-pubertal ($\chi^2(4) = 7.5, P = 0.11, AIC = −0.5$) and post-pubertal ($\chi^2(4) = 6.4, P = 0.17, AIC = −1.6$) subjects compared to the saturated ACE model. Additive genetic factors for pre- and post-pubertal subjects were 27.8% and 31.5%, and unique environmental effects were 72.2% and 68.5%, respectively. Thus the relative contribution of genetic and environmental factors did not appreciably change with the onset of puberty.

Lastly, for the multivariate models an AE model that included all 3 Cholesky factors provided a better fit to the data than the saturated ACE model. The AE with 3 factors model was then compared to one in which the third insomnia-specific genetic factor was removed, and there was not a significant loss of model fit ($\Delta\chi^2(1) = 0.004, P = 0.95, \Delta\text{AIC} = −2.0$). The model fit also did not significantly change when the second factor was removed ($\Delta\chi^2(3) = 0.001, P = 0.99, \Delta\text{AIC} = −6.0$). The final model contained a single genetic factor and 3 trait specific unique environmental factors. Standardized path coefficients for each of the significant pathways can be found in Figure 1A. When this analysis was repeated using depression as the last phenotype, the final model again contained a single genetic factor and three environmental factors as depicted in Figure 1B.

Table 1—Frequency of insomnia symptoms

<table>
<thead>
<tr>
<th>Variable</th>
<th>% Positive From Child Rating</th>
<th>% Positive From Parent Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rating of clinically significant insomnia</td>
<td>19.5%</td>
<td>6.6%</td>
</tr>
<tr>
<td>Initial insomnia</td>
<td>14.5%</td>
<td>4.9%</td>
</tr>
<tr>
<td>Middle insomnia</td>
<td>19.6%</td>
<td>6.3%</td>
</tr>
<tr>
<td>Early morning awakenings</td>
<td>4.9%</td>
<td>0.9%</td>
</tr>
<tr>
<td>Medication for insomnia</td>
<td>0.4%</td>
<td>0.2%</td>
</tr>
</tbody>
</table>

Table 2—Rates of youth and parent agreement for insomnia symptoms

<table>
<thead>
<tr>
<th>Variable</th>
<th>Absent</th>
<th>Present</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rating of clinically significant insomnia</td>
<td>n = 2086</td>
<td>n = 450</td>
</tr>
<tr>
<td>Initial insomnia</td>
<td>77.1%</td>
<td>16.6%</td>
</tr>
<tr>
<td>Middle insomnia</td>
<td>n = 98</td>
<td>n = 74</td>
</tr>
<tr>
<td>Early morning awakenings</td>
<td>3.6%</td>
<td>2.7%</td>
</tr>
</tbody>
</table>

Table 3—Average cross twin- cross trait tetrachoric correlations between insomnia, depression, and overanxious disorder in MZ and DZ twins

<table>
<thead>
<tr>
<th>Variable</th>
<th>MZ Twins</th>
<th>Overanxious Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insomnia</td>
<td>0.18*</td>
<td>0.09*</td>
</tr>
<tr>
<td>Depression</td>
<td>0.10*</td>
<td>0.12*</td>
</tr>
<tr>
<td>Overanxious Disorder</td>
<td>0.25*</td>
<td>0.12*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>DZ Twins</th>
<th>Overanxious Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insomnia</td>
<td>0.05</td>
<td>0.08</td>
</tr>
<tr>
<td>Depression</td>
<td>0.10*</td>
<td>0.10*</td>
</tr>
<tr>
<td>Overanxious Disorder</td>
<td>0.25*</td>
<td>0.12*</td>
</tr>
</tbody>
</table>

*P < 0.05
DISCUSSION

This study examined the genetic and environmental contributions to insomnia symptoms, both in isolation and in relation to depression and anxiety, in youth ages 8-16 years. Insomnia symptoms were prevalent, particularly when relying on youth rather than parental reports. Almost one in five subjects reported insomnia symptoms, which is higher than prior studies that diagnostic criteria for an insomnia disorder,29-32 but comparable to the rate of insomnia symptoms in another study.33 Given that poor sleep has been associated with lower school performance and other negative outcomes for youth,34-37 insomnia could be associated with a substantial public health burden for this segment of the population.

Rates of insomnia symptoms were considerably lower when based on parental reports. This is consistent with other studies that have found higher rates of internalizing symptoms by youth report compared to parent report.38,39 Gregory and colleagues also found this pattern in a study of 300 8-year-old twins, in which rates of sleep problems were higher on child reports (45%) than parental reports (17%) of sleep latency, as assessed with the Children’s Sleep Habits Questionnaire, although other sleep variables were less discrepant.40 Unless youth alert parents about their difficulties sleeping, parents may be less likely to be aware of insomnia since the disturbance occurs when parents are likely asleep. This pattern of higher heritability for parental estimates was also reported in the Gregory and colleagues study.40

The overall heritability of insomnia symptoms based on combined youth and parental reports is moderate, with genetic factors accounting for about 37% of the variance. By means of comparison, using youth reports from these data, the heritability of overanxious disorder was 30% for males and 46% for females, and the heritability for depression was 11% for males and 19% for females (note the presence of sex-linked effects for these disorders).22 The rate for insomnia symptoms is highly consistent with previous twin studies of insomnia symptoms in adults that relied on self-report methods.2,5-7 Thus, self-report vs. clinician ratings may not be a significant factor for determining the heritability of insomnia, which is important because of the number of large-scale genetic studies that have only included measures with sleep related items (e.g., items found in most depression rating scales such as 41). The phenotypic data from these studies may be sufficient for initial analyses of the genetics of insomnia.

In adults, the prevalence of insomnia in women is higher than in men but the reasons for the gender differences are not known. In this younger sample there were no phenotypic differences between males and females. The genetic analyses further suggest that there are no gender differences in the relative contributions of genes and environment in this age group. Further research is needed to determine the age at which gender differences in insomnia prevalence begin to emerge as well as the factors underlying this transition.

The most significant finding from these analyses was that there was no evidence for insomnia-specific additive genetic factors, but insomnia-specific unique environmental factors were supported. This is visually depicted in Figure 1A, for which the only significant pathways are those with coefficients provided. This suggests that there may be substantial overlap between the genetics of insomnia with that for depression and anxiety. The same pattern was found when the order of the phenotypes was reversed, indicating that the rarity of depression did not skew the model. These results are in contrast to previous studies using different analytic approaches. Gregory and colleagues approached this overlap from a different perspective by fitting ACE models separately to sleep problems and depression in children and then computing correlations between these factors.6 The correlation between the additive genetic factors was r = 0.64 indicating substantial, but not complete, overlap. Using this approach in the current data, the correlation was 0.96, suggesting a stronger degree of overlap than in their study. In adults, Kendler and colleagues conducted a factor analysis of the items from a scale of depression and anxiety in a large sample of twins from the Australian Twin Registry.42 The analysis led to a three-factor solution, with the third factor loading only on two sleep-related items that accounted for ~6% of the overall variance. When examined together, these studies provide mixed evidence for the existence of unique insomnia-specific genetic factors that are distinct from other symptoms of depression and anxiety.

This study had several limitations. The presence or absence of insomnia, although an aggregation of multiple questions, ultimately was rated as a single item. A number of factors, such as the schedule imposed by school start times, could have influenced reporting of insomnia symptoms but are not specifically addressed by the CAPA. The use of a validated instrument that yields a score indicative of insomnia severity may have better captured the wider range of insomnia manifestations. Further, the wording of the items on the CAPA may have influenced results. For example, the list of follow up questions in the sleep module contains a reference to fear of the dark, which may have fit better in the overanxious disorder module. Similarly, the anxiety module contains the question of whether worry keeps them up at night. To the extent that these items influenced the orthogonality of insomnia, depression, and anxiety, there may have been some impact on the genetic models. Objective assessment of sleep, either via polysomnography or actigraphy, may also have yielded different results because of their insensitivity to the biases inherent in self-report and interview methods. The assessment of sleep also did not include a measure of circadian tendency which, may have played an etiologic role, or a measure of other sleep disorders. Lastly, the small number of youth with depression or overanxious disorder preclude the ability to make subtle distinctions among the factors, but the results establish a prima facie case for an overall common genetic basis to the three traits. This genetic finding does not preclude clinically significant effects specific to insomnia, but raises the possibility that these might be environmental rather than genetic in origin.

In summary, these results indicate that clinician ratings of insomnia symptoms have moderate heritability but are not influenced by shared environmental factors. In this 8- to 16-year-old sample, this pattern of results was consistent across gender. Genetic factors related to the etiology of insomnia overlap with those related to depression and anxiety but there are distinct insomnia-specific environmental effects. Treatments for depression and anxiety may also improve sleep, and vice versa, although the distinct environmental effects suggest that insom-
nia-specific treatment components will also be necessary. Treatment of insomnia in youth may also reduce risk for later onset of depression and anxiety disorders. Further research into the genetic and environmental bases for insomnia needs to more comprehensively assess sleep and circadian rhythms in order to better understand the nature of the phenotype. It is likely that insomnia is a heterogeneous phenotype and a thorough assessment will help to identify subgroups that may be more appropriate for genetic studies. This line of research may shed light not only on the mechanisms of disturbed sleep but also on the pathophysiology of mood and anxiety disorders.

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