The Heritability of Insomnia Progression during Childhood/Adolescence: Results from a Longitudinal Twin Study

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Abstract

Study Objectives: To determine prevalence and heritability of insomnia during middle/late childhood and adolescence; examine longitudinal associations in insomnia over time; and assess the extent to which genetic and environmental factors on insomnia remain stable, or whether new factors come into play, across this developmental period.

Design: Longitudinal twin study.

Setting: Academic medical center.

Patients or Participants: There were 739 complete monozygotic twin pairs (52%) and 672 complete dizygotic twin pairs (48%) initially enrolled and were followed up at three additional time points (waves). Mode ages at each wave were 8, 10, 14, and 15 y (ages ranged from 8-18 y).

Interventions: None.

Measurements and Results: Clinical ratings of insomnia symptoms were assessed using the Child and Adolescent Psychiatric Assessment (CAPA) by trained clinicians, and rated according to Diagnostic and Statistical Manual of Mental Disorders (DSM)-III-R criteria for presence of 'clinically significant insomnia', over four sequential waves. Insomnia symptoms were prevalent but significantly decreased across the four waves (ranging from 16.6% to 31.2%). 'Clinically significant insomnia' was moderately heritable at all waves (h^2 range = 14% to 38%), and the remaining source of variance was the nonshared environment. Multivariate models indicated that genetic influences at wave 1 contributed to insomnia at all subsequent waves, and that new genetic influences came into play at wave 2, which further contributed to stability of symptoms. Nonshared environmental influences were time-specific.

Conclusion: Insomnia is prevalent in childhood and adolescence, and is moderately heritable. The progression of insomnia across this developmental time period is influenced by stable as well as new

genetic factors that come into play at wave 2. Molecular genetic studies should now identify genes related to insomnia progression during childhood and adolescence.

Key Words: genetics, insomnia, sleep, twins

Introduction

The transition from childhood to adolescence is accompanied by numerous physiological and social changes. During this time, it is perhaps not surprising that sleep disturbances are common.[1] Indeed, prevalence of insomnia symptoms has been estimated to range from 4% to 41% in early childhood and adolescence, depending on sample, age, and mode of assessment.[2–8] Insomnia manifests difficulties initiating or maintaining sleep, early morning awakening, or feeling that the sleep period was non-restorative or unrefreshing, with the sleep problem causing significant distress or impairment.[9] Despite our knowledge that insomnia exists in early childhood and adolescence, we know relatively little about its developmental course. In adults it has been demonstrated that when insomnia reaches clinical significance, it is likely to persist over time.[10] Longitudinal studies in young children and adolescents have provided mixed results regarding the persistence of insomnia over time. A study of individuals aged 12 to 18 y demonstrated that more than 50% of adolescents who reported insomnia symptoms at baseline continued to exhibit insomnia at 4-y follow-up.[11] A similar pattern of symptom persistence was observed over the course of 2 y between the ages of 13 to 15 y.[12] Studies of younger children, however, find little degree of persistence of insomnia symptoms,[13, 14] although one study demonstrated that approximately 60% of children between the ages of 9 and 11 y reported persistent difficulties initiating sleep over 1 y.[5] Studies spanning childhood and adolescence are also mixed. Over the course of 5 y, Strauch and colleagues reported some degree of stability of insomnia symptoms from age 10 to 14 y,[15] although only 2% exhibited symptoms at all time points. Likewise, Gregory and colleagues observed some stability of sleep disturbance in children aged 4 y who were followed up in midadolescence ($r = 0.29$), although sleep disturbances

largely decreased over time.[16] One source of the inconsistencies in persistence rates may be differences in mode of assessment (i.e. parent report versus child report). Regardless of these inconsistencies, it is unequivocal that sleep disturbances in early childhood and adolescence may have detrimental effects on brain development, and long-term physical and mental health, given the role of sleep in synaptic homeostasis,[17] brain plasticity,[18] brain maturation,[19] and immune function.[20] For these reasons, it is important to understand factors contributing to insomnia and its potential persistence over time in early childhood and adolescence.

Accumulating evidence from large-scale twin datasets points to the possibility that, in adults, insomnia is to some extent heritable, with genetic factors accounting for approximately 30-60% of variability.[21] Twin studies in early childhood and adolescence, however, have largely focused on broadly defined sleep disturbances rather than specifically investigating the heritability of insomnia *per se*. For example, Van den Oord and colleagues estimated that genetic influences contributed approximately 60% of variance in sleep disturbances assessed by the Child Behavior Checklist (CBCL) in 3-y-old twins.[22] Gregory and colleagues have repeatedly demonstrated the heritability of broadly defined sleep disturbances in early childhood, ranging from 18-20% in 3- to 4-y-old twins,[23] to ~60-70% at 8-10 y of age.[24–26] Studies of adolescents report heritability estimates more akin to adult estimates.[27–30]

Although these studies identify the presence of genetic factors on sleep disturbances during discrete time points, they tell us little about its developmental course. Longitudinal genetically informative designs allow us to examine the extent to which genetic and environmental factors contribute to the associations in a phenotype over time, as well as examining the extent of stability (overlap) and change in the contribution of such influences. Using such methodology, Gregory and colleagues reported that the association between sleep disturbances at 8 and 10 y of age share some genetic overlap (46% shared genetic effects).[26] Although this suggests some degree of stability in the genetic

influences on sleep disturbances in this age group, it also suggests that new genetic influences come into play at 10 y.

Longitudinal twin studies mapping the developmental course of insomnia from early childhood through adolescence are lacking. Because of this, the question of whether genetic and environmental factors contributing to insomnia in early childhood and adolescence remain stable over time, or whether new etiological factors come into play during this period, remains unknown. It is possible that specific genes contribute to the initial onset of insomnia. However, it is also possible that different genes are partially responsible for its maintenance, given the many physiological and social changes that occur from the transition from early childhood to adolescence through puberty, including changes in the organization of the circadian system, as well as sleep timing, quality, and architecture.[1] Moreover, pubertal development has been associated with increases in sleep disturbances,[31] making it likely that genetic factors controlling puberty contribute to sleep disturbances occurring during this developmental age. Examining the extent of stability and change in the genetic and environmental influences on insomnia over time will allow us to further progress toward identifying specific genetic mechanisms underlying insomnia. In addition, such examination will enable us to identify specific environmental factors contributing to insomnia, given that they may be time specific.

With these considerations in mind, the objectives of the current study are to determine the prevalence and heritability of insomnia symptoms, including difficulties initiating sleep, maintaining sleep and early morning awakenings, across four time points spanning the period of middle/late childhood to adolescence in a longitudinal sequential sample of twins aged 8-18 y. Further, this study will examine the longitudinal associations in insomnia over time, and assess the extent to which genetic and environmental factors on insomnia remain stable, or whether new factors come into play, across this developmental time period.

Methods

Participants

The data for this study are derived from the Virginia Twin Study of Adolescent Behavioral Development (VTSABD), a longitudinal sequential cohort of 8- to 17-y-old Caucasian twins born between 1974-1983 focused on developmental trajectories of adolescent psychopathology and associated risk factors,[32, 33] as well as the Young Adult Follow-Up (YAFU) study,[34] of the same twins when they were 18 y of age. Twin pairs were identified through the state school system and participating private schools in the state of Virginia in 1989-1990 and were then contacted by mail. Interested families were scheduled for detailed assessments of behavioral development and psychopathology, and were invited to participate in up to two comprehensive interview-based follow-up assessments. At wave 1, 1,412 twin families participated (2,822 individual twins aged 8-18 y). At wave 2, which took place on average 1.52 y following wave 1, 1,047 families participated whose children continued to meet age and residence requirements for the study (80% of those targeted). At wave 3, which took place on average 3.3 years following wave 2, 628 families participated (81% of those targeted). All twins who participated at wave 1 were recontacted as young adults (when aged 18 y or older) to participate in a telephone interview as part of the YAFU study (termed wave 4 in the current analyses). Wave 4 took place over a variable number of years from the study's conception as participants were contacted when they reached 18 y of age. At wave 4, 1,185 twin families participated (84% of those targeted). Twenty-four percent of those who participated in the YAFU participated in only the first wave of the VTSABD, 32% participated in two waves, 31% in three waves, and 13% in all four waves.[35] Participating families were representative of the Virginia population in terms of socioeconomic status.[36] More details of sample ascertainment, participation rates, ages of assessment, and socioeconomic bias for the four waves of the study have been reported elsewhere.[32, 35–37] Because this is a sequential longitudinal cohort that contains individuals spanning the ages of 8 to 18 y at all waves, results are interpreted in terms of the

progression across time, rather than differences between discrete age groups. Every family provided signed consent forms, which were completed by parents when twins were younger than 14 y, and by the twins themselves when aged 14 y or older. Ethical approval was granted by the Institutional Review Board at Virginia Commonwealth University, consistent with US federal guidelines.

Measures

Child and Adolescent Psychiatric Assessment: Insomnia symptoms were assessed by the Child and Adolescent Psychiatric Assessment (CAPA), a semistructured interview designed to assess a number of behavioral and psychological symptoms based on the Diagnostic and Statistical Manual of Mental Disorders (DSM)-III-R,[38] as this was the current diagnostic manual in use at the time of data collection. The modules for sleep problems by child/adolescent report were used for the current analyses. The DSM-III-R criteria for insomnia vary to some extent to the current criteria for insomnia disorder set forth in DSM-V,[9] and consist of (1) difficulty initiating or maintaining sleep, or nonrestorative sleep; (2) sleep difficulty that occurs three or more times per week for at least 1 mo, and (3) clinically significant distress or impairment. The sleep module of the CAPA interview taps into these criteria, although it is more aligned to DSM-V in terms of duration (i.e., it focuses on a period of 3 mo), and 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. In each area, the presence of symptoms over the past 3 mo was ascertained, along with the frequency of occurrence, duration, and earliest age of onset (if symptoms were present). For all questions, a rating of 0 was used if it was determined that a disorder was not present. A rating of 2 indicated that the disorder was present at least at the minimum level of severity (if the insomnia covers a period between 1 and 2 h), and a rating of 3 that the disorder was present at a higher level

of severity (if the insomnia duration was greater than or equal to 2 h per night). 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. For these analyses, ratings of 2 and 3 were combined to create a dichotomous (yes/no) insomnia rating, henceforth referred to as 'clinically significant insomnia'. For descriptive purposes, additional ratings of the timing of insomnia during the night (difficulty initiating sleep [initial insomnia], difficulty maintaining sleep [middle insomnia], or early morning awakening [late insomnia]), and the presence of any insomnia symptom were examined in the current analyses. These ratings were repeated within the same sample at four time points (waves) from age 8-18 y (only participants aged 18 y or younger were retained in the study at each wave).

Zygosity: Zygosity was inferred using an algorithm that incorporates data from parental responses to a questionnaire and ratings of photographs, and validated in a subset of 231 twin pairs for whom zygosity was confirmed by blood group typing or DNA polymorphisms. Additional details of zygosity determination in this sample have been published previously.[30, 32]

Data Analyses: Descriptive statistics and tetrachoric correlations between waves were computed. Significant differences in the proportion of dichotomous insomnia symptom variables across waves were tested using χ^2 tests. Similarly, significant differences between males and females on dichotomous insomnia symptom variables were tested using χ^2 tests. Differences in age between cases of insomnia symptoms versus no symptoms at each wave were computed using *t*-tests. Twin model fitting was performed in Mx (computer software designed to analyse genetically informative designs) using structural equation modeling and the method of maximum likelihood estimation,[39] on 'clinically significant insomnia'. Twin studies allow us to estimate the relative contribution of genetic and environmental influences upon traits by comparing the similarity between monozygotic (MZ) twins, who share almost 100% of their genetic material, and dizygotic (DZ) twins, who share on average 50% of their segregating genes. Using this information it is possible to parse the variance in

a phenotype into additive genetic influences (A), dominant (nonadditive/ interactive) genetic influences (D), shared/common environmental influences (C) (which act so as to make family members more similar), and nonshared environmental influences (E) (unique environmental influences that contribute to dissimilarity between family members).[27] It is not possible to examine D and C simultaneously because they predict different MZ:DZ correlation ratios, which are confounded if examined together.[40] Accordingly, it is typical to examine separate ACE and ADE models if data suggest that nonadditive genetic effects may be likely. Nonadditive genetic effects are implied if MZ twin correlations are greater than double DZ twin correlations.

Because of the categorical nature of the variables, liability threshold models were used, which assume an underlying normal distribution to the categories, with thresholds that discriminate the classes (0, 1), estimated from the relative cell proportions of the data. Initially, univariate models were run to investigate the relative contribution of genetic and environmental influences on 'clinically significant insomnia' at each wave. The fit statistic provided by Mx for raw data modeling is −2LL (minus twice the log likelihood of the observations). Saturated models, which provide a perfect fit to the data, were first approximated to the data, and the resulting -2LL was then subtracted from the -2LL of the genetic models. The difference between the -2LL for the saturated and genetic models is χ^2 distributed with equal *df* and so provides a relative fit index. A nonsignificant difference in fit between the genetic and saturated models indicates that the genetic model does not fit the data significantly worse than the saturated model, thus providing a good description of the data. Akaike's Information Criterion (AIC) also provides information regarding fit (calculated as $\Delta\chi 2 - 2 \times \Delta df$), which accounts for the number of parameters being estimated and the goodness-of-fit. A good fit is indicated by lower, negative values of AIC.[41] Both ACE and ADE models were tested as the pattern of twin correlations suggested possible nonadditive genetic effects, followed by more restricted models where one of the parameters was removed (i.e. the AE, DE, and CE models were run), and compared to the fuller models to determine their significance. For the best-fitting models

(those that were the most parsimonious, that did not significantly deviate from the fit of the saturated model), likelihood-based 95% confidence intervals (CIs) on the parameter estimates were obtained in order to determine their precision.

Following the univariate analyses, multivariate Cholesky genetic models[40] were used to model 'clinically significant insomnia' at all four waves simultaneously. This model allows us to test the etiological specificity across the four waves. This model decomposes the variances and covariances between the phenotypes into latent common (shared between the phenotypes) and unique (specific to each phenotype) genetic and environmental components (see Figure 1 for an example of a DE model – A was dropped for simplicity of presentation). This model provides us with four pieces of information. First, it indicates the genetic and environmental influences common to 'clinically significant insomnia' at all four waves (D1, E1). Second, it indicates whether a second set of genetic and environmental influences come into play that are common to the second, third, and fourth waves (D2, E2). Third, it indicates whether a third set of influences are common to the third and fourth waves (D3, E3). Finally it indicates whether a unique set of influences contribute to the fourth wave (D4, E4). In all cases, the model allows the estimation of unique genetic factors, indicated by the significance of the diagonal elements (e.g. d11, d22, d33, d44). If there are common genetic factors influencing more than one wave, the off-diagonal parameter estimates would be significantly distinguishable from zero (e.g., d21, d31, d41, d32, etc.). The same logic applies to the environmental factors. Each of the parameter estimates can be squared to estimate the proportion of the variance at each wave accounted for by the genetic and environmental factors. As with the univariate analyses, the fit of the full model was compared to more restricted models that sequentially dropped individual parameter estimates. Both ACE and ADE models were tested. The most parsimonious model that did not fit significantly worse than the saturated model was selected for interpretation. Sex differences in the etiological influences in both univariate and multivariate

models were not computed given the small cell sizes by sex/zygosity group for later waves (see Table 2). The analyses are performed on raw data.

Results

Descriptives

A total of 1,412 complete twin pairs participated in the study at wave 1. Overall, there were 46% males and 54% females at wave 1. Zygosity was available from 1,411 twin pairs. The sex/zygosity groups for the twin pairs were as follows: 322 MZ male (MZM), 417 MZ females (MZF), 180 DZ males (DZM), 194 DZ females (DZF), and 298 DZ opposite sex pairs (DZO). The modal ages at the different waves were as follows: 8.3 y (range, 8-18 y) at wave 1; 10.7 y (range, 9-18 y) at wave 2; 14.2 y (range, 12-18 y) at wave 3; and 15.3 y (range, 14-18 years) at wave 4. Age spread at each wave was largely homogenously distributed (e.g., although age 8.3 y was most common at wave 1, there was a relatively similar distribution of other ages within this wave). Complete data on all sleep variables were available from 2,789 individuals at wave 1 (98.8% of those targeted); 1,981 (94.6% of those targeted) at wave 2; 1,142 (90.9% of those targeted) at wave 3; and 357 (15.1% of those targeted) at wave 4. In total, 325 individuals provided complete sleep data at all four waves. There did not appear to be significant differences in insomnia ratings at wave 1 among those who did and did not participate at all four waves ($\chi^2[1] = 0.15$, $P = 0.70$), indicating no evidence of selective attrition. Retrospective reports from parents indicated that MZ twins were significantly more likely than DZ twins to share a bedroom with their co-twin in young childhood (99% of MZ twins shared a bedroom always, usually or sometimes; compared to 94% of DZs: $\chi^2[3] = 143.66$, $P = 0.00$) as well as at the time of initial assessment (64% of MZ twins shared a bedroom always, usually, or sometimes; compared to 35% of DZs: $\chi^2[3] = 117.61$, $P = 0.00$). Whether or not twins shared a bedroom did not reliably contribute to twin similarity on our measure of clinically significant insomnia (analyses available upon request from the first author).

Frequency of insomnia symptoms for the total sample and categorized by sex is shown in Table 1. The proportion of individuals meeting criteria for a rating of 'clinically significant insomnia' based on child/adolescent ratings significantly decreased across all waves, from 19.5% at wave 1 to 11.5% at wave 4 (overall: $\chi^2[3] = 14.58$, $P = 0.00$; all $\chi^{2's}$ individually comparing waves 1-3 versus wave 4: $P < 0.05$). Significance of the decrease in the proportion of individual insomnia symptoms across waves is shown in Table 1.

At wave 2, there were significant sex differences in ratings of 'clinically significant insomnia' ($\chi^2[1] = 4.43$, $P = 0.04$), middle insomnia ($\chi^2[1] = 5.54$, $P = 0.02$), and the presence of any insomnia symptom ($\chi^2[1] = 6.06$, $P = 0.02$). At wave 3, there were significant sex differences in ratings of 'clinically significant insomnia' ($\chi^2[1] = 5.15$, $P = 0.02$), middle insomnia ($\chi^2[1] = 11.71$, $P = 0.001$), and the presence of any insomnia symptom ($\chi^2[1] = 9.61$, $P = 0.00$). At wave 4, there were significant sex differences in ratings of 'clinically significant insomnia' ($\chi^2[1] = 4.07$, $P = 0.05$), and initial insomnia ($\chi^2[1] = 6.44$, $P = 0.02$). In all cases, insomnia symptoms were more prevalent in females than males. There were no other significant sex differences in insomnia variables at all waves.

At wave 1 there were significant age differences in the presence of middle insomnia ($t[2792] = 3.82$, $P = 0.00$). At wave 2 there were significant age differences in the presence of middle insomnia ($t[1984] = 2.53$, $P = 0.01$) and any insomnia symptom ($t[1984] = 2.38$, $P = 0.02$). At wave 3 there were significant age differences in the presence of middle insomnia ($t[1135] = 2.46$, $P = 0.01$). In all cases, younger children were more likely than older children to experience insomnia symptoms at the same wave.

Insert Table 1 here

Frequency of cases (individuals categorized as 'yes' for ratings of 'clinically significant insomnia' present) split by sex and zygosity is shown in Table 2. Because of the small number of cases in each

sex/zygosity group at each wave, it was not possible to perform genetic model fitting analyses by sex. As such, genetic model fitting analyses are performed for the total sample only.

Insert Table 2 here

Twin Correlations

Twin correlations for ratings of 'clinically significant insomnia' at different waves are shown in Table 3a. MZ twin correlations were greater than corresponding DZ twin correlations for 'clinically significant insomnia' at all waves, suggesting the influence of genetics on this phenotype. Because the MZ twin correlations were greater than double the DZ twin correlations, nonadditive genetic effects were implied and so ADE model fitting analyses were performed in addition to ACE models.

Phenotypic Correlations: Tetrachoric correlations for ratings of 'clinically significant insomnia' across waves are shown in Table 3b. There were significant associations between insomnia symptoms at adjacent waves (wave 1 with 2; wave 2 with 3; and wave 3 with 4) but not at nonadjacent waves (e.g., wave 1 with wave 3 or 4).

Cross-Twin Cross-Trait Correlations: Cross-twin cross-trait correlations (shown in Table 3c) were only significant for MZ twins on the association between ratings of 'clinically significant insomnia' at waves 1 and 2. Despite the nonsignificance of the other associations, in all cases MZ twin correlations were greater than DZ correlations, suggesting possible genetic effects on the cross-wave associations.

Insert Table 3 here

Univariate Genetic Model Fitting Analyses

Model fitting analyses are shown in Table 4. At waves 1, 2, and 4, the best-fitting models were ones in which additive genetic influences were dropped, and shared environmental influences were

replaced with nonadditive genetic effects (DE models). In these models, nonadditive genetic effects contributed 33%$_{[95\%\ CI\ .20\text{-}.46]}$, 38%$_{[.22\text{-}.78]}$ and 24%$_{[.00\text{-}.66]}$ of the total variance at waves 1, 2 and 4, respectively. At wave 3, the best-fitting model was one in which shared environmental influences were dropped (AE model). In this model, additive genetic influences contributed 14%$_{[.00\text{-}.35]}$ of the variance in ratings of 'clinically significant insomnia'. At all waves, the remaining source of variance was the nonshared environment (accounting for 67%$_{[.54\text{-}.80]}$, 62%$_{[.48\text{-}.78]}$, 86%$_{[.65\text{-}1.00]}$, and 76%$_{[.34\text{-}1.00]}$ of variance explained for waves 1, 2, 3, and 4, respectively).

Insert Table 4 here

Multivariate Cholesky Model Fitting Analyses

For the fullest multivariate Cholesky models, an ADE model provided a better fit to the data than an ACE model (as indicated by lower AIC). In addition, a DE model including all four Cholesky factors provided a better fit to the data than the saturated ADE model ($\Delta\ \chi^2(10) = 2.04$, P = 0.99, ΔAIC = -17.96). Subsequent models were then run to test the significance of each of the Cholesky parameters. Dropping the unique genetic factor at wave 4 did not result in a significant loss of model fit ($\Delta\chi^2(1) = 0.00$, P = 1.00, ΔAIC = -2.00). Additionally dropping the genetic factors at wave 3 (both unique and shared with wave 4) did not result in a significant loss of model fit ($\Delta\chi^2(3) = 0.56$, P = 0.91, ΔAIC = -5.44). Further dropping the genetic factors at wave 2 (both unique and shared with subsequent waves) did not significantly reduce model fit ($\Delta\ \chi^2(6) = 8.98$, P = 0.17, ΔAIC = -3.02), but examination of the ΔAIC value indicated that the best-fitting model was the previous model, which allowed genetic factors from waves 1 and 2 to map onto subsequent waves. Removal of any of the nonshared environmental factors significantly reduced model fit in all cases (all $P < 0.05$). Standardized path coefficients for each of the significant paths from the best-fitting model are shown in Figure 1.

Insert Figure 1 here

Discussion

This set of analyses sought to determine the extent to which genetic and environmental influences on insomnia are stable across childhood and adolescence. Our analyses focus on data from a sequential sample of twins followed up across time, with time points representative of children and adolescents aged 8, 10, 14, and 15 y across the four waves. There are four noteworthy findings from this research. First, prevalence of 'clinically significant insomnia' was relatively high compared to expected figures for adulthood in middle/late childhood, but significantly decreased to levels in line with adults by adolescence. Similarly, individual insomnia symptoms (initial insomnia, middle insomnia, and early morning awakening) significantly decreased across waves. This decrease in insomnia symptoms by adolescence is consistent with a study demonstrating a decrease in broadly defined sleeping difficulties in children age 4 y though adolescence.[16] Another study documented a decrease in insomnia symptoms (specifically difficulties initiating sleep) from age 10 to 13 y in a longitudinal study of more than 1,000 children.[42] The current study extends this previous work by demonstrating the continued decrease in insomnia symptoms throughout adolescence. One possibility for this greater proportion of insomnia symptoms in younger children in comparison with adolescents could be that insomnia symptoms in younger children may be largely behavioral in nature (i.e., behavioral insomnia of childhood), and stem from poor sleep hygiene and inappropriate associations of the bedroom environment with wakefulness (i.e., children often use their bedrooms for play), which may cease by adolescence. Alternatively, it is possible that as parents often set bedtimes in younger children, timing of sleep does not coincide with the child's feelings of tiredness or their optimal time for sleep onset as governed by that child's circadian rhythm. As a consequence, the child may lie awake, unable to sleep for periods of time. During adolescence, parents may be less stringent about bedtimes, allowing their children to go to bed at times more in line with their circadian rhythm, and as such adolescents may experience fewer sleep difficulties if they attempt

sleep at times in line with circadian rhythmicity. The decrease in sleep disturbances may also reflect changes in maturation and sleep architecture, which occur during this time.[43]

Second, there were associations between 'clinically significant insomnia' between adjacent waves, suggesting that within childhood and adolescence, insomnia persists, but that continuity of symptoms across time within childhood and adolescence is minimal. This is also reflected by the smaller phenotypic correlation between waves 2 and 3 (the mode ages of which span these developmental time periods), in comparison to the phenotypic correlations between waves 1 and 2; and 3 and 4. This, again, reflects the possible changes in sleep that occur during the transition from childhood to adolescence.

Third, genetic factors contributed to ratings of 'clinically significant insomnia' at all waves, from 33%, 38%, 14%, and 24% in waves 1, 2, 3, and 4, respectively. The genetic estimates are in line with estimates we would expect in adults[21] in our sample at wave 1 and wave 2; yet are somewhat lower in our sample at later waves. This highlights the greater importance of the nonshared environment during adolescence in comparison with that in younger children, in whom a host of environmental and social changes are likely to take place, which may consequently interfere with sleep. Interestingly, our results highlight the contribution of nonadditive genetic effects at waves 1, 2, and 4, providing us with insight into the possible genetic mechanisms at play. However, the greater within-pair correlations in MZ twins compared with those of DZ twins could suggest an alternative explanation. Such a pattern of results could suggest the presence of sibling interaction, where one twin's behavior affects that of the co-twin, rather than nonadditive genetic effects.[44, 45] This seems plausible in the context of sleep, as the sleep behavior of one twin may similarly influence that of the co-twin if twins share a bedroom. Indeed, in the current sample, MZ twins were significantly more likely than DZ twins to share a bedroom with their co-twin in young childhood as well as at the time of assessment. That said, evidence of sibling interaction also requires greater variance in DZ twins as in comparison with MZ twins for the phenotypes of interest (i.e., insomnia). In the current sample,

variances for MZ twins were comparable to those for DZ twins at each wave (unreported, but available upon request from the first author), making the pattern of results more consistent with an interpretation based on nonadditive genetic effects rather than sibling interaction. Although there is statistical support for a nonadditive component, our sample size has limited power to resolve the reduction in DZ correlations because of nonadditive effects from that caused by the effects of sibling interaction.

Fourth, evaluation of the multivariate model indicated that genetic factors influencing insomnia at wave 1 contribute to the maintenance of insomnia through adolescence. This is consistent with a study demonstrating that the stability of sleep difficulties from age 8 to 10 y was to the result of shared genetic effects.[26] Additionally, new genetic influences come into play at wave 2, which further contribute to the maintenance of insomnia through adolescence. In contrast, no new genetic influences come into play at waves 3 and 4. It is likely that genes controlling the sleep-wake system are implicated in insomnia (such as those controlling the regulation of the sleep-wake switch, including the activity of acetylcholine, glutamate, gamma-aminobutyric acid (GABA), and the monoamines). Indeed, molecular genetic studies in adults have demonstrated associations between several of such genes and insomnia or poor sleep quality, including the serotonin transporter gene (5HTTLPR),[46–49] monoamine oxidase-A,[50] and GABA,[51] among others.[52] Other candidates may be genes implicated in the control of the circadian clock. Indeed, a polymorphism of the CLOCK 3111T/C polymorphism has been associated with insomnia in a sample of patients with major depression,[53] although results are mixed.[46, 54] However, most molecular genetic studies focus on variation in normal sleep characteristics, or are speculative studies on sleep phenotypes in *Drosophila*, rather than focusing on clinically significant insomnia. Although this handful of studies provide clues as to the likely genes involved, further studies specifically focusing on insomnia populations are required. Furthermore, molecular genetic studies in childhood and adolescence will allow us to determine

whether the same genetic pathways are involved in symptoms during these developmental periods as in adulthood.

The stability of genetic effects from wave 2 through wave 4 implies that the same set of genetic factors may contribute to insomnia over this time period. Studies spanning adolescence and adulthood are now required to chart the stability of genetic effects over longer time frames. This will enable us to determine whether insomnia in early childhood, adolescence, and adulthood stem from the same genetic pathways, and whether they are, genetically speaking, similar phenotypes.

In addition to understanding the genetic mechanisms involved, the current study allows us to make inferences about the role of the environment. In univariate models, nonshared environmental influences accounted for the majority of variance in insomnia. In the multivariate model, only time-specific nonshared environmental influences were significant (with the exception of a small amount of overlapping nonshared environmental factors between waves 3 and 4), suggesting little overlap in the environmental influences contributing to insomnia. This finding suggests that environmental factors have only a transient effect on sleep, rather than contributing to sleep over time. This is in line with Spielman's '3P' model of insomnia, which proposes that 'precipitating' factors (which may include environmental factors such as stressful life events) act as a trigger for the onset of insomnia in individuals with a predisposition to insomnia (such as genetic vulnerability); yet the maintenance of insomnia is influenced by distinct 'perpetuating' factors after the precipitating factor has been surpassed.[55]

Despite these findings, this study has several limitations. First, although a strength of this study, these results reflect a sequential longitudinal cohort that contains individuals spanning the ages of 8 to 18 y at all waves; therefore, the results must be interpreted in terms of changes across time, rather than specifically focusing on discrete age groups. However, in each of the waves, particular ages were more common, and the sample mostly represents children and adolescents aged 8, 10,

14, and 15 y across the four waves. Although it would be theoretically possible to perform analyses based on discrete age groups irrespective of wave, the small sample size in the latter age groups would provide limited power to meaningfully report on age-related changes in the etiological influences. Second, the data are subjective in nature rather than measures of objective sleep difficulties. That said, insomnia is considered a subjective complaint, as clinical diagnosis is based purely on subjective measures,[9] and it is often the case that individuals with insomnia exhibit no objectively recorded sleep deficit despite the subjective dissatisfaction with sleep quality or quantity.[56] Accordingly, measuring insomnia by subjective methods appears most appropriate. Third, and on a related note, it is possible that our insomnia measures are confounded by traits that are typically associated with insomnia, such as depression and neuroticism.[57, 58] This would mean that our estimates of heritability, rather than purely reflecting insomnia, may to some extent reflect an underlying mood or personality disorder. In order to address these potential confounds, we additionally examined point biserial correlations between each of our insomnia variables and depression (measured using the Mood and Feelings Questionnaire [MFQ][59]) and neuroticism (measured using the Emotionality, Activity, Sociability, and Impulsivity Temperament Survey [EASI-III][60]) at waves 1-3 (as data from the MFQ and EASI were only available at theses waves; analyses available upon request from the first author). Although all of these correlations (with the exception of two) were significant, all were small (ranging between r = 0.05-0.26), suggesting minimal overlap between our insomnia variables, depression, and neuroticism. Accordingly, we can be confident that our estimates of heritability reflect sources of variance attributable to insomnia, to some extent independent of these potential confounds (we acknowledge that the best method to control for these potential confounds would be to regress out the effects of depression/neuroticism from our insomnia variables and examine the resulting change in A, C, and E; however, because these data were available only from waves 1-3 of the study, we are unable to treat the data equally across the four waves). Fourth, the current analyses are based on self-report responses from the CAPA

interview rather than parent-reported symptoms. Although the accuracy of self-report in young children could be questioned, one study demonstrated that children as young as 8 y are able to report on their own symptoms.[61] Other studies in young children largely focus on parent-reported symptoms, and so comparison with these studies should take this point into consideration. However, studies specifically comparing parent- and child-reported symptoms typically find that parents underestimate sleep disturbances in their children.[62] Indeed, a previous paper reporting on insomnia symptoms from wave 1 of the current sample also demonstrate this pattern.[30] Similarly, a study comparing adolescent- and parent-reported sleep patterns with actigraphy over the course of 1 w demonstrated little concordance between raters.[63] Adolescents were more accurate at reporting on their sleep than were their parents. The general trend for parents to become progressively more inaccurate at reporting on their offsprings' sleep is likely because of their lack of awareness of the childrens' nighttime behavior. The current analyses may be the best representation of the sleep of these individuals. Finally, the small sample size in later waves meant that it was not possible to examine sex differences in the etiology of insomnia over time. Given that insomnia is typically more prevalent in females[64] (a pattern that was also mirrored in the current data), it is possible that different mechanisms are at play between the sexes. Further investigation of sex specific genetic effects is warranted.

In conclusion, these findings contribute to our knowledge of the prevalence of insomnia symptoms and factors influencing insomnia in middle/late childhood through to adolescence. Insomnia symptoms were more prevalent in younger children, decreasing to estimates akin to those typically observed in adults, by adolescence. 'Clinically significant insomnia' (as rated by clinicians) was moderately heritable at all waves, and is in line with heritability observed in adulthood in younger children, but somewhat lower during adolescence. At all waves the remaining source of variance was the nonshared environment, with no influence of family-wide (shared environmental) factors. Genetic influences on 'clinically significant insomnia' showed a substantial degree of stability from

wave 1 through wave 4, with new genetic factors coming into play at wave 2. Molecular genetic studies of childhood and adolescent insomnia are now required in order to determine the mechanism through which insomnia manifests and is maintained through these developmental periods. Such knowledge will provide us with clues as to biological mechanisms involved, and could facilitate the development of pharmaceutical treatments to target these pathways.

Tables:

Table 1. Prevalence of child/adolescent reported insomnia symptoms (n cases in parentheses)

	Wave 1	Wave 2	Wave 3	Wave 4
'Clinically significant insomnia'				
Total	19.5% (546)	17.9% (356)	17.4% (199)	11.5% (41)[a]
Males	18.4% (237)	16%* (150)	14.8%* (82)	7.8%* (13)
Females	20.5% (309)	19.7% (206)	19.9% (117)	14.7 (28)
Initial insomnia				
Total	14.6% (408)	13.6% (269)	14.1% (161)	9.0% (32)[a]
Males	13.9% (179)	12.2% (114)	12.1% (67)	4.8%* (8)
Females	15.2% (229)	14.8% (155)	16% (94)	12.6% (24)
Middle insomnia				
Total	19.6% (548)	20.6% (409)	15.4% (175)	9.0% (32)[b]
Males	19.5% (251)	18.3%* (172)	11.6%* (64)	9.8% (16)
Females	19.7% (297)	22.6% (237)	18.9% (111)	8.3% (16)
Early morning awakenings				
Total	4.9% (136)	4.4% (88)	3.2% (36)	2.5% (9)[c]
Males	5.3% (68)	3.9% (37)	2.7% (15)	3.0% (5)
Females	4.5% (68)	4.9% (51)	3.6% (21)	2.1% (4)
Any insomnia symptom				
Total	30.9% (862)	31.2% (619)	26.6% (303)	16.6% (59)[d]
Males	30.6% (394)	28.2%* (267)	22.5%* (124)	14% (23)
Females	31.2% (468)	33.6% (352)	30.6% (179)	18.8% (36)

For these analyses, ratings of 2 and 3 were combined and compared to those rated 0 to create dichotomous (yes/no) insomnia ratings. Percentages reflect responses of 'yes' to insomnia symptom questions.

*Significant sex differences in proportion of cases (χ^2), $P < 0.05$.

[a] Significant differences in prevalence between all waves versus wave 4, individually, $P < 0.05$.

[b] Significant difference in prevalence between wave 1 versus wave 3, wave 2 versus wave 3, wave 2 versus wave 4, and wave 3 versus wave 4; individually, $P < 0.05$.

[c] Significant difference in prevalence between wave 1 versus wave 3, wave 1 versus wave 4; individually, $P < 0.05$. [d] Significant difference in prevalence between wave 1 versus wave 3, wave 1 versus wave 4, wave 2 versus wave 3, wave 2 versus wave 4, and wave 3 versus wave 4; individually, $P < 0.05$.

Table 2. Frequencies of self-reported 'clinically significant insomnia' by zygosity (total n of those with and without insomnia in parentheses)

	Wave 1	Wave 2	Wave 3	Wave 4
MZM	118 (635) – 18.6%	78 (483) – 16.1%	40 (276) – 14.4%	8 (93) – 8.6%
DZM	63 (356) – 17.7%	36 (251) – 14.3%	26 (165) – 15.8%	4 (46) – 8.7%
MZF	156 (828) – 18.8%	122 (588) – 20.7%	64 (340) – 18.8%	14 (121) – 11.6%
DZF	87 (383) – 22.7%	39 (250) – 15.6%	30 (132) – 22.7%	10 (43) – 23.3%
DZO	121 (587) – 20.6%	80 (409) – 19.6%	39 (229) – 17%	5 (54) – 9.3%
MZ	274 (1463) – 18.7%	200 (1071) -18.7%	104 (616) – 18.9%	22 (214) – 10.3%
DZ	271 (1326) – 20.4%	155 (910) – 17%	95 (526) – 18.1%	19 (143) – 13.3%
Total	545 (2789) – 19.5%	355 (1981) – 17.9%	199 (1142) – 17.4%	41 (357) – 11.5%

Values represent percentage of the total sample reporting clinically significant insomnia.

DZ = all dizygotic twins; DZF = dizygotic female twins; DZM = dizygotic male twins; DZO = dizygotic opposite sex twins; MZ = all monozygotic twins; MZF = monozygotic female twins; MZM = monozygotic male twins.

Table 3a. Cross twin correlations (and 95% confidence intervals) for ratings of 'clinically significant insomnia'

	Wave 1	Wave 2	Wave 3	Wave 4
MZ	0.33 (0.19-0.46)	0.39 (0.23-0.53)	0.14 (-0.11-0.37)	0.26 (-0.27-0.68)
DZ	0.10 (-0.05-0.25)	0.05 (-0.16-0.25)	0.06 (-0.20-0.31)	-0.05 (-0.56-0.50)

Table 3b. Phenotypic correlations (and 95% confidence intervals) for ratings of 'clinically significant insomnia'

	Wave 1	Wave 2	Wave 3	Wave 4
Wave 1	1			
Wave 2	0.31 (0.23-0.39)	1		
Wave 3	0.04 (-0.09-0.16)	0.18 (0.06-0.30)	1	
Wave 4	-0.08 (-0.31-0.16)	0.03 (-0.22-0.28)	0.38 (0.14-0.59)	1

Table 3c. Cross-twin cross-trait correlations (and 95% confidence intervals) for ratings of 'clinically significant insomnia' (MZ below diagonal, DZ above diagonal)

	Wave 1	Wave 2	Wave 3	Wave 4
Wave 1	/	-0.09 (-0.23-0.05)	-0.10 (-0.28-0.09)	0.29 (-0.06-0.59)
Wave 2	0.25 (0.14-0.36)	/	0.11 (-0.08-0.29)	0.06 (-0.33-0.44)
Wave 3	0.16 (-0.01-0.32)	0.16 (-0.00-0.32)	/	-0.10 (-0.47-0.30)
Wave 4	0.18 (-0.12-0.45)	-0.14 (-0.47-0.22)	0.23 (-0.10-0.53)	/

DZ = dizygotic; MZ = monozygotic.

Table 4. Fit statistics for univariate genetic model fitting analyses for ratings of 'clinically significant insomnia'

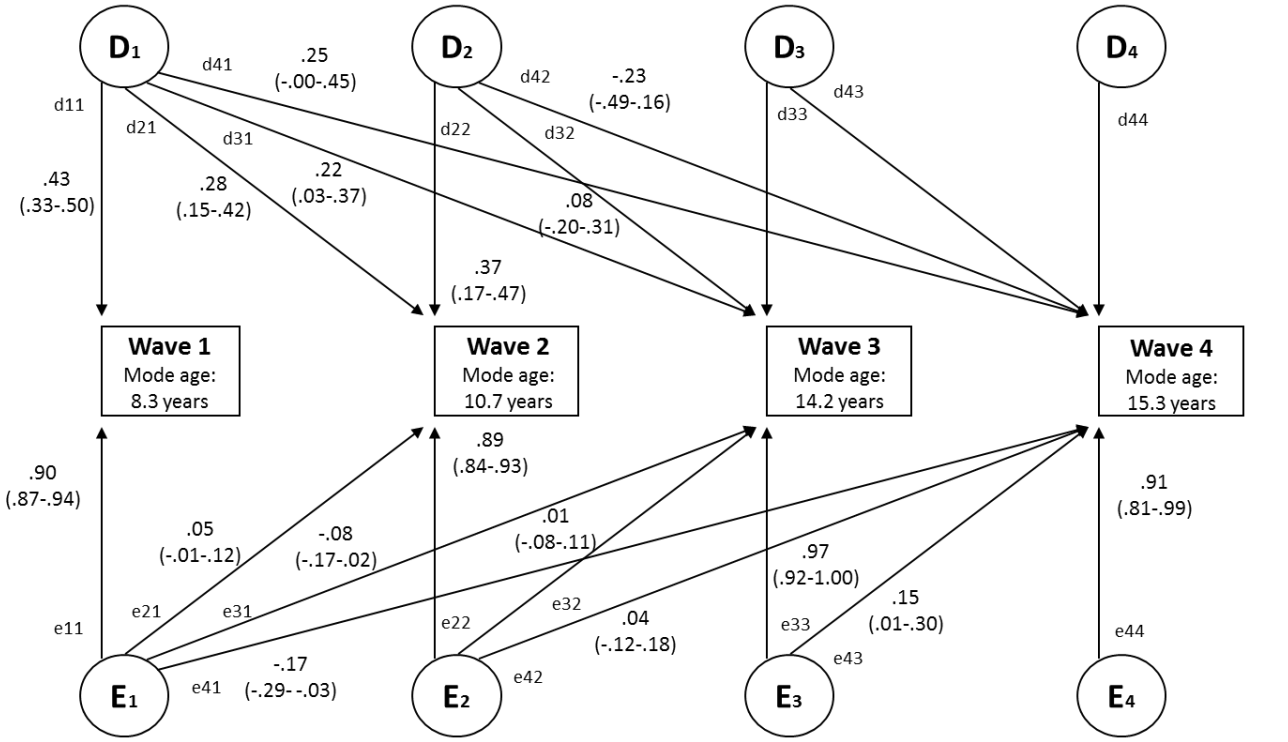
Fit			Fit relative to saturated model			
Model	-2LL	*df*	$\Delta\chi^2$	Δdf	P	AIC
WAVE 1						
1. Saturated	2726.84	2783				
2. ACE	2734.01	2786	7.17	3	0.07	1.17
3. ADE	2733.35	2786	6.51	3	0.09	0.51
4. CE	2738.42	2787	11.58	4	0.02	3.58
5. DE	**2733.38**	**2787**	**6.54**	**4**	**0.16**	**-1.46**
6. AE	2734.01	2787	7.17	4	0.13	-0.83
WAVE 2						
1. Saturated	1838.01	1975				
2. ACE	1842.70	1978	4.69	3	0.20	-1.31
3. ADE	1841.17	1978	3.16	3	0.37	-2.84
4. CE	1847.77	1979	9.76	4	0.04	1.76
5. DE	**1841.17**	**1979**	**3.16**	**4**	**0.53**	**-4.84**
6. AE	1842.70	1979	4.69	4	0.32	-3.31
WAVE 3						
1. Saturated	1051.98	1136				
2. ACE	1055.11	1139	3.13	3	0.37	-2.87
3. ADE	1055.10	1139	3.12	3	0.37	-2.88
4. CE	1055.31	1140	3.33	4	0.50	-4.67
5. DE	1055.98	1140	3.15	4	0.53	-4.85
6. AE	**1055.11**	**1140**	**3.13**	**4**	**0.54**	**-4.87**
WAVE 4						
1. Saturated	249.39	351				

2. ACE	253.92	354	4.53	3	0.21	-1.47
3. ADE	253.76	354	4.37	3	0.22	-1.63
4. CE	254.21	355	4.82	4	0.31	-3.18
5. DE	**253.76**	**355**	**4.37**	**4**	**0.36**	**-3.63**
6. AE	253.92	355	4.53	4	0.34	-3.47

Best-fitting model indicated in bold.

A = additive genetic influence; AIC = Akaike's Information Criterion statistic (calculated as $\chi^2 - 2df$); C = shared environmental influence; D = nonadditive genetic influence; E = nonshared environmental influence; -2LL = -2*(log likelihood); df = degrees of freedom; $\Delta\chi^2$ and Δdf = change in chi-square statistic and corresponding degrees of freedom (computed as the difference in likelihood and df between each model and the saturated model). All estimates were obtained from Mx.

Figure 1. Multivariate Cholesky decomposition with parameter estimates (95% CI) from best-fitting DE model.



Note. Figure is shown for one twin only. D = Non-additive genetic influence; E = Non-shared Environmental Influence. Figure displays unsquared parameter estimates for significant paths. The parameter estimates can be squared to indicate relative proportions of variance (%). The extent to which genetic influences account for the phenotypic correlations between variables can be calculated as follows: (d11*d21)/r(wave 1 and wave 2); (d11*d31)/r(wave 1 and wave 3); (d11*d41)/r(wave 1 and wave 4); (d21*d31) + (d22*d32)/r(wave 2 and wave 3); (d21*d41) + (d22*d42)/r(wave 2 and wave 4); (d31*d41) + (d32*d42) + (d33*d43)/r(wave 3 and wave 4). The same principles apply for calculating the relative proportions of variance accounted for by non-shared environmental influences.

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