A longitudinal twin and sibling study of associations between insomnia and depression symptoms in young adults

Short Title: Associations between insomnia and depression

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**For submission to:** SLEEP.

**Institution at which work was performed:** Goldsmiths, University of London and the Institute of Psychiatry, Psychology & Neuroscience, King’s College London

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**Financial Disclosures for All Authors:** None reported.

**Conflicts of Interests for All Authors:** None reported.

**Authorship responsibilities:** TCE is the founder of the G1219 study. AMG ran waves 4 and 5 of the G1219 study. FR and NB ran the analyses for this study. All authors contributed to the drafting of this manuscript.

**Financial support:** Waves 1-3 funded by the W T Grant Foundation, the University of London Central Research fund and a Medical Research Council Training Fellowship (G81/343) and Career Development Award to Thalia C. Eley. Wave 4 supported by the Economic and Social Research Council (RES-000-22-2206) and the Institute of Social Psychiatry (06/07 – 11) to Alice M. Gregory. Wave 5 supported by funding from Goldsmiths, University of London to Alice M. Gregory.

**Total number of tables:** 4 & 4 supplementary tables

**Total number of figures:** 1

**Statement of significance:** In this twin/ sibling study, we show that insomnia and depression symptoms share common genetic influences. This study is the first to demonstrate substantial genetic contributions to the concurrent and longitudinal associations between insomnia and depression in young adults. Non-shared environmental influences for insomnia and depression symptoms also overlapped, but to a lesser extent. The nonshared environment contributed to both concurrent and longitudinal associations between variables. This knowledge can be usefully employed in studies attempting to identify genetic variants, and specify non-shared environmental influences, involved in insomnia and depression.

Study objectives: To estimate genetic and environmental influences on the associations between insomnia and depression symptoms concurrently and longitudinally.

Design: Longitudinal twin/ sibling study.

Setting: Population based twin/ sibling registry from the U.K.

Patients or Participants: One thousand five hundred and fifty six twins and siblings participated at Time 1 (mean age = 20.3 years, SD = 1.76). Eight hundred and sixty two participated at Time 2 (mean age = 25.2 years, SD = 1.73 years).

Interventions: N/A

Measurements and Results: The Insomnia Symptoms Questionnaire and the Short Mood and Feelings Questionnaire were used to assess symptoms of insomnia and depression respectively. Genetic effects accounted for 33-41% of the variance of the phenotypes. The phenotypic correlations were moderate (r = .34 to r = .52). The genetic correlations between the variables were high (.73 – 1.00). Genetic effects accounted for a substantial proportion of the associations between variables (50-90%). Non-shared environmental effects explained the rest of the variance and covariance of the traits.

Conclusions: While genetic effects play a modest role in insomnia and depression symptoms separately, they appear to play a more central role in concurrent and longitudinal associations between these phenotypes. This should be acknowledged in theories explaining these common associations.

Keywords: Insomnia, Depression, Genetics, Twins, Longitudinal

Longitudinal associations between insomnia and depression symptoms are well established. (for reviews and meta-analyses, see 1;2;3) While there is some suggestion that insomnia symptoms are more likely to predict depression than vice versa, a recent review of the literature concluded that the best evidence to date suggests that, within adulthood, the associations are likely bidirectional. (1)

 What is less-well established is the reason for the association between poor sleep and depression. Explanations are diverse and include the suggestion that insomnia and depression symptoms are due to hyperarousal (4) or heightened emotional reactivity. (5) Neural processes underlying the association include the possibility that poor sleep moderates the association between amygdala response to threat stimuli and depression. (e.g. 6; see also, 7) Sleep disruption may also disturb prefrontal cortex functioning (8) which plays an important role in the emotional and cognitive processing central to depression. (e.g. 9) Other explanations have highlighted the possibility that fragmentation of rapid eye movement (REM) sleep could lead to both the subjective sense of having slept poorly and depression. (10)

 The extent to which genetic predisposition underlies such processes and explains the association between insomnia symptoms and depression has received limited attention. (for a review of twin studies focusing on sleep, see 11) Nonetheless, initial work in this domain has been enlightening and genetically informative studies may further clarify the association between insomnia and depression. (e.g. 4) Twin studies to date typically focus on *concurrent associations* between sleep disturbances and depression symptoms. Genetic effects appear to play a role in explaining these associations in childhood, (12) adolescence, (13) early adulthood, (14) and in adulthood more generally. (15) These studies suggest that sleep disturbances are perhaps part of the same genetic cluster of disorders as depression (which is also considered to have strong genetic links to anxiety, 16).

Fewer twin studies have attempted to establish the direction of effects between sleep disturbances and depression or have tried to understand the longitudinal links between the phenotypes. One used cross-sectional genetic analyses to attempt to establish the direction of causation between poor sleep and depression in twins aged 18-87 years old. (17) The authors concluded that while depression caused poor sleep (and not vice versa) in young females, there was evidence for reciprocal causation between the phenotypes in older females. The direction of causation was less clear for males, who were underrepresented in the sample. A *longitudinal study* by our own team found that within childhood, generally defined sleep problems at 8 years of age predicted depression symptoms at 10 years. (18) Overall it was concluded that genetic influences may be the most important source of variance that is carried over across time points although the sample was too small to draw definitive conclusions.

 Understanding the mechanisms underlying longitudinal links between phenotypes may help to identify those at risk for later problems, with the ultimate aim of developing preventative programmes or improving treatment. Given the importance of the research question and the limited research addressing this topic to date, the aim of this study was to assess a sample of young adult twins and siblings (19) over a 5-year period in order to examine both concurrently and longitudinally:

1. associations between insomnia and depression symptoms;
2. genetic and environmental influences on the associations between these phenotypes.

**Methods**

*Participants:*

The present analyses focus on waves 4 and 5 of the G1219 twin/ sibling study. (19) At wave 4 (for ease of presentation referred to here-on-in as time 1) a total of 1556 individuals participated in the G1219 study. At wave 5 (referred to as time 2) a total of 862 individuals participated. At these waves of the study written informed consent was obtained from the participants themselves. The mean age at time 1 was 20.33 years (SD = 1.76, range = 18-27 years) and 62% of the sample were female. The mean age at time 2 was 25.18 years (SD = 1.73, range = 22-32 years) and 66% of the sample were female. The majority of participants were close in age within each time-point (at time 1, 90% of the participants were aged 18-22 years, and at time 2, 90% of the participants were aged 22-27 years), but the inclusion of siblings inevitably created some age-spread.

Zygosity was established through a questionnaire measure completed by mothers at waves 2 and 3 assessing physical similarities between twins. (20) **Table 1** shows the number of monozygotic (MZ), dizygotic (DZ) and sibling individuals as well as the number of full pairs for each variable.

*Ethical Approval:*

Ethical approval for the collection of data at different waves comes from the Research Ethics Committees of the Institute of Psychiatry, South London and Maudsley NHS trust, and/ or Goldsmiths, University of London Ethics Committee. The protocol for data collection conformed to international ethical standards. (21)

*Predictors of Attrition:*

Logistic regression, focussing on variables which have previously been associated with attrition in this sample, demonstrated that responders at time 2 were significantly more likely than non-responders to be female (odds ratio = .60, *p* < .001) and have more highly educated mothers (odds ratio = 1.14, *p* < .001, where mother’s education was rated from the lowest level 0 to 8). There were no significant differences between respondents and non-respondents in terms of housing, insomnia symptoms, depression symptoms or prosocial behaviour at earlier waves (all *p*’s > .05).

*Measures:*

Insomnia Symptoms

Insomnia symptoms were measured using 6 items from the Insomnia Symptoms Questionnaire (22) (e.g. Difficulty falling asleep; difficulty staying asleep). Items measure the frequency of insomnia symptoms occurring per week during the past month on a 5-point Likert scale (0 = never/ don't know; 1 = rarely; 2 = sometimes; 3 = frequently; 4 = always). The total scale score is the sum of these responses (ranging from 0 to 24; higher scores = more severe insomnia). The total score demonstrated good internal consistency in the total sample (Cronbach’s α = .87 at both time-points).

Depression

Depression symptoms were measured using the Short Mood and Feelings Questionnaire. (SMFQ, 23) This 13 item measure assesses key symptoms of depression (e.g. “I felt miserable or unhappy”) over the previous two weeks. Responses are given on a 3-point Likert scale (0 = not true; 1 = sometimes; 2 = true). The psychometric properties of the SMFQ are well-established (24;25) and in the current study demonstrated good internal consistency (Cronbach’s α = .90 at both time-points). While this measure was originally designed for use with children, it has been validated in older adolescents/ young adults. (26) Of note, none of the items in the depression scale measured sleep. One item, ‘I felt so tired I just sat around and did nothing’ tapped fatigue, which could be related to a plethora of different conditions including depression, diabetes or anaemia. (27) As this item could also have reflected a sleep disorder, we conducted preliminary sensitivity analyses, by excluding this item from our measure of depression at Time 2. Correlations with insomnia symptoms did not change meaningfully. We therefore focused on the full depression scale in the analyses reported here.

*Statistical Analyses:*

Data Preparation

Skew was not problematic for insomnia symptoms from the total sample at either time-point (time 1 insomnia symptoms mean = 6.27 [SD = 5.29]; skew = .79, [SE = .06]; time 2 insomnia symptoms mean = 6.44 [5.23]; skew = .73, [SE = .08]. Depression symptom scores were positively skewed at both time-points (time 1 depression symptoms mean = 6.44 [SD = 5.23]; skew = 1.26, [SE = .06]; time 2 depression symptoms mean = 5.26 [5.29]; skew = 1.42 [SE = .08]). Depression symptom scores were therefore log transformed prior to model fitting analyses. This successfully reduced skew (time 1 depression skew = -.35 [SE = .06]; time 2 depression symptoms skew = -.15 [SE = .08]). Outliers of 3 or more standard deviations above or below the means on all variables were omitted (n = 6 cases). Additionally, prior to analysis the variables were age and sex regressed as a standard procedure for twin modelling. (28)

Analytic Principles using Twin and Sibling Data

 Twin studies compare the similarity within MZ twin pairs to the similarity within DZ twin pairs (with additional full sibling pairs) to estimate genetic and environmental influences on traits. Since MZ twins share 100% of their segregating genes while DZ twins and full siblings share on average half, the difference in covariance is used to estimate the relative contribution of three sources of variance impacting on a phenotype: additive genetic influences (A) (where alleles at all loci ‘add up’ to influence behaviour); shared environmental influences (C) (environmental influences that act to make individuals within a family similar); and non-shared environmental influences, (E) (environmental influences that act to make individuals within a family different; this source of variance also incorporates measurement error). If the correlation between MZ pairs is greater than that of DZ/sibling pairs, genetic influences are indicated. MZ twin correlations equivalent to DZ/sibling correlations indicate the importance of the shared environment, and the extent to which MZ twin correlations are smaller than 1 indicates the magnitude of non-shared environmental factors. (see 29)

Descriptive Statistics, Phenotypic and Twin Correlations

 Descriptive statistics for the untransformed scores are first presented (**Table 1**). Then phenotypic correlations are estimated in a constrained model which specifies: one overall set of means and *within-individual* *cross-trait* correlations (**Table 2**, i.e. equated across groups and twin/sibling order). Next, a set of MZ, DZ and sibling *cross-twins/siblings*, *within-trait* correlations; and a set of MZ, DZ and sibling *cross-twins/siblings,* *cross-trait* correlations are presented (**Table 3**). The twin/ sibling correlations provide an indication of the relative sources of variance on individual phenotypes and their associations.

Multivariate Genetic Model Fitting

 A correlated factors model was fitted to the 2 time point data to examine genetic and environmental influences on the association between phenotypes (**Figure 1)**. This model specifies a different set of male and female loadings for the genetic, shared and non-shared environmental factors influencing each variable in the model (qualitative sex differences), while the correlations between the A, C and E factors are the same across sex. This specification is necessary when modelling multivariate data containing opposite sex pairs. (30) This was followed by a model in which the male and female parameters were constrained to be equal, providing a 12 df sex-differences test. Finally, we tested an AE model to see whether we could drop the C parameters without a significant decrease in fit.

Analyses were conducted in the program OpenMx, a widely used programme for analysing genetically sensitive data, using raw maximum likelihood estimation. (31) The fit statistic provided for raw data analysis is minus twice the log likelihood of the observations (-2LL). Differences in fit between models are evaluated by likelihood ratio testing since the difference in -2LL is χ2 distributed. The 95% confidence intervals provide information about the precision of parameter estimates.

[Insert **Figure 1** here]

**Results**

*Descriptives*

**Table 1** shows the means and standard deviations of the raw insomnia symptoms and depression symptom scores for both time 1 and 2, split by sex and zygosity. Compared to males, females experienced greater insomnia symptoms at time 1 (Χ2 = 14.38, df *=* 1, *p* < .001) and at time 2 (Χ2 = 6.82, df *=* 1, *p* < .01). Compared to males, females also experienced greater depressive symptoms at time 1 (Χ2 = 13.09, df *=* 1, *p* < .001) and at time 2 (Χ2 = 8.7, df *=* 1, *p <* .01). Apart from time 2 insomnia symptoms, the standard deviation was significantly higher in females compared to males for time 1 insomnia and depression and time 2 depression (Χ2 = 4.74, 5.91, 6.57, p=.02, .02 and .01, respectively). There were no significant zygosity differences for any of the variables. Comparing twins and siblings, there were no significant differences in means and standard deviations, apart from depression symptoms at time 2 which showed a lower mean (Χ2 = 5.95, df *=* 1, *p* < .02), and standard deviation (Χ2 = 5.95, df *=* 1, *p* < .02) in siblings. The male-female differences in means are accounted for by specifying a free set of mean parameters for each group (even in the no-sex-difference variance components model).

[Insert **Table 1** here]

*Correlations*

The within-individual cross-trait correlations are presented in **Table 2**. At both time-points, greater insomnia symptoms were associated with more depression symptoms (time 1: *r* = .50 [95% confidence intervals, (CI) = .46-.54]; time 2: *r* = .52 [CI = .47-.56]). There was a substantial degree of stability in the traits across time (insomnia symptoms: *r* = .50 [CI = .44-.54]; depression symptoms: *r* = .50 [CI = .44-.54]). The cross-trait longitudinal correlations indicated that insomnia symptoms at time 1 were significantly associated with depression symptoms at time 2 (*r* = .34 [CI = .28-.39]). Likewise, depression symptoms at time 1 were significantly associated with insomnia symptoms at time 2 (*r* = .38 [CI = .32-.44]).

*Twin Correlations*

The cross-member correlations for MZ and DZ twins and siblings are presented in **Table 3**. This model is interpreted due to the lack of sex differences detected. For the correlation matrices given by group (zygosity) and sex, please see **Table S1 and S2 in supplemental material**. All MZ and DZ within-trait twin correlations were significant: (range *r* = .31-.44 and *r* = .15-.22, respectively). All within-trait sibling correlations were non-significant (range *r* = -.02-.14). However, overlapping 95% CI indicate that they were not significantly different from the DZ twin pairs: equating the sibling and DZ correlations resulted in a non-significant drop in fit (Χ2 = 17.50, df = 10, p = .06), justifying modelling sibling data as DZ twin pairs in the genetic models. The cross-twin cross-trait correlations for insomnia symptoms and depression symptoms at both time-points were, in general, higher in MZ compared to DZ pairs and siblings, suggesting the possibility of genetic effects on the insomnia-depression association. The extent to which this is the case is formally estimated and tested in the genetic model fitting analysis.

[Insert **Table 2** and **3** here]

*Genetic Analyses*

 The model equating the ACE parameter estimates across males and females (-2LL = 27641.05, df = 4668) did not show a significant decline in fit (Χ2 = 12.09, df = 12, p = .44) when compared to the quantitative sex-differences model (-2LL = 27628.95, df = 4656). Furthermore, it was possible to drop C (factor loadings and correlations) from the model without decrease in fit (Χ2 = 2.04, df = 10, p = .99). For simplicity, the more parsimonious AE no-sex-differences model is interpreted here (**Table 4**), but the full ACE model estimates are provided in **Tables S3 and S4 in supplemental material**.

[Insert **Table 4** here]

The genetic and non-shared environmental correlations between the variables are presented in the top part of **Table 4**. For example, the genes influencing insomnia symptoms at time 1 are highly correlated with those influencing depression symptoms at time 1 (rA = .80, CI = .65-.94). All of the genetic correlation between traits were high (ranging from .73 for the genetic correlation between insomnia and depression symptoms at time 2 to 1.00 for the correlation between insomnia symptoms at times 1 and 2). The non-shared environmental correlations were smaller (ranging from .05 for the association between insomnia symptoms at time 1 and depression symptoms at time 2; to .40 for the association between insomnia and depression symptoms at time 2). The lower part of **Table 4** shows the standardised estimates for genetic and non-shared environmental influences within each trait (diagonal elements). Additive genetic influences accounted for between 33-41% of the variance. The off-diagonal elements represent the proportion of covariance determined by correlating genetic and non-shared environmental factors. Most of the association between variables is due to genetic factors (explaining 50-90% of the covariance).

Discussion

*Phenotypic associations*

This was the first twin study to examine the longitudinal associations between insomnia and depression symptoms within adulthood. As expected, there were moderate phenotypic associations between insomnia and depression symptoms both within and across time-points, in line with the plethora of literature highlighting links between these phenotypes. (for reviews and meta-analyses, see 1;2;3;4)

*Genetic and environmental influences on associations*

When decomposing the concurrent associations between insomnia and depression symptoms into genetic and environmental influences we found a strong genetic correlation between the two phenotypes and a large proportion of the phenotypic correlations could be explained by genes. This is in line with a handful of comparable studies in this area. (e.g. 13;15) Of note, we have previously reported on the concurrent associations between sleep quality and depression and anxiety symptoms at time 1 – unsurprisingly producing similar results to the time 1 analyses reported in this current manuscript. (14)

What is novel here is that when considering the longitudinal associations between the phenotypes, the genetic overlap appeared to be just as strong as for the concurrent associations – and overall, genes appeared to play an even larger role in the association between the phenotypes longitudinally than concurrently.

*Persistence of symptoms over time*

While not a key focus of the current study, these data also provided an understanding of why symptoms of insomnia and depression may persist over time. Again, genetic factors appear to play the largest role – with a perfect correlation between genetic factors influencing insomnia symptoms at times 1 and 2 – suggesting that the same genetic factors may be influencing insomnia symptoms across ones 20s. There was also a high genetic correlation for depression symptoms at times 1 and 2 and overall, genetic factors appeared to explain roughly three quarters of the persistence between each of the phenotypes over time. These sleep data are largely consistent with previous behavioural genetic work examining the persistence of sleep disturbances and insomnia symptoms over time by highlighting an important role for genetic factors – although previous research also suggests that new genetic influences may also come into play over time. (18;32) Similarly, the depression symptom data reported here fits with previous research from our group (including Time 1 data reported here, 33); and from others showing that genes account for stability in depression symptoms over time although new genetic influences may also come into play over time. (e.g. 34)

*Genetic influences*

The general conclusion that genetic factors are important in the persistence and associations between disorders chimes well with the ‘generalist genes hypothesis’ which proposes that genes are important in explaining the *overlap* between disorders and over time - but that environmental influences are perhaps more important in explaining *differences* between disorders and across time-points. (35)

The obvious next step of specifying genes involved in the associations between insomnia and depression symptoms has proven to be much more difficult than expected, with ‘missing heritability’ reported for all complex phenotypes. (36) Large scale Genome Wide Association Study (GWAS) collaborations and decreasing costs of next-generation sequencing will help to move forward the currently poor understanding of the genetics of sleep difficulties. (see 37)

*Environmental influences*

While genetic factors appeared to be key in explaining the *associations* between insomnia and depression symptoms both concurrently and longitudinally, it is important to note that the non-shared environment also played a role. *Univariately*, nonshared environmental influences (which include error) accounted for roughly two thirds of the variance of each phenotype. There were also small to moderate overlaps between the nonshared environmental influences for different bivariate combinations of phenotypes and overall, nonshared environment accounted for a small to moderate proportion of the associations between phenotypes, with the greatest influence for the concurrent associations between phenotypes at each wave. While it was beyond the scope of this study to specify environmental influences involved in the association, candidates come from previous work. For example, important environmental influences might include negative life events, which are plausibly associated with poorer sleep quality (38) and depression symptoms.(39) Such influences are able to explain both concurrent and longitudinal relationships between variables, given the dynamic nature of the associations between stress and depression over time. (39) How these environmental influences ‘get under the skin’ to lead to both insomnia and depression symptoms is an area for further research, and our group has recently used the MZ differences approach to examine the possibility that epigenetic differences can account for extreme differences in phenotypes between twins who are genetically identical (for work focused on depression and diurnal preference see, 40;41). Our future work will explore differences in insomnia symptoms between MZ twins (for a review focusing on this topic see, 42).

*Limitations*

The results of this study need to be considered alongside the limitations. First, insomnia and depression symptoms were assessed using symptom count measures, which focused on frequency, but not severity of symptoms. We also focused on symptoms rather than diagnoses. This approach is standard when dealing with twin data (e.g. for insomnia, 43). Furthermore, the convergence of results found here and in previous work using a more clinical approach is reassuring. For example, genetic influence on insomnia symptoms are here estimated at 35% at time 1 and 37% at time 2, which corresponds well with estimates from other twin samples (e.g. 31% 13). Furthermore, the estimates for depressive symptoms at time 1 (41%) and time 2 (33%) correspond to a genetic estimate from a meta-analysis of the genetic epidemiology of major depression (37%, 44). While research on a plethora of phenotypes suggests that the same influences are likely to account for individual differences in the full range as at the extremes, (see 29) this assumption is yet to be tested for insomnia symptoms.

A second limitation is that we did not systematically assess the multiple factors which could have caused insomnia in our participants (such as circadian sleep disorders and medical conditions). Furthermore, we did not assess the use of drugs prescribed for depression in our sample. It is possible that such drug use could have been important in accounting for some of the association between the variables reported here. For example, sleep problems can be a side-effect of selective serotonin reuptake inhibitors. (45). We did assess past-month use of prescribed or over the counter drugs to aid sleep, and found that only 9% of our sample had used such drugs at Time 2. When we re-ran phenotypic analyses excluding those who had taken these drugs at Time 2, we found very similar results.

A third limitation concerns the sample which was relatively small for a twin study due to inevitable attrition across the waves of data collection. Nonetheless, the sample size reported here is comparable with other twin studies of sleep difficulties. (e.g. 18) While the data need to be interpreted considering the large confidence intervals, it was reassuring that results reported here are in line with comparable studies using larger sample sizes. Furthermore, there was no selective attrition for the key variables assessed here, namely insomnia and depression symptoms. However, those who stayed in the study from Time 1 to Time 2 were more likely than those who dropped out to be female and have more highly educated mothers. This is noteworthy given that the G1219 study as a whole initially comprised families including parents who are more educated and more likely to own their own homes than representative samples 19 Heritability is a population statistic, meaning that our results may not apply to other cohorts. This needs to be considered when interpreting the results of this study.

Finally, standard twin limitations need to be considered (for a discussion see elsewhere, 29). Years of careful consideration of these limitations leads to the realisation that different limitations influence genetic and environmental estimates unsystematically and that estimates should be interpreted generally.

*Conclusion*

The overall conclusion that genes are important in the association between insomnia and depression symptoms goes to reinforce the general conclusion that genes are important for all complex traits (46) and therefore need to be acknowledged when developing theories describing the mechanisms underlying phenotypes and their associations. Genome-wide approaches to these questions will be the next step, (47) as we consider whether genetic markers across the genome associated with, for example insomnia, also influence major depressive disorders. This approach is highly complementary to the one used here, and has the added benefit of producing data that applies to an individual, not just population variance. However, it also requires huge sample sizes so progress is inevitably somewhat slow. Another way to explore this question further is to see whether reducing one difficulty (for example using a psychological therapy for insomnia) influences the other (e.g. depression), and examining the role of genetic effects on such changes. We have been studying genetic influences on outcome following psychological therapy in anxiety disorders. As with any area of psychiatric genetics, the work requires large sample sizes and most studies to date have been underpowered (e.g. for work on pediatric anxiety, see 48). However there are preliminary indications that there are genetic influences on response to psychological treatment, (49) indicating that this is a fruitful avenue for further research. Future work by our group will examine genetic prediction of response to CBT for insomnia symptoms and whether improving those symptoms has positive effects on depression symptoms.

**Acknowledgements:** We thank the families for their participation as well as numerous staff and students from the Social Genetic Developmental Psychiatry Centre, Institute of Psychiatry, Psychology & Neuroscience, King’s College London and Goldsmiths, University of London. The authors thank Monika Waszczuk for her input and help with Figure 1.

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| Table 1. Means (SD) for raw insomnia and depression scores and number of individual (N) and full pairs (FP) |
|  | Total | Males  | Females | MZ | DZ | Sibs |
| Time 1 INS | 6.27 (5.29)N=1546 | 5.75 (5.00)N=595 | 6.84 (5.50)N=951 | 6.00 (5.21)N=415FP=187 | 6.30 (5.31)N=769FP=324 | 6.61 (5.38)N=329FP=128 |
| Time 1 DEP  | 6.51 (5.74)N=1549 | 5.97 (5.41)N=596 | 7.06 (5.95)N=953 | 6.32 (5.62)N=417FP=189 | 6.61 (5.76)N=769FP=324 | 6.53 (5.86)N=329FP=128 |
| Time 2 INS  | 6.44 (5.23)N=857 | 5.94 (4.96)N=294 | 6.84 (5.38)N=563 | 6.07 (4.93)N=222FP=89 | 6.56 (5.41)N=402FP=143 | 6.62 (5.16)N=216FP=67 |
| Time 2 DEP  | 5.26 (5.29)N=861 | 4.70 (4.86)N=296 | 5.68 (5.54)N=565 | 5.34 (5.53)N=223FP=89 | 5.81 (5.64)N=403FP=144 | 4.61 (4.22)N=218FP=69 |

*Note.* Time 1 = Wave 4; Time 2 = Wave 5; INS = Insomnia Symptoms; DEP = Depression Symptoms; MZ = Monozygotic; DZ = Dizygotic; Sibs = Siblings. Number of MZ + DZ + sibs ≠ total number of participants due to missing zygosity information

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| Table 2. Within person phenotypic correlations between insomnia and depression symptoms at times 1 and 2 (95% confidence intervals in parentheses) |
|  | Time 1 INS | Time 1 DEP | Time 2 INS | Time 2 DEP |
| Time 1 INS | 1 |  |  |  |
| Time 1 DEP | .50 (.46-.54) | 1 |  |  |
| Time 2 INS | .50 (.44-.54) | .38 (.32-.44) | 1 |  |
| Time 2 DEP | .34 (.28-.39) | .50 (.44-.54) | .52 (.47-.56) | 1 |

*Note.* Time 1 = Wave 4; Time 2 = Wave 5; INS = Insomnia Symptoms; DEP = Depression Symptoms.

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| Table 3. Twin correlations (within and across traits) for insomnia and depression symptoms at times 1 and 2 (95% confidence intervals in parentheses) |
| Twin 1/Sibling1 |
| MZ twins |
| Twin 2 |  | Time 1 INS | Time 1 DEP | Time 2 INS | Time 2 DEP |
| Time 1 INS | .34 (.21-.45) |  |  |  |
| Time 1 DEP | .35 (.25-.43) | .44 (.33-.54) |  |  |
| Time 2 INS | .39 (.26-.50) | .33 (.21-.43) | .31 (.11-.48) |  |
| Time 2 DEP | .32 (.20- 42) | .37 (.26-.46) | .26 (.11-.39) | .35 (.17-.50) |
| DZ twins |
| Twin 2 |  | Time 1 INS | Time 1 DEP | Time 2 INS | Time 2 DEP |
| Time 1 INS | .22 (.11-.32) |  |  |  |
| Time 1 DEP | .10 (.01-.18) | .15 (.04-.25) |  |  |
| Time 2 INS | .15 (.04-.22) | .11 (.01-.21) | .22 (.07-.35) |  |
| Time 2 DEP | .12 (.02-.21) | .16 (.06-.26) | .10 (-.01-.21) | .19 (.05-.32) |
| Siblings |
| Sibling 2 |  | Time 1 INS | Time 1 DEP | Time 2 INS | Time 2 DEP |
| Time 1 INS | .04 (-.12-.20) |  |  |  |
| Time 1 DEP | .10 (-.02-.23) | .14 (-.03-.30) |  |  |
| Time 2 INS | .22 (.06-.35) | .13 (-.03-.27) | .09 (-.14-.32) |  |
| Time 2 DEP | .17 (.02-.31) | .13 (-.03-.29) | .08 (-.11-.26) | -.02 (-.25-.21) |

*Note.* Time 1 = Wave 4; Time 2 = Wave 5; INS = Insomnia Symptoms; DEP = Depression Symptoms; MZ = Monozygotic; DZ = Dizygotic. Shaded cells represent within-trait cross twin/sibling correlations.

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| Table 4. Parameter estimates from best fitting multivariate AE model (95% confidence intervals) |
|  | Time 1INS | Time 1DEP | Time 2INS | Time 2DEP |
| Additive genetic and nonshared environmental overlap between phenotypes |
| Time 1INS | // |  |  |  |
| Time 1DEP | rA = .80 (.65 - .94)rE = .32 (.22 - .41) | // |  |  |
| Time 2INS | rA = 1 (.83 - 1)rE =.22 (.10 - .34) | rA = .79 (.57 - 1) rE = .12 (-.02 - .27) | // |  |
| Time 2DEP | rA = .89 (.63 - 1)rE = .05 (-.09 - .19) | rA = .98 (.78 - 1)rE = .22 (.09 - .35) | rA = .73 (.50-.96)rE = .40 (.27 - .52)  | // |
| Standardized additive genetic and nonshared environmental influences on the phenotypes and their associations |
| Time 1INS | A = .35 (.25 - .45)E = .65 (.55 - .75) |  |  |  |
| Time 1DEP | A = .61 (.45 - .75)E = .39 (.25 - .54) | A = .41 (.31 - .50)E = .59 (.50 - .69) |  |  |
| Time 2 INS | A = .72 (.54 - .88)E = .28 (.12 - .46) | A = .80 (.56 - 1.04)E = .20 (-.04 - .44) | A = .37 (.23 - .50)E = .63 (.51 - .77) |  |
| Time 2DEP | A = .90 (.63 - 1.18)E = .10 (-.18 - .37) | A = .73 (.54 - .89)E = .27 (.11 - .46) | A = .50 (.28 - .69)E = .50 (.31 - .72) | A = .33 (.20 - .47)E = .67 (.53 - .80)  |

*Note.* rA = genetic correlation; rE = non-shared environmental correlation; A = additive genetics; E = non-shared environmental influences. 95% confidence intervals not spanning zero indicate significance at the p<.05 level. The shaded cells of the lower part of the table represent within-trait standardized components of variance; the off-diagonals represent the standardized components of covariance. The components of covariance (and their 95% confidence intervals) are not bounded between 0-100%, since the phenotypic overlap between traits can be due to opposite sign contributions of the A and E component. Time 1 = Wave 4; Time 2 = Wave 5; INS = Insomnia Symptoms; DEP = Depression Symptoms.

Figure 1 Legend:

Multivariate Correlated Factors Model. A = Additive genetic influence; E = Non-shared environmental influence

**Supplemental Material:**

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| Table S1. Within person phenotypic correlations across traits for males and females |
|  | Time1 INS | Time 1 DEP | Time 2 INS | Time 2 DEP |
| Males |
| Time 1 INS |  **1** |  |  |  |
| Time 1 DEP | **.43 (.27-.56)** | **1** |  |  |
| Time 2 INS | **.50 (.30-.64)** | **.45 (.24-.60)** | **1** |  |
| Time 2 DEP | **.33 (.10-.50)** | **.48 (.26-.63)** | **.48 (.28-.63)** | **1** |
| Females |
| Time 1 INS |  **1** |  |  |  |
| Time1 DEP | **.56 (.48-.63)** | **1** |  |  |
| Time 2 INS | **.58 (.46-.67)** | **.41 (.28-.52)** | **1** |  |
| Time 2 DEP | **.43 (.30-.54)** | **.46 (.34-.56)** | .**53 (.40-.62)** | **1** |

*Note:* 95% confidence intervals not spanning zero indicate significance at the p<.05 level (bold); Time 1 = Wave 4; Time 2 = Wave 5; INS = Insomnia Symptoms; DEP = Depression Symptoms.

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| Table S2. Twin correlations within and across traits for each sex-by-zygosity twin group and same and opposite sex sibling pair group |
| **Tw1/Tw2** | Time 1 INS | Time 1 DEP | Time 2 INS | Time 2 DEP |
| MZM |
| Time 1 INS | **.34 (.10-.53)** |  |  |  |
| Time 1 DEP | **.28 (.08-.44)** | **.45 (.20-.62)** |  |  |
| Time 2 INS | **.37 (.14-.54)** | **.46 (.25-.61)** | **.36 (.03-.61)** |  |
| Time 2 DEP | **.37 (.15-.55)** | **.48 (.25-.63)** | **.31 (.05-.52)** | .30 (-.08-.57) |
| DZM |
| Time 1 INS | **.27 (-.02-.50)** |  |  |  |
| Time 1 DEP | .07 (-.13-.26) | .09 (-.14-.31) |  |  |
| Time 2 INS | .25 (-.01-.47) | .09 (-.14-.30) | .19 (-.20-.52) |  |
| Time 2 DEP | .02 (-.23-.27) | .04 (-.19-.26) | .02 (-.26-.29) | .24 (-.11-.53) |
| MZF |
| Time 1 INS | **.37 (.21-.50)** |  |  |  |
| Time 1 DEP | **.40 (.28-.49)** | **.45 (.32-.56)** |  |  |
| Time 2 INS | **.42 (.26-.54)** | **.31 (.16-.43)** | **.35 (.10-.53)** |  |
| Time 2 DEP | **.31 (.16-.44)** | **.32 (.19-.44)** | **.27 (.08-.42)** | **.37 (.14-.54)** |
| DZF |
| Time 1 INS | **.22 (.04-.38)** |  |  |  |
| Time 1 DEP | **.19 (.05-.32)** | **.30 (.13-.45)** |  |  |
| Time 2 INS | .11 (-.07-.27) | **.18 (.01-.33)** | **.34 (.11-.52)** |  |
| Time 2 DEP | .14 (-.02-.29) | **.19 (.03-.34)** | .09 (-.08-.26) | .06 (-.15-.26) |
| DOS |
| Time 1 INS | **.21 (.04-.35)** |  |  |  |
| Time 1 DEP | .03 (-.10-.15) | .06 (-.10-.22) |  |  |
| Time 2 INS | .12 (-.03-.27) | .07 (-.08-.22) | .08 (-.14-.29) |  |
| Time 2 DEP | .1 (-.02-.27) | **.22 (.07-.36)** | .16 (-.01-.31) | **.34 (.13-.50)** |
| Male-Male Siblings |
| Time 1 INS | **.34 (.04-.55)** |  |  |  |
| Time 1 DEP | **.41 (.16-.58)** | .20 (-.19-.51) |  |  |
| Time 2 INS | **.41 (.11-.62)** | .36 (-.05-.64) | -.09 (-.49-.37) |  |
| Time 2 DEP | .15 (-.11-.37) | .24 (-.12-.51) | -.002 (-.34-.34) | -.02 (-.42-.39) |
| Female-Female Siblings |
| Time 1 INS | -.04 (-.30-.23) |  |  |  |
| Time 1 DEP | -.05 (-.25-.17) | -.25 (-.49-.07) |  |  |
| Time 2 INS | .07 (-.21-.34) | -.26 (-.48-.10) | -.11 (-.49-.47) |  |
| Time 2 DEP | .09 (-.18-.33) | -.04 (-.30-.29) | -.16 (-.45-.24) | -.39 (-.66-.06) |
| Male-Female Siblings |
| Time 1 INS | -.04 -(.26-.19) |  |  |  |
| Time 1 DEP | .07 (-.11-.24) | **.27 (.04-.46)** |  |  |
| Time 2 INS | **.21 (.01-.40)** | **.20 (.02-.36)** | .20 (-.09-.44) |  |
| Time 2 DEP | **.31 (.09-.48)** | .18 (-.04-.36) | .23 (-.04-.43) | .14 (-.21-.46) |

*Note:* 95% confidence intervals not spanning zero indicate significance at the p<.05 level (bold); Tw1 / Tw2 = Twin 1 / 2; Time 1 = Wave 4; Time 2 = Wave 5; INS = Insomnia Symptoms; DEP = Depression Symptoms. MZ = Monozygotic Twins; DZ = Dizygotic Twins; M = Male; F = Female; DOS = Male-Female Dizygotic Twin Pairs.

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| Table S3. Genetic, shared and nonshared environmental correlations from the ACE no-sex-differences model (with 95%CI) |
|  | Time 1 INS | Time 1 DEP | Time 2 INS | Time 2 DEP |
| rA |
| Time 1 INS | **1** |  |  |  |
| Time 1 DEP | **1 (.69-1)** | **1** |  |  |
| Time 2 INS | **1 (.77-1)** | **.90 (.51-1)** | **1** |  |
| Time 2 DEP | **.89 (.52-1)** | **.97 (.76-1)** | **.90 (.30-1)** | **1** |
| rC |
| Time 1 INS | **1** |  |  |  |
| Time 1 DEP | -1 (-1-1) | **1** |  |  |
| Time 2 INS | 1 (-1-1) | -.16 (-1-1) | **1** |  |
| Time 2 DEP | 1 (-1-1) | 1 (-1-1) | -.63 (-1-1) | **1** |
| rE |
| Time 1 INS | **1** |  |  |  |
| Time 1 DEP | **.30 (.21-.40)** | **1** |  |  |
| Time 2 INS | **.24 (.11-.36)** | .12 (-.03-.28) | **1** |  |
| Time 2 DEP | .06 (-.07-.21) | .10 (-.08-.36) | **.39 (.25-.52)** | **1** |

*Note:* Time 1 = Wave 4; Time 2 = Wave 5; INS = Insomnia Symptoms; DEP = Depression Symptoms; 95% confidence intervals not spanning zero indicate significance at the p<.05 level (bold); rA = genetic correlation; rC = shared environmental correlation; rE = non-shared environmental correlation.

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| Table S4. Standardized estimates for genetic, shared and nonshared environmental influences from the ACE no-sex-differences model (with 95%CI) |
|  | A | **C** | E |
| Time 1 INS | **.29 (.13-.43)** | .05 (.00-.16) | **.66 (.56-.76)** |
| Time 1 DEP | **.39 (.24-.49)** | .01 (.00-.11) | **.60 (.50-.70)** |
| Time 2 INS | **.31 (.08-.49)** | .04 (.00-.22) | **.65 (.51-.79)** |
| Time 2 DEP | **.32 (.11-.46)** | .02 (.00-.17) | **.66 (.54-.80)** |

*Note:* Time 1 = Wave 4; Time 2 = Wave 5; INS = Insomnia Symptoms; DEP = Depression Symptoms; 95% confidence intervals not spanning zero indicate significance at the p<.05 level (bold); A = additive genetics; C = shared environment; E = non-shared environmental influences.

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