Twin Research and Human Genetics
Volume 15 ▌ Number 6 ▌ pp. 720–726 ▌ © The Authors 2012 ▌ doi:10.1017/thg.2012.60

The Genetic and Environmental Structure of the Covariation Among the Symptoms of Insomnia, Fatigue, and Depression in Adult Females

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Although the co-occurrence among symptoms of insomnia, fatigue, and depression has been frequently reported, the etiology of this co-occurrence remains poorly understood. A total of 3,758 adult female twins in the United Kingdom completed a mail-out survey including six questions concerning frequency and severity of symptoms of insomnia, fatigue, and depression. Correlations among the scores of the three symptoms ranged from 0.35 to 0.44. Among various multivariate models we tested, the common-pathway model explained the data best. In the best-fitting model, the common factor was explained approximately equally by genetic and unique environmental factors (49% and 51%, respectively). In addition to the common variance, there was a significant specific variance in each symptom, where unique environmental factors were much larger than genetic factors. These results imply that although there are shared genetic liabilities for the development of symptoms of depression, fatigue, and insomnia, it is environmental experiences that make etiological distinctions among three symptoms.

Keywords: twin, insomnia, fatigue, depression, genetics, comorbidity

While some researchers have shown that fatigue and depression occur concurrently (Farmer et al., 1995; Henningsen et al., 2003), others have found that fatigue is both predictive and a consequence of depression (Harvey et al., 2008; Huibers et al., 2007; Skapinakis et al., 2004). In addition, symptoms of insomnia have been reported to be common among depressed and chronic fatigue syndrome (CFS) patients (Afari & Buchwald, 2003; Skapinakis et al., 2000; Sunderajan et al., 2010). Even though many twin studies of insomnia, depression, and fatigue have been conducted, the etiology of the comorbidity among these three symptoms remained unclear. For example, Watson et al. (2003) compared subjective and objective measures of insomnia among monozygotic (MZ) twins discordant for CFS. They found that the CFS twins reported insomnia more frequently than did their healthy cotwins only when insomnia was measured subjectively. In the Watson et al. study, there were no significant differences between the CFS and healthy twins in objective measures of insomnia. From these results, the authors concluded that the association between symptoms of insomnia and fatigue might occur as a result of the sleep-state misperception common among patients with CFS. In another cotwin control study, Roy-Byrne et al. (2002) found that twins with CFS were significantly more depressed than their cotwins with no CFS, indicating a significant association between depression and fatigue. Intra-pair differences in depression in the Roy-Byrne et al. study were similar in MZ and dizygotic (DZ) twins, suggesting that the comorbidity between CFS and depression may be mediated by common environmental rather than common genetic factors. As Roy-Byrne et al. acknowledged, however, their failure to detect common genetic factors could be due to reduced statistical power associated with small sample sizes in their study (69 MZ and 31 DZ twin pairs). More recently, Lessov-Schlaggar et al. (2008) analyzed the relationship between daytime sleepiness and depressive symptoms in elderly male twins and found a modest but statistically significant genetic overlap between the two

RECEIVED 22 January 2012; ACCEPTED 27 August 2012. First published online 24 September 2012.

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phenotypes, suggesting that genetic factors may be at least in part responsible for the relationship between sleep disturbance and depression.

Prior twin and family studies have demonstrated that symptoms of fatigue, insomnia, and depression are moderately heritable, with heritability coefficients on the order of 30–50% for depression (Sullivan et al., 2000), 6–50% for various fatiguing illnesses (Sullivan et al., 2003, 2005), and 20–40% for insomnia and other sleep problems (McCarren et al., 1994). Non-genetic variances were mostly attributable to unique environmental factors, as family environments were shown to play very little etiological role. Given these findings, it is likely that the covariation among symptoms of insomnia, fatigue, and depression is due to the genetic and unique environmental overlap among the three symptoms.

The goals of this study were twofold. First, using a large, relatively representative sample of adult female twins in the United Kingdom, we aimed to establish the degree of the covariation among symptoms of insomnia, fatigue, and depression. Second, we attempted to explore the genetic and environmental etiology of the covariation among the three symptoms by fitting multivariate genetic models.

Method

Subjects

Subjects were female twin participants drawn from the TwinsUK Register (Spector & Williams, 2006) who returned the year 2000 mail-out survey of self-report questionnaires. Recruitment to the TwinsUK Register began in 1994 through a national media campaign. Participants were not selected for any specific behavioral trait or health status, nor did they have prior knowledge of the precise nature of the study. Zygosity was established through a standardized questionnaire and by deoxyribonucleic acid confirmation in doubtful cases. Ethics committee approval had been obtained. In total, 3,758 twins consisting of 893 complete pairs of MZ and 884 complete pairs of DZ twins and 204 individual twins were included in data analyses. The mean age of MZ twins was 50.0 years (*SD* 13.2 years, range = 18–81 years) and of DZ twins was 50.0 years (*SD* 12.3 years, range = 19–81 years) in this study.

Measures

In the year 2000 mail-out survey, twins were asked to rate the frequency of occurrence and the severity with which they experienced insomnia, fatigue, and depression during one year prior to the survey. Each symptom consisted of two items, resulting in six items in total. Example items for insomnia are as follows. (1) How often did you have insomnia (trouble sleeping) in the last year? (2) How much did the insomnia (trouble sleeping) bother you in the last year? Each item was rated on a 3-point scale (0 = never; 1 = sometimes; 2 = often) and a total score for each symptom was obtained by summing the scores of the two items. For all three symptoms, higher scores indicate greater severity and more frequent symptoms. Correlations between the frequency and the severity item ranged from 0.75 for fatigue, 0.80 for depression, and 0.81 for insomnia.

Data Analysis

To estimate genetic and environmental influences on symptoms of insomnia, fatigue, and depression, we carried out univariate model-fitting analyses for each symptom. Then, multivariate model-fitting analyses were conducted to determine the underlying genetic and environmental architecture of the covariation among symptoms of insomnia, fatigue, and depression. We fit three multivariate models to the data: the Cholesky factorization, the independent- and common-pathway model (Neale & Cardon, 1992). All three models assume that the total variance is a linear combination of the three factors: additive genetic, shared environmental, and unique environmental factors. As additive genetic factors represent the sum of the average effect of all genes that influence a trait, we set additive genetic variances to be correlated at 1.0 and 0.5 for MZ and DZ twins, respectively. Because shared environmental factors include all environmental components shared by both members of a twin pair, we set shared environmental variances to be correlated at 1.0 for both MZ and DZ twins. Finally, unique environmental factors represent those environmental variances specific to each member of a twin pair and measurement error and, therefore, are not correlated within a pair of twins.

The Cholesky factorization model shows that each of the three Cholesky factors (insomnia, fatigue, and depression) is decomposed into three sets of the additive genetic, and shared and unique environmental factors. The first set of Cholesky additive genetic, shared environmental, and unique environmental factors have effects on all three symptoms (insomnia, fatigue, and depression); the second Cholesky factors have an impact on subsequent two symptoms (fatigue and depression). The third Cholesky factors are those unique to the last symptom (depression). In the Cholesky analysis, the order of the variables is arbitrary.

Both the independent- and common-pathway models assume that a common genetic factor (A), a common shared environmental factor (C), and a common unique environmental factor (E) influence the three symptoms simultaneously. In addition to these three common factors, both models assume the existence of specific variance in each symptom, which was divided into additive genetic (a), shared environmental (c), and unique environmental factors (e). The independent-pathway model posits that A, C, and E affect each symptom directly and separately, having its own path to each symptom. The common-pathway model, on the contrary, hypothesizes that a latent common factor intervenes between the three symptoms and A, C,

https://doi.org/10.1017/thg.2012.60 Published online by Cambridge University Press

TABLE 1

Phenotypic Correlations, Twin Correlations, and Cross-Trait Cross-Twin Correlations for the Symptoms of Insomnia, Fatigue, and Depression for Monozygotic (MZ) and Dizygotic (DZ) Twins

		Twin correlation			Cross-trait cross-twin correlation			
Variables	Phenotypic correlation	Symptom	MZ	DZ		Insomnia 1	Fatigue 1	Depression 1
Insomnia —- Fatigue	0.44**	Insomnia	0.27**	0.15**	Insomnia 2	–	0.16**	0.07*
Insomnia —- Depression	0.35**	Fatigue	0.36**	0.25**	Fatigue 2	0.18**	–	0.15**
Fatigue —- Depression	0.43**	Depression	0.35**	0.18**	Depression 2	0.15**	0.21**	–

Note: Range for all three symptom scores: 0–8. The double-entry method was used to calculate cross-trait cross-twin correlations, where p values were adjusted for the single-entry sample size.
MZ and DZ cross-trait cross-twin correlations are reported below and above the diagonal, respectively.
*$p < .05$, **$p < .01$.

and E so that the covariance among the three symptoms is determined by the phenotypic relationships of the three symptoms with the latent common factor. That is, the association among fatigue, insomnia, and depression is mediated through a latent common factor that is influenced by a single set of genes and environments. It should be noted that an independent pathway model estimates the same number of parameters as a Cholesky model when the model includes three variables. However, the common pathway model estimates fewer parameters than the independent pathway model and therefore is more parsimonious. For a baseline comparison, we used a saturated model that estimated 6 × 6 matrices of variances and covariances among the three symptom scores.

We took two steps to carry out multivariate model-fitting analyses. First, we compared goodness-of-fit statistics among the Cholesky factorization, and the independent- and the common-pathway models to choose a model that best explains the covariance structure. Second, variations of the chosen model were made by reducing parameters to determine the most parsimonious model. We used two criteria in deciding on the best-fitting, most parsimonious model: The likelihood ratio χ^2 test (LRT) and Akaike Information Criterion (AIC; AIC $= \chi^2 - 2df$). If two models are nested, the change in χ^2 is itself distributed as a χ^2, which enables evaluations of the models. AIC quantifies the information content of a model in terms of the joint criterion of fit and parsimony. In general, small χ^2 values from models with few free parameters lead to small AICs, representing maximum parsimony, whereas large χ^2 values from models with many parameters yield large AICs, representing a lack of parsimony (Akaike, 1987).

Results

Descriptive Statistics

Using the maximum likelihood raw data option in Mx (Neale et al., 2003), we tested differences in means and variances between the two zygosity groups as well as between twin 1 and twin 2 (numbering assigned arbitrarily upon registration and not related to birth order) for all three symptoms. None of the three symptoms showed a significant difference in the mean level or in variance between MZ and DZ twins or between twin 1 and twin 2 within zygosity, fulfilling assumptions for data analyses using twins. The distribution of the depression symptom score was significantly skewed (skewness = 1.3). Prior to twin correlation and model-fitting analyses, we performed square-root transformation of the individual score of the depression, which resulted in a distribution of acceptable symmetry (skewness = 0.48). Modest correlations of the three symptoms with age ($-0.13 < r < 0.08$) were found. The mean effects of age, therefore, were regressed out for genetic analyses.

Correlational Analyses

Before we conducted model-fitting analyses, we examined phenotypic correlations and twin and cross-trait cross-twin correlations for insomnia, fatigue, and depression (Table 1). The cross-trait cross-twin correlation is a correlation within a twin pair across two traits (e.g., correlation of twin 1's insomnia symptom score with twin 2's fatigue symptom score). Twin and cross-trait cross-twin correlations were computed on the basis of complete twin pairs. MZ twin correlations were consistently higher than DZ twin correlations for all three symptoms, indicating the presence of genetic influences on variation of these symptoms. It appears that genetic effects were primarily additive, and shared environmental influences were small for all three symptoms because DZ twin correlations were approximately half the size of MZ twin correlations.

Phenotypic correlations among three symptoms ranged from 0.35 to 0.44, providing supportive evidence for comorbidity among symptoms of insomnia, fatigue, and depression. Cross-trait cross-twin correlations were consistently higher among MZ than among DZ twins, indicating that the phenotypic covariance among three symptoms is due in part to shared genetic factors. However, cross-trait cross-twin correlations in MZ twins were relatively low, which indicated a large amount of unique environmental influences on the covariation among three symptoms.

https://doi.org/10.1017/thg.2012.60 Published online by Cambridge University Press

TABLE 2

Multivariate Model-Fitting Results for Symptoms of Fatigue, Insomnia, and Depression

	Variance components		Goodness-of-fit statistics					
Model	Common	Specific	−2LL	*df*	AIC	$\Delta\chi^2$	Δdf	*p*
1. Saturated	–	–	34,526.7	12,956	8,614.7			
2. Cholesky	–	–	34,560.1	12,980	8,600.1	33.4	24	.10
3. Independent	A, C, E	a, c, e	34,560.3	12,980	8,600.3	33.6	24	.10
4. Common	A, C, E	a, c, e	34,564.1	12,984	8,596.1	37.4	28	.10
4.1 Common	–	a, c, e	39,117.3	12,987	13,143.3	4,553.2	3	.00
4.2 Common	C, E	c, e	34,591.5	12,988	8,615.5	27.4	4	.00
4.3 Common	**A, E**	**a, e**	**34,566.4**	**12,988**	**8,590.4**	**2.3**	**4**	**.68**
4.4 Common	E	a, e	34,694.8	12,989	8,716.8	130.8	5	.00
4.5 Common	A, E	e	34,680.5	12,991	8,698.5	116.5	7	.00

Note: A = additive genetic effects; C = shared environmental effects; E = unique environmental effects including measurement error; AIC = Akaike Information Criterion. The best-fitting model is indicated in bold.

Model-Fitting Analyses

Univariate model fitting. Univariate model-fitting analyses showed that for all three symptoms, a model with additive genetic and unique environmental factors fits the data best (the results of analyses available upon request). Additive genetic and unique environmental factors in the best-fitting model were, respectively, 28% (95% confidence interval [CI]: 25–31%) and 72% (95% CI: 69–75%) for insomnia, 38% (95% CI: 36–39%) and 62% (95% CI: 61–64%) for fatigue, and 34% (95% CI: 32–36%) and 66% (95% CI: 64–68%) for depression. These results were generally consistent with observations made from twin correlations.

Multivariate model fitting. Table 2 presents the results of multivariate model-fitting analyses. The common-pathway model yielded the lowest AIC among the three models we tested. To examine the significance of the common factor structure in the common-pathway model, we dropped all parameters associated with the common factor (A, C, and E; see Model 4.1). This procedure produced a drastic change in χ^2 ($\Delta\chi^2 = 4{,}553.2$, $df = 3$, $p < .0001$), indicating the importance of the common factor to explain the covariation among symptoms of insomnia, fatigue, and depression. Dropping the common and symptom-specific genetic variances (A and a) from the full common-pathway model significantly worsened the fit of the model (Model 4.2). However, a non-significant change in χ^2 occurred when we eliminated shared environmental factors that explain the common factor and symptom-specific variances (C and c; see Model 4.3). From Model 4.3, we further removed the common genetic factor (A, see Model 4.4) and symptom-specific genetic factors (a, see Model 4.5), respectively. All these procedures yielded a significant deterioration in the model fit. Thus, we concluded that Model 4.3 is the best fit. Model 4.3 shows that there exists a latent common factor imposed upon symptoms of insomnia, fatigue, and depression and that genetic and unique environmental factors influence this common factor as well as the variance specific to each of the three symptoms.

Figure 1 shows standardized parameter estimates in the best-fitting model. Squaring the path coefficients in Figure 1 provides the proportions of variance explained. The loadings of three symptoms on the common latent factor were substantial and significant: They were 0.73 for fatigue, 0.62 for insomnia, and 0.58 for depression. These factor loadings strongly support the importance of the latent common factor to explain the association among the three symptoms. Figure 1 also shows that this common factor was influenced by a single set of genes (49%) and unique environments (51%). In addition to the common factor, there were significant variances specific to each symptom. These symptom-specific variances were largely influenced by unique environmental factors. The magnitude of symptom-specific genetic variances tended to be modest.

Table 3 shows common and symptom-specific variances decomposed into genetic and unique environmental components. As expected from Figure 1, genetic and unique environmental factors approximately equally contributed to the variance of the common factor for all three symptoms (0.19 vs. 0.19 for insomnia, 0.26 vs. 0.27 for fatigue, and 0.16 vs. 0.17 for depression). For symptom-specific variances, however, unique environmental variances were much larger than genetic variances for all three symptoms (51% vs. 11% for insomnia, 36% vs. 11% for fatigue, and 49% vs. 18% for depression).

Discussion

The etiology of the comorbidity among symptoms of fatigue, depression, and insomnia is still a controversial issue in spite of great research interests. Our multivariate analyses using a large sample of adult twins yielded three main findings. First, the association among symptoms of fatigue, insomnia, and depression was significant, ranging from 0.35 to 0.44. Second, this association was mediated by a common factor that was explained approximately equally by genetic factors (49%) and unique environmental factors (51%). Finally, in addition to the common variance, there was a significant specific variance in each symptom,

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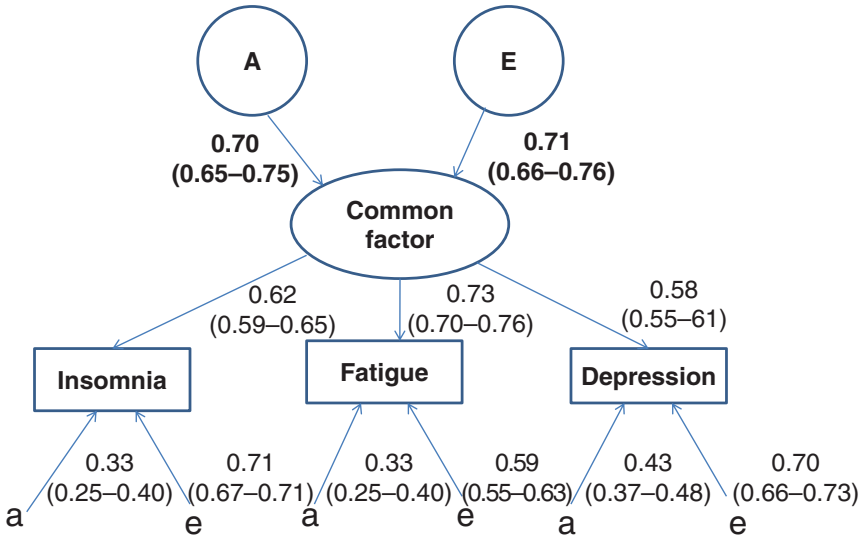

FIGURE 1

(Colour online) Parameter estimates and their 95% CI in the best-fitting common-pathway model.

TABLE 3

Standardized Parameter Estimates in the Best-Fitting Common-Pathway Model and Their 95% CI

	Common variance		Symptom-specific variance	
Symptom	A	E	a	e
Insomnia	0.19 (0.15–0.24)	0.19 (0.15–0.24)	0.11 (0.06–0.16)	0.51 (0.45–0.50)
Fatigue	0.26 (0.21–0.32)	0.27 (0.21–0.33)	0.11 (0.06–0.16)	0.36 (0.30–0.40)
Depression	0.16 (0.13–0.21)	0.17 (0.13–0.21)	0.18 (0.14–0.23)	0.49 (0.44–0.53)

Note: 95% CIs are in parentheses.
A and a = additive genetic variance; E and e = unique environmental variance.

where unique environmental factors were much larger than genetic factors consistently for all three symptoms.

This study established a significant association among symptoms of fatigue, insomnia, and depression when measured concurrently. As we used self-report questions to measure all three symptoms at the same time, one can argue that due to the shared method variance, the magnitude of correlation among three symptoms may have been inflated, leading to biased estimates of model parameters in our study. However, the estimates of heritability for three symptoms in univariate analysis were within the range of those reported in other studies, which may ensure validity of our results.

Our finding of a substantial amount of genetic risk to the variance of the common factor of symptoms of insomnia, fatigue, and depression points out that there may be pleiotrophic genes that act largely in a non-specific way to influence the overall level of the three symptoms, leading to a covariation among these symptoms at the phenotypic level. That is, a common set of genes may put the individual at risk for developing all three symptoms. An implication of our finding is that identification of genes for one of the three symptoms can help search genes for the other symptoms. Recent molecular genetic studies have shown that the serotonin system genes are involved in susceptibilities to all three symptoms (Deuschle et al., 2010; Falkenberg et al., 2011; Uher & McGuffin, 2008), which support our results. In our best-fitting model, symptom-specific genetic variances were relatively small. It would be interesting for future molecular genetic studies to examine patients with a history of all three symptoms and those with a single symptom separately to identify overlapping genes versus symptom-specific genes.

Our study demonstrated that approximately half of the variance of the common factor was explained by unique environmental factors, suggesting that there are environmental risk factors common to all three symptoms. Examples of environmental factors that can increase risk for developing all three symptoms in adulthood include a lack of social support, low social class, experience of abuse in early life, stressful life events, and adversity (Kendler & Baker, 2007). It has been argued that these environmental stressors may precipitate psychiatric illnesses through the mechanism of epigenetic modifications in brain regions (Bell & Spector, 2011; McGowan & Szyf, 2010).

Variance specific to each symptom was explained largely by unique environmental factors, indicating that the distinctions among symptoms of fatigue, insomnia, and depression are made primarily by idiosyncratic environmental experiences than by genes. That is, even if there are shared genetic liabilities for the development of symptoms of depression, fatigue, and insomnia, it is the environmental experiences that play a significant role to determine which symptom is expressed in a vulnerable individual. For

https://doi.org/10.1017/thg.2012.60 Published online by Cambridge University Press

example, it is possible that certain infectious agents can trigger the development of fatigue symptoms, while exerting little influences on the development of depression or insomnia. Although these results clearly point out a need of research to search environmental factors specific to each symptom, one should keep in mind that measurement error and interaction effects of genes and environment were confounded with the estimates of unique environmental components reported in this study. In general, our results are consistent with a large body of psychiatric illness literature which suggests that the comorbidity among many disorders grouped together is largely due to shared genetic liability, whereas environments have specific effects so that they contribute to making etiological distinctions among the disorders (Kendler et al., 1992).

This study has several limitations. First, as our measures of fatigue, insomnia, and depression symptoms were based on short, self-report questions rather than clinical diagnosis, one can argue that our measures may be broad and imprecise. However, because symptom questions in our study were independent from each other, the correlation among three symptom scores found in our study may reflect a real co-occurrence rather than an artifact resulting from overlapping definition criteria for depression, fatiguing illnesses, and insomnia. If we rely on clinical diagnosis, the comorbidity can be inflated due to overlapping symptomatic criteria sets among the disorders. Second, the twin participants in this study were not selected for any specific behavioral trait or health status. Given that fatiguing illnesses have been found to be concurrent with various medical conditions including fibromyalgia (Buchwald, 1996), irritable bowel syndrome (Riedl et al., 2008), sleep apnea (Libman et al., 2009), and migraine headache (Ravindran et al., 2011), some of the twins who scored high on the fatigue questions in our sample may suffer from these conditions rather than CFS. In the future study, twin subjects have to be sorted out a priori by medical conditions to better understand underlying processes of comorbidities. Third, our findings were on the basis of female twins and, therefore, cannot be generalized to adult males because sex differences in genetic and environmental variances in depression and fatigue have been reported in prior studies (Hur, 2008; Kendler et al., 2001). Finally, twins in the present sample had a large age range. We cannot exclude a possibility that the association among three symptoms can vary with age, although we controlled main effects of age using a regression method. To address age effects on the association among symptoms, one should employ a longitudinal design.

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