HHS Public Access

Author manuscript

Chronobiol Int. Author manuscript; available in PMC 2016 February 18.

Published in final edited form as:

Chronobiol Int. 2015 April ; 32(3): 303–309. doi:10.3109/07420528.2014.971366.

A twin-study of genetic contributions to morningness–eveningness and depression

Rosemary Toomey[1], **Matthew S. Panizzon**[2,3], **William S. Kremen**[2,3,4], **Carol E. Franz**[2,3], and **Michael J. Lyons**[1]

[1]Department of Psychological and Brain Sciences, Boston University, Boston, MA, USA

[2]Department of Psychiatry, University of California, San Diego, La Jolla, CA, USA

[3]Twin Research Laboratory, Center for Behavioral Genomics, University of California, San Diego, La Jolla, CA, USA

[4]Center of Excellence for Stress and Mental Health, VA San Diego Healthcare System, San Diego, CA, USA

Abstract

Circadian rhythms are associated with the preference for sleep–wake timing, also known as morningness–eveningness (ME). Both circadian rhythms and ME are influenced by genetic factors. Studies show an association between eveningness and depression. This study investigates the heritability of ME and whether ME and depression share common genetic influences. Study participants (n = 1237) were from the Vietnam Era Twin Study of Aging, a longitudinal study of aging with a baseline in midlife. Participants received the Morningness–Eveningness Questionnaire (MEQ) and the Center for Epidemiologic Studies Depression (CES-D) Scale as part of an extensive neurocognitive and psychosocial assessment. MEQ correlations between members of twin pairs were 0.41 (95% CI 0.31–0.49) for monozygotic (MZ) twins and 0.28 for dizygotic (DZ) twins (95% CI 0.19–0.41). CES-D correlations were 0.38 (95% CI 0.28–0.46) for MZ twins and 0.24 (95% CI 0.14–0.36) for DZ twins. Greater eveningness (i.e. lower MEQ scores) was significantly related to more depression symptoms (phenotypic correlation = −0.15 (95% CI −0.21 to −0.09). In the best fitting model, the heritability estimates are 0.42 for the MEQ and 0.37 for the CES-D. A significant genetic correlation of −0.21 indicated that ME and depression share a significant amount of their underlying genetic variance. The genetic covariance between ME and depression accounted for 59.1% of the phenotypic correlation. Of the CES-D sub-scales, Depressed Mood and Interpersonal Difficulties were significantly heritable, while only Well-Being had a significant genetic correlation with ME. ME and depression are both heritable (ME 0.42, depression 0.37) and share common genetic factors, suggesting an overlap in etiology and

Correspondence: Rosemary Toomey, 648 Beacon Street, 2nd Floor, Boston, MA 02215, USA. Tel: (617) 358-2037. Fax: (617) 358-1380. toomey@bu.edu.

DECLARATION OF INTEREST

This work was supported by National Institute on Aging Grants R01 AG018386, AG022381, and AG022982 (to William S. Kremen), R01 AG018384 (to Michael J. Lyons). This material was, in part, the result of work supported with resources of the VA San Diego Center of Excellence for Stress and Mental Health Healthcare System. The content is solely the responsibility of the authors and does not necessarily represent official views of the NIA, NIH, or VA. The Cooperative Studies Program of the U.S. Department of Veterans Affairs provided financial support for development and maintenance of the Vietnam Era Twin Registry.

the relevance of circadian rhythms to depression. Further study of this relationship may help elucidate etiological factors in depression and targets for treatment.

Keywords

Circadian rhythms; depression; diurnal preference; morningness–eveningness; genetic; twin studies; VETSA

INTRODUCTION

Circadian rhythms are biological phenomena observed in many organisms. They represent endogenous rhythmicity, but can be influenced by exogenous factors. In humans, endogenous rhythms are noted in body temperature, hormone levels, number of immune cells in the blood, cortisol, melatonin and the sleep–wake cycle (Vink et al., 2001). Exogenous factors affecting these rhythms include the light–dark cycle, level of physical activity, temperature changes, time cues, (Czeisler et al., 1981; Kerkhof, 1985) and seasonal changes (Kloppel, 1982). The human trait of morningness–eveningness (ME) represents an individual's preference for sleep–wake timing that is thought to reflect endogenous circadian rhythm. The ME trait is colloquially reflected in the language of being a "lark" versus an "owl". Larks are those who get up easily and are more alert in the morning and fall asleep easily at night. In contrast, owls can sleep later in the morning and go to bed later, and are more alert in the evening.

The first attempt to measure ME was a questionnaire developed in Sweden in 1900. By 1976, Horne and Ostberg revised earlier questionnaires and developed an English language ME questionnaire (MEQ). The MEQ predicts undisturbed sleeping habits (Drennan, 1991), but is independent of sleep duration (Horne & Ostberg, 1976). ME is significantly related to various endogenous rhythms: body temperature (Dunlap, 1996; Reppert & Sauman, 1995), blood pressure and heart rate (Kerkhof, 1985; Wuth, 1931), and cortisol levels (Bailey & Heitkemper, 2001).

Animal research has defined the structure and function of a circadian clock gene in mice (Ishida et al., 1999; King et al., 1997; Vitaterna et al., 1994) and shown that mice with a mutant clock gene show an eveningness pattern of diurnal rhythm of body temperature, spontaneous activity and wake duration, while mice without the mutant gene show the morning preference (Sei et al., 2001). Human clock genes are related to MEQ (Mishima et al., 2005) and to familial advanced sleep phase syndrome (FASPS) (Toh et al., 2001), a disorder characterized by persistent early evening sleep onset and early morning awakening with a corresponding shift in both melatonin circadian rhythms and morningness (Reid et al., 2001). Vanselow et al. (2006) discovered that the mutated clock gene PERIOD2 characterizes many cases of FASPS. Thus, in mammals, ME is linked to the molecular basis of the circadian clock system.

Studies have found that higher levels of eveningness are associated with greater depression (Chelminski et al., 1999; Drennan, 1991; Hidalgo et al., 2009; Merikanto et al., 2013), but it is as yet unclear whether eveningness is a consequence of the depressive state, a premorbid

vulnerability factor, or whether they are simply co-occurring phenomena. Corruble et al. (2014) found that a change toward morningness occurred when treating depression with the medication agomelatine. Furthermore, morningness at baseline was an independent predictor of positive response to the treatment. Kitamura et al. (2010) found that extreme evening type was associated with an increased incidence of depressive states while the extreme morning type had the opposite association, and that these associations were independent of nocturnal awakening, subjective sleep quality, and daytime sleepiness. Taillard et al. (1990) found that the circadian rhythm of heart rate might represent a chronobiological marker of some depressions. Others have demonstrated an increased variance in circadian temperature phase in depressives compared to controls (Kripke et al., 1979; Tsujimoto et al., 1990).

Evidence shows that when examined independently, both depression and ME are genetically influenced. For ME, Drennan et al. (1992) found a heritability of 0.56 for males and 0.48 for females (mean age = 42) using the MEQ in twins. This was replicated by Hur et al. (1998) using an abbreviated MEQ (13 items) in a larger sample in their mid-forties (heritability 0.54). Vink et al. (2001) examined adolescent twins, their parents, and a sample of older twins using one ME question: “Are you a morning-active person or an evening-active person?” Heritability was 0.44 for the adolescents and 0.47 for the older subjects in their mid-forties. The correlation of monozygotic (MZ) pairs was more than twice the correlation of dizygotic (DZ) twin pairs, suggesting the possibility that the genes influencing this trait may not operate in an additive manner. The genetic correlation –which reflects the degree of shared genetic variance (Carey, 1988) – between adolescent twins and their parents was estimated at 0.30, suggesting that different genes for ME may be expressed as people age. Koskenvuo et al. (2007) examined 2836 adult MZ twin pairs and 5917 like-sexed DZ pairs on one ME question. The overall heritability estimate, including both additive (0.12) and dominance (0.38) effects was 0.50, similar to that of older adults in the Vink et al. study. Heritability estimates were similar for young and old and males versus females, although eveningness prevalence decreased with age. In a Hutterite family sample, Klei et al. (2005) found heritability of 0.23 using the 13-item MEQ. Using a twin sample ranging in age from 19 to 93, Barclay et al. (2014) demonstrated that additive genetic influences on ME are attenuated in middle age (34%), in comparison to both younger and older adulthood (44%), perhaps reflecting the increased importance of work, family life, and social factors during middle adulthood. Jones et al. (2007) examined age related changes in the role of PER3 on ME in a sample of adults (age 18–50+). Frequencies of the PER3 4- and 5-repeat alleles were examined in separate age groups for those with extreme diurnal preference. The 4-repeat allele was significantly more frequent in evening types, and the 5-repeat allele more frequent in morning types, but the strength of this association attenuated with age and was significant only in the youngest group (18–29 years).

The current study aims to replicate the findings of a genetic influence on ME using the full MEQ in a larger, older sample than previously examined. In addition, we sought to examine whether there are shared genetic influences between ME and depressive symptoms. Our sample is both narrower in age range and older than other samples examined to date. Given the longitudinal nature of the study, we will have useful data for later assessments to evaluate the degree to which ME is affected by aging.

MATERIALS AND METHODS

Participants

Data collection began in 2003 for the Vietnam Era Twin Study of Aging (VETSA), a longitudinal study of aging with baseline in middle age (Kremen et al., 2006, 2013). Study participants were from the Vietnam Era Twin (VET) Registry, a population-based sample of male-male twin pairs living throughout the United States. VET Registry members were born between 1939 and 1957, served in the military at some point from 1965 to 1975, and are representative of all veterans from the Vietnam War era on a variety of socio-demographic variables (Eisen et al., 1989; Goldberg et al., 1987). In the early 1990s approximately 3300 VET Registry twin pairs participated in a study of psychological health (Tsuang et al., 2001). In the present study, we randomly selected from those twin pairs who had participated in that study. In total, 1237 individuals participated in wave 1 of the VETSA. Participants were evaluated at Boston University or the University of California San Diego, or in select cases, research assistants conducted assessments in the participant's home city. Zygosity for 92% of the sample was determined by analysis of 25 satellite markers obtain from blood samples. For the remainder of the sample zygosity was determined by a combination of questionnaire and blood group typing (Eisen et al., 1989). Within the VETSA sample, a comparison of these two approaches has demonstrated a 95% agreement rate. The present study utilized data from 1231 of the 1237 VETSA participants for whom complete data were available: 344 monozygotic (MZ) pairs, 264 dizygotic (DZ) pairs, and 15 unpaired twins. Participants ranged in age from 51 to 60 (Mean = 55.4, SD = 2.5). The average number of years of education at time of assessment was 13.8 (SD = 2.1; Range: 8–20).

Measures

Morningness–eveningness Questionnaire—The Morningness–eveningness Questionnaire (MEQ) is a self-report measure consisting of 19 questions assessing tendencies toward morningness versus eveningness (Horne & Ostberg, 1976). Most of the questions are forced choice, with answers indicating morning versus evening preferences. A few questions use a time scale, requiring the participant to indicate which hours of the day are preferable for waking, going to bed, or engaging in work-related activities. Each question is assigned a weight and the scores for all questions are added to create a continuous index of ME toward preferred timing of behavior. Low scores reflect more of an evening orientation whereas high scores reflect a morning orientation. Data can also be summarized into five classification categories: definite morning type, moderate morning type, neither type, moderate evening type, and definite evening type. In the present study, MEQ data were omitted from 6 individuals who either did not complete the questionnaire, or left more than one of the items missing. In 25 cases the participant did not answer 1 of the 19 items; therefore, we prorated the missing response using the mean of 18 completed items.

Center for Epidemiologic Studies Depression Scale—The Center for Epidemiologic Studies Depression Scale (CES-D) is a validated and reliable 20-item, self-report scale designed to detect the presence of current depressive symptoms (Radloff, 1977). Scores range from 0 to a high of 60, with higher scores indicating more severe depressive

symptoms. A standard cutoff score of greater than or equal to 16 has a sensitivity of about 80% and a specificity of about 73%, compared with a structured clinical interview for major depression (Mulrow et al., 1995). The CES-D includes four sub-scales: Somatic Complaints (sometimes also referred to as psychomotor retardation), Depressed Mood, Well-Being (sometimes referred to as positive affect, in contrast with negative affect), and Interpersonal difficulties.

Data analysis

Within the twin design, the variance of any trait is accounted for by additive genetic effects (A), common or shared environmental effects (C) and unique or unshared environmental effects (E) that are incorporated into what are referred to as ACE models (Eaves et al., 1978; Neale & Cardon, 1992). Since MZ twins generally share 100% of their genes, they correlate perfectly in terms of the additive genetic influence. DZ twins, on the other hand, share on average 50% of their segregating DNA, resulting in correlations of roughly 0.50 for additive genetic influences. The common or shared environmental factors, aspects of the environment that make twins more similar to one another, are assumed to be equal and not affected by the zygosity of the twins. All other sources of variation in a trait are subsumed under the unique environmental variance, including variance attributable to measurement error.

In order to determine the magnitude of genetic and environmental influences on ME, depressive symptoms, and their degree of genetic and environmental relatedness, we used the maximum-likelihood based structural equation modeling package OpenMx (Boker et al., 2011). Specifically, we fit a bivariate Cholesky decomposition to the data in order to estimate the contribution of genetic and environmental factors to the variance of each phenotype, as well as the degree of genetic and environmental covariance between the phenotypes. The covariance estimates were then used to calculate the genetic and environmental correlations between ME and depressive symptoms. Genetic and environmental correlations indicate the degree to which the genetic and environmental determinants of one phenotype are predictive of the determinants of another (Carey, 1988). In order to maximize our power to detect significant genetic influences, as well as significant genetic and environmental correlations between ME and depressive symptoms, both phenotypes were examined as continuous measures.

Model fit was evaluated using the likelihood-ratio chi-square test (LRT), which is calculated as the difference in the −2 log likelihood (−2LL) of the model in question relative to that of a fully saturated model. The saturated model recaptures the means, variances and covariances of the data perfectly, and served as a standard against which each genetically informative model was compared. The LRT is distributed as a chi-square (χ^2) with degrees of freedom equal to the difference in the number of parameters between the two models. Non-significant LRT values ($p>0.05$) indicate that a model does not result in a significant change in fit relative to the saturated model, and can therefore be considered as an accurate representation of, or good fit to, the data. The Akaike Information Criterion (AIC) was used as an additional indicator of goodness-of-fit (Akaike, 1987). Calculated as the LRT value

minus twice the difference in degrees of freedom, smaller AIC values represent a better balance on the part of the model between goodness-of-fit and parsimony.

RESULTS

Total scores on the MEQ ranged from 30 to 80 (Mean = 60.3, SD = 8.1). The majority of participants (55.2%) defined themselves as moderate morning types, with only 1 participant falling into the definite evening classification (see Table 1 for a complete breakdown). A small but significant relationship was observed between the age of the participants and the self-reported level of ME ($r = 0.09$, $p<0.01$) with increasing age associated with greater morningness. MEQ correlations between members of twin pairs were 0.41 (95% CI 0.31–0.49) for monozygotic (MZ) twins and 0.28 for dizygotic (DZ) twins (95% CI 0.19–0.41).

Total scores on the CES-D ranged from 0 to 52 (Mean = 8.3, SD = 8.3). Based on the cutoff score of greater than or equal to 16 on the CES-D, 185 individuals (15% of the sample) met the criterion for major depression. As with the total score on the MEQ, a small but significant correlation with age was observed ($r = -0.11$, $p<0.001$) with increasing age associated with fewer symptoms of depression. CES-D correlations between members of twin pairs were 0.38 (95% CI 0.28–0.46) for MZ twins and 0.24 (95% CI 0.14–0.36) for DZ twins.

Scores from both the MEQ and the CES-D were mildly to moderately skewed and required transformation prior to formal twin analyses (MEQ, square-root transformation; CES-D, log transformation). Preliminary univariate analysis of each phenotype revealed that ACE models for both the MEQ total score and CES-D total score resulted in non-significant changes in fit relative to univariate saturated models. We did not examine models that included non-additive genetic influences because the MZ correlations were less than double the DZ correlations in the case of both the MEQ and CES-D and thus, there could not be any non-additive genetic effects.

Table 2 presents the standardized variance components derived from the full ACE bivariate Cholesky, as well as a reduced AE Cholesky in which the nonsignificant C influences were fixed to zero. Both models were a good fit relative to the saturated model (ACE Cholesky: LRT = 21.39, ΔDF = 17, $p = 0.21$; AE Cholesky: LRT = 23.15, ΔDF = 20, $p = 0.28$); however, the AE Cholesky possessed the smaller AIC value (1886.71 versus 1890.94). In the ACE model, additive genetic influences accounted for 30% of the variance in ME (95% CI = 0.03–0.49, significant), and 24% of the variance in depressive symptoms (95% CI = 0.00–0.44). Common environmental influences accounted for 11% and 12% of the variance, respectively; however, neither estimate was significant based on the 95% confidence intervals. In the AE model, the magnitude of the additive genetic influences was 0.42 for MEQ and 0.37 for CES-D, both significant values.

Genetic and environmental correlations between ME and depressive symptoms are presented in Table 3. At the phenotypic level, total scores on the MEQ and CES-D were significantly negatively correlated with one another, $r_p = -0.15$ (95% CI = −0.21 to −0.09). In other words, being more eveningness prone was related to more depressive symptoms.

Despite the significant phenotypic correlation, in the ACE Cholesky neither the genetic, common environmental, nor unique environmental correlations were significant based on 95% confidence intervals. Genetic factors nevertheless accounted for roughly 45.6% of the observed phenotypic correlation. In the AE Cholesky, there was a significant genetic correlation, $r_g = -0.21$ (95% CI = −0.37 to −0.04). The genetic contribution to the observed phenotypic correlation was 59.1%. As with the previously described standardized variance components, the estimates of genetic influence derived from the AE model are likely biased by the presence of common environmental influences, making them appear larger than they really are.

We conducted post hoc analyses because of the possibility that some aspects of depression as measured by the CES-D may be more heritable than others and may be more related to ME, such as the somatic symptoms of depression. The four sub-scales of the CES-D include: Somatic Complaints (psychomotor retardation), Depressed Mood, Well-Being (positive affect), and Interpersonal Difficulties. We found that the sub-scales of Depressed Mood (0.32; 95% CI 0.09–0.42) and Interpersonal Difficulties (0.24; 95% CI 0.02–0.33) were significantly heritable. Somatic Complaints had the lowest heritability estimate of 0.03 (95% CI 0.00–0.31), with Well-Being at 0.26 (95% CI 0.00–0.35), but with a confidence interval that was not significant. No sub-scale had a significant genetic correlation with MEQ in the bivariate ACE Cholesky decomposition, while Well-Being had a significant genetic correlation with MEQ in the AE bivariate Cholesky (−0.23; 95% CI −0.43 to −0.03). The Well-Being scale included 4 items reflecting feeling as good as others, being hopeful about the future, being happy and enjoying life.

DISCUSSION

We found a heritability estimate of 0.42 for the MEQ, which is comparable to estimates from other studies (0.56, Drennan et al., 1992; 0.54, Hur et al., 1998; 0.44, Vink et al., 2001; 0.50, Koskenvuo et al., 2007). None of the best fitting models identified by Hur et al., Vink et al., and Koskenvuo et al. included the common or shared environment, similar to our model. All of these samples included women, but none of the best fitting models allowed parameters to vary by sex. Our heritability estimate for depressive symptoms (0.37) is quite similar to our heritability of 0.36 using diagnoses based on clinical interview and a larger sample that we previously published and was the largest twin study of major depression in men (Lyons et al., 1998), and to our estimates using the CES-D scale (Franz et al., 2011, 2012) and slightly higher than the heritability of 0.29 in men reported by Kendler et al. (2006).

To our knowledge, this is the first study to examine the genetic relationship between ME and depressive symptoms. Our current findings replicate previous phenotypic findings by showing a significant relationship between depression and eveningness, using both continuous and categorical measures of depression. While only 2.2% of our sample was in the categories of “moderate evening type” or “definite evening type”, these low proportions are similar to that found by Evans et al. (2011) in their male sample Old Order Amish community in Lancaster County, Pennsylvania (mean age of 41.9 and only 1% being moderate or definite evening types).

In the present study, familial factors accounted for 59.1% of observed phenotypic correlation between MEQ and depressive symptoms in the AE model and genetic factors accounted for 45.6% of the observed phenotypic correlation between MEQ and depressive symptoms in the ACE model. The fact of shared genetic variance between ME and depressive symptoms and the relationship of both of these traits to circadian rhythms suggests that some endogenous aspect of circadian rhythms or, alternatively, a genetic vulnerability to exogenous factors that influences the expression of circadian rhythms (e.g. seasons) is what is shared genetically between these two traits.

Drennan et al. (1991) found multimodality in the distribution of the MEQ in their depressed group from a clinical sample, but a normal distribution in controls, suggesting there may be different subgroups of depressives in regard to their circadian functioning. In contrast, we found a normal distribution of MEQ in our population-based depressed group. Nevertheless, depression may be characterized by increased variability of circadian rhythms such as body temperature (Kripke et al., 1979; Tsujimoto et al., 1990). For example, Taillard et al. (1990) found that the circadian rhythm of heart rate might represent a chronobiological marker for some, but not all, depressions. The most reproduced genetic associations with chronotype has been the variable number tandem repeat (VNTR) polymorphism in PER3 (Adan et al., 2012), but the literature has identified a somewhat different pattern of associations of circadian rhythm with unipolar as compared to bipolar mood disorders, with the following genes of note as reviewed by Etain et al. (2011): the promoter region of AANAT (arylalkylamine Nacetyltransferase), CRY1, NPAS2, ASMT (Acetyl Serotonin Methyl Transferase, the rate-limiting enzyme for melatonin synthesis), TIMELESS, NR1D1, CRY2, and the melatonin receptor 2 gene. Further exploration of how these genes relate to ME in unipolar depression would be useful.

In exploratory analyses to evaluate CES-D subscales, we found that Depressed Mood and Interpersonal Difficulties were significantly heritable, while Well-Being had a significant genetic correlation with MEQ in the AE bivariate Cholesky. Gatz et al. (1992) reported that their older cohort were more likely to indicate an absence of feelings of well-being compared to their younger cohort, and nonshared environmental variances accounted for 80% of the variance on well-being in the older cohort. Hasler et al. (2010) found that increasing eveningness was associated with greater depression, lower sensitivity of the Behavioral Activation System, and lower positive affect, but was not directly associated with negative affect. They concluded that behavioral activation and positive affect mediated the effects of ME on depression. Further research is needed to explore the relationship between specific types of depressive symptoms and ME.

It must be acknowledged that we cannot know if our results are generalizable to women. Our sample is all male and of a restricted age range and thus, our results may not apply to females or to younger or older adults. We also note that although the C estimates were small and nonsignificant, dropping C influences in our AE models may have slightly inflated the heritability estimates. The true heritabilities may, therefore, lie somewhere in between the estimates based on the ACE and AE models. In summary, we replicated the significant heritability of both ME and depressive symptoms and the finding that people with more of a tendency toward eveningness are more likely to have depressive symptoms than are morning

types. In a novel analysis, we found that the significant genetic correlation between ME and depressive symptom (−0.21) accounted for 59.1% of the phenotypic correlation between ME and depressive symptoms, suggesting an overlap of the genetic influences on the two traits, and the relevance of circadian rhythms to depression at the genetic level.

Acknowledgments

The authors gratefully acknowledge the continued cooperation and participation of the members of the VET Registry and their families. Without their contribution this research would not have been possible. We also appreciate the time and energy of many staff and students on the VETSA projects.

References

Adan A, Archer SN, Hidalgo MP, et al. Circadian typology: A comprehensive review. Chronobiol Int. 2012; 29:1153–75. [PubMed: 23004349]

Akaike H. Factor analysis and AIC. Psychometrika. 1987; 52:317–32.

Bailey SL, Heitkemper MM. Circadian rhythmicity of cortisol and body temperature: Morningness–eveningness effects. Chronobiol Int. 2001; 18:249–61. [PubMed: 11379665]

Barclay NL, Watson NF, Buchwald D, Goldberg J. Moderation of genetic and environmental influences on diurnal preference by age in adult twins. Chronobiol Int 2014. 2014; 31:222–31.

Boker S, Neale MC, Maes HH, et al. OpenMx: An open source extended structural equation modeling framework. Psychometrika. 2011; 76:306–17. [PubMed: 23258944]

Carey G. Inference about genetic correlations. Behav Genet. 1988; 18:329–38. [PubMed: 3219111]

Chelminski I, Ferraro FR, Petros TV, Plaud JJ. An analysis of the “eveningness-morningness” dimension in “depressive” college students. J Affect Disord. 1999; 52:19–29. [PubMed: 10357014]

Corruble E, Frank E, Gressier F, et al. Morningness–eveningness and treatment response in major depressive disorder. Chronobiol Int. 2014 Oct 15.31:283–9. [PubMed: 24128195]

Czeisler CA, Richardson GS, Zimmerman JC, et al. Entrainment of human circadian rhythms by light–dark cycles: A reassessment. Photochem Photobiol. 1981; 34:239–47. [PubMed: 7267730]

Drennan MD, Selby J, Kripke DF, et al. Morningness/eveningness is heritable. Soc Neurosci Abstracts. 1992; 18:196.

Drennan MD. The effects of depression and age on the Horne–Ostberg morningness–eveningness score. J Affect Disord. 1991; 23:93–8. [PubMed: 1753041]

Dunlap JC. Genetics and molecular analysis of circadian rhythms. Annu Rev Genet. 1996; 30:579–601. [PubMed: 8982466]

Eaves LJ, Last KA, Young PA, Martin NG. Model-fitting approaches to the analysis of human behavior. Heredity. 1978; 41:249–320. [PubMed: 370072]

Eisen S, Neuman R, Goldberg J, et al. Determining zygosity in the Vietnam Era Twin Registry: An approach using questionnaires. Clin Genet. 1989; 35:423–32. [PubMed: 2736790]

Etain B, Milhiet V, Bellivier F, Leboyer M. Genetics of circadian rhythms and mood spectrum disorders. Eur Neuropsychopharmacol. 2011; 21:S676–82. [PubMed: 21835597]

Evans DS, Snitker S, Wu SH, et al. Habitual sleep/wake patterns in the Old Order Amish: Heritability and association with non-genetic factors. Sleep. 2011; 34:661–9. [PubMed: 21532960]

Franz CE, Panizzon MS, Eaves LJ, et al. Genetic and environmental multidimensionality of well- and ill-being in middle aged twin men. Behav Genet. 2012; 42:579–91. [PubMed: 22484556]

Franz CE, York TP, Eaves LJ, et al. Adult romantic attachment, negative emotionality, and depressive symptoms in middle aged men: A multivariate genetic analysis. Behav Genet. 2011; 41:488–98. [PubMed: 21213033]

Gatz M, Pederson NL, Plomin R, et al. Importance of shared genes and shared environments for symptoms of depression in older adults. J Abnorm Psychol. 1992; 101:701–8. [PubMed: 1430610]

Goldberg J, True W, Eisen S, et al. The Vietnam Era Twin (VET) Registry – Ascertainment bias. Acta Genet MedGemellol. 1987; 36:67–78.

Hasler BP, Allen JJ, Sbarra DA, et al. Morningness–eveningness and depression: Preliminary evidence for the role of the behavioral activation system and positive affect. Psychiatry Res. 2010; 176:166–73. [PubMed: 20132992]

Hidalgo MP, Caumo W, Posser M, et al. Relationship between depressive mood and chronotype in healthy subjects. Psychiatry Clin Neurosci. 2009; 63:283–90. [PubMed: 19566758]

Horne JA, Ostberg O. A self-assessment questionnaire to determine morningness–eveningness in human circadian rhythms. Int J Chronobiol. 1976; 4:97–110. [PubMed: 1027738]

Hur Y, Bouchard TJ Jr, Lykken DT. Genetic and environmental influence on morningness–eveningness. Pers Individual Differences. 1998; 25:917–25.

Ishida N, Kaneko M, Allada R. Biological clocks. Proc Natl Acad Sci USA. 1999; 96:8819–20. [PubMed: 10430850]

Jones KH, Ellis J, von Schantz M, et al. Age-related change in the association between a polymorphism in the PER3 gene and preferred timing of sleep and waking activities. J Sleep Res. 2007; 16:12–16. [PubMed: 17309758]

Kendler KS, Gatz M, Gardner CO, Pedersen NL. A Swedish national twin studyof lifetime major depression. Am J Psychiatry. 2006; 163:109–14. [PubMed: 16390897]

Kerkhof GA. Inter-individual differences in the human circadian system: A review. Biol Psychol. 1985; 20:83–112. [PubMed: 3888298]

King DP, Zhao Y, Sangoram AM, et al. Positional cloning of the mouse circadian clock gene. Cell. 1997; 89:641–53. [PubMed: 9160755]

Kitamura S, Hida A, Watanabe M, et al. Evening preference is related to the incidence of depressive states independent of sleep–wake conditions. Chronobiol Int. 2010; 27:1797–812. [PubMed: 20969524]

Klei L, Reitz P, Miller M, et al. Heritability of morningness–eveningness and self-report sleep measures in a family-based sample of 521 Hutterites. Chronobiol Int. 2005; 22:1041–54. [PubMed: 16393707]

Kloppel, HB. Circannual changes of the circadian phase position in man. In: Hildebrandt, G.; Hensel, H., editors. Biological adaptation. Stuttgart: Thieme; 1982. p. 104-07.

Koskenvuo M, Hublin C, Partinen M, et al. Heritability of diurnal type: A nationwide study of 8753 adult twin pairs. J Sleep Res. 2007; 16:156–62. [PubMed: 17542945]

Kremen W, Thompson-Brenner H, Leung Y, et al. Genes, environment, and time: The Vietnam Era Twin Study of Aging (VETSA). Twin Res Hum Genet. 2006; 9:1009–22. [PubMed: 17254445]

Kremen WS, Franz CE, Lyons MJ. VETSA: The Vietnam Era Twin Study of Aging – Addendum. Twin Res Hum Genet. 2013; 16:403. [PubMed: 23394194]

Kripke DF, Mullaney DJ, Atkinson MS, et al. Circadian rhythm phases in affective illnesses. Chronobiologia. 1979; 6:367–75.

Lyons MJ, Eisen SA, Goldberg J, et al. A registry-based twin study of depression in men. Arch Gen Psychiatry. 1998; 55:468–72. [PubMed: 9596050]

Merikanto I, Lahti T, Kronholm E, et al. Evening types are prone to depression. Chronobiol Int. 2013; 30:719–25. [PubMed: 23688117]

Mishima K, Tozawa T, Satoh K, et al. The 3111T/C polymorphism of hClock is associated with evening preference and delayed sleep timing in a Japanese population sample. Am J Med Genet B Neuropsychiatr Genet. 2005; 133:101–4. [PubMed: 15578592]

Mulrow CD, Williams J Jr, Gerety MB, et al. Case-finding instruments for depression in primary care settings. Ann Intern Med. 1995; 122:913–21. [PubMed: 7755226]

Neale, MC.; Cardon, LR. Methodology for genetic studies of twins and families. Dordrecht, The Netherlands: Kluwer; 1992.

Radloff LS. The CES–D Scale: A self-report depression scale for research in the general population. Appl Psychol Meas. 1977; 1:385–401.

Reid KJ, Chang A, Dubocovich ML, et al. Familial advanced sleep phase syndrome. Arch Neurol. 2001; 58:1089–94. [PubMed: 11448298]

Reppert SM, Sauman I. Period and timeless tango: A dance of two clock genes. Neuron. 1995; 15:983–6. [PubMed: 7576665]

Sei H, Oishi K, Morita Y, Ishida N. Mouse model for morningness/eveningness. Neuroreport. 2001; 12:1461–4. [PubMed: 11388430]

Taillard J, Sanchez P, Lemoine P, Mouret J. Heart rate circadian rhythm as a biological marker of desynchronization in major depression: A methodological and preliminary report. J Chronobiol Int. 1990; 7:305–16.

Toh KL, Jones CR, He Y, et al. An hPer2 phosphorylation site mutation in familial advanced sleep phase syndrome. Science. 2001; 291:1040–3. [PubMed: 11232563]

Tsuang MT, Bar JL, Harley RM, Lyons MJ. The Harvard Twin Study of Substance Abuse: What we have learned. Harv Rev Psychiatry. 2001; 9:267–79. [PubMed: 11600486]

Tsujimoto T, Yamada N, Shimoda K, et al. Circadian rhythms in depression. Part II: Circadian rhythms in inpatients with various mental disorders. J Affect Disord. 1990; 18:199–210. [PubMed: 2139065]

Vanselow K, Vanselow JT, Westermark PO, et al. Differential effects of PER2 phosphorylation: Molecular basis for the human familial advanced sleep phase syndrome (FASPS). Genes Dev. 2006; 20:2660–72. [PubMed: 16983144]

Vink JM, Groot AS, Kerkhof GA, Boomsma D. Genetic analysis of morningness and eveningness. Chronobiol Int. 2001; 18:809–22. [PubMed: 11763988]

Vitaterna MH, King DP, Chang A, et al. Mutagenesis and mapping of a mouse gene, clock, essential for circadian behavior. Science. 1994; 264:719–25. [PubMed: 8171325]

Wuth O. Klinik und therapie der schlafstorungen. Schweiz Med Wochenschr. 1931; 61:833–7.

TABLE 1

Descriptive statistics of the VETSA sample.

	Mean	SD	*n*
Age	55.4	2.5	1231
Years of education	13.8	2.1	1231
MEQ total score	60.3	8.1	1231
CES-D total score	8.3	8.3	1231
	%		n
MEQ Classifications			
Definite morning type	9.8%		121
Moderate morning type	55.2%		680
Neither type	32.8%		403
Moderate evening type	2.1%		26
Definite evening type	0.1%		1
CES-D defined major depression	15%		185

TABLE 2

Standardized variance components from the bivariate Cholesky analysis.

	A	C	E
ACE Cholesky			
ME	**0.30** (0.03; 0.49)	0.11 (0.00; 0.33)	**0.59** (0.51; 0.68)
Depressive symptoms	0.24 (0.00; 0.44)	0.12 (0.00; 0.35)	**0.64** (0.56; 0.73)
AE Cholesky			
ME	**0.42** (0.34; 0.50)	–	**0.58** (0.50; 0.66)
Depressive symptoms	**0.37** (0.29; 0.45)	–	**0.63** (0.55; 0.71)

95% confidence intervals are presented in parentheses under each estimate. Significant results are in bold font. All variables are adjusted for the effects of age. A = Additive Genetic Influences; C = Common/Shared Environmental Influences; E = Unique Environmental Influences

TABLE 3

Genetic and environmental correlations between ME and depressive symptoms.

	Correlations			
Model	r_g	r_c	r_e	**Genetic contribution to phenotypic correlation**
ACE Cholesky	−0.24 (−1.0; 1.0)	−0.14 (−1.0; 1.0)	−0.10 (−0.20; 0.00)	45.6%
AE Cholesky	**−0.21** (−0.37; −0.04)	–	−0.10 (−0.19; 0.00)	59.1%

95% confidence intervals are presented in parentheses under each estimate. Significant results are in bold font. All variables are adjusted for the effects of age. r_g = Genetic Correlation; r_c = Common Environment Correlation; r_e = Unique Environment Correlation