Sleep During a Regular Week Night: A Twin-Sibling Study

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Previous genetic investigations of variation in normal sleep have focused on measures that describe sleep over longer periods of time. We undertook a study with the aim of evaluating whether heritability can be found in single-night sleep traits. A classical twin study design of monozygotic and dizygotic twins, enriched with siblings of twins was employed. The study included adult twin pairs and their siblings (N = 813 subjects from 342 families). A subsample of 66 individuals participated twice. For a single night, bedtime, awakening time and subjective sleep quality were assessed using a diary. The diary also assessed smoking, alcohol and coffee consumption, and the subjective evaluation of stress. Resemblance between family members was used to estimate the heritability of bedtime, awakening time, sleep problems and sleep quality as a function of sex. Most sleep measures showed familial clustering, but results differed for men and women. Heritability for bedtime and sleep problems was seen in women; and for awakening time in men. We conclude that heritability can be demonstrated for bedtime and subjective evaluation of even a single night of sleep. The contribution of the genetic make-up is sex specific. In women variance in awakening time is so affected by environmental circumstances, that the genetic contribution to the variance becomes negligible. In contrast, for males, variance in the evening bedtime is so affected by environmental circumstances, that the genetic contribution to the variance becomes negligible.

Keywords: extended twin study, single night sleep, heritability, sleep quality, sleep timing, sex differences

Sleep is a complex state, of which the description requires a large set of behavioral and physiological parameters including, for example, habitual sleep timing, duration, subjective quality, stage distribution and electroencephalo–graphic power spectral density. People differ markedly on these parameters, and not only due to differences in environmental demands.

Genetic involvement has recently become evident in a limited number of sleep *pathologies*. Families have been described with an autosomal dominant mode of inheritance for the delayed or advanced sleep phase syndrome (Ancoli-Israel et al., 2001; Jones et al., 1999; Reid et al., 2001). For an even more limited subset of these familial sleep pathologies, molecular studies have begun to characterize candidate genes involved in the disease. For example, HLA genes may be involved in narcolepsy, sleepwalking and the Kleine-Levin syndrome. In one family with advanced sleep phase syndrome, a PER2 gene mutation was found (Toh et al., 2001). A mutation in the gene encoding the β3 subunit of the $GABA_A$ receptor was reported in a patient with chronic insomnia (Buhr et al., 2002). The best characterization may be for fatal familial insomnia, where a point mutation in the prion protein gene is involved (Montagna et al., 2003). Several reviews give a good overview of the present state of the field (Dauvilliers et al., 2005; Franken & Tafti, 2003; Hamet & Tremblay, 2006; Raizen et al., 2006; Tafti et al., 2005).

Genetic factors that influence individual differences within the range regarded as *normal* sleep are less well characterized. Twin studies provide an important tool to dissect the relative contribution of genetic and environmental factors in the complex phenotypes of normal sleep. For sleep parameters like duration and subjective sleep quality, a heritability (h^2, the proportion of variance explained by the effects of genes) of 0.30 to 0.40 has typically been reported. Heritability values of 0.38 to 0.54 have also been reported for daytime aspects of sleep regulation: daytime sleepiness and fatigue (Roy-Byrne et al., 2002; Watson et al., 2006).

For quantitative parameters derived from the wake electroencephalogram, we have reported heritability estimates up to 0.89, placing such parameters among the most heritable human characteristics (van Beijsterveldt et al., 1996). Recent studies on genetics of sleep in mice strains confirm the superiority of quantitative EEG measures to characterize genetic differences (Dauvilliers et al., 2005). Although twin-

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sib studies that focus on the heritability of sleep parameters based on EEG measures might provide valuable information, polysomnography in a large number of people is a costly endeavor. A preselection of subgroups is therefore commendable. Ideally, only a single night of sleep recording would be performed: the requirement of recording multiple nights would strongly decrease the feasibility of such a large-scale sleep-EEG study. However, given some between-night variability in sleep measures (van Someren et al., 2007), it remains to be investigated whether there is any a priori chance of finding heritability in sleep measures based on information of only a single night; previous studies have used questionnaires that ask about measures during the past weeks or months. We therefore undertook a questionnaire screening on the subjective sleep quality, timing and duration of a single night of sleep in a twin-sibling study, with the primary aim of evaluating whether heritability can be demonstrated in single-night sleep estimates.

The study involved 813 Dutch adult twins and their siblings who are registered with The Netherlands Twin Register. They reported in a diary on the timing and subjective quality of their sleep of the previous night. We analyzed the variation in these measures as a function of genetic and environmental factors. Variation between individuals in complex traits may be caused by differences in genotype and by non-genetic differences ('environment'). The relative contributions of genotype (G) and environment (E) to phenotypic variation can be assessed from data of monozygotic twins and dizygotic twins and siblings (Martin et al., 1997; Boomsma et al., 2002; Posthuma & Boomsma, 2000).

Methods

Participants

There were 813 participants (548 twins and 265 siblings; 304 men and 509 women) who provided data on a single-night's sleep; 66 individuals participated twice, on two separate occasions, on average 3 years and 4 months apart. Participants were recruited from the Netherlands Twin Register (NTR; Boomsma et al., 2006) for a study of cardiovascular risk factors that also included assessment of sleep quality and timing.

Participants came from 342 families. There were 39 families with one participant, 186 with two, 84 with three, 22 with four, and 7, 2, 1, and 1 family with five, six, seven and eight participants, respectively. The average age of the participants was 31 years (*SD* = 11). There were 311 twin pairs (74 incomplete pairs, in which only one twin participated, and 237 complete pairs) and 31 families in which only siblings took part. Tables 1a and 1b give a complete description of the sample. For 236 same-sex twins zygosity was assessed by DNA typing; for the other pairs it was based on survey information. There were 125 MZ, 109 same-sex DZ and 77 DZ opposite-sex pairs (table 1b). Family members usually took part in the study on separate days. The Ethics Committee of the VU University Medical Centre, Amsterdam approved the study protocol and participants gave written consent.

Table 1a

Number of Participants and Average Age (Mean and Standard Deviation)

	N	Age (mean ± *SD*)
Male twins	200	30.4±10.5
Female twins	348	29.2±10.7
Brothers	104	33.4±12.4
Sisters	161	34.6±11.5

Table 1b

Number of Incomplete and Complete Monozygotic (MZ) and Dizgygotic (DZ) Twin Pairs

	N: Complete/incomplete	Total
MZ Male	40 / 6	46
DZ Male	24 / 9	33
MZ Female	69 / 10	79
DZ Female	55 / 21	76
DZ Opposite sex	49 / 28	77
Total	237 / 74	311

Measures

For a single night, bedtime, awakening time, time in bed and subjective sleep quality were assessed using the Dutch Groningen Sleep Questionnaire (GSQ; de Weerd et al., 2004), which asked for sleeping time and contained 14 items that could be answered on a 2-point scale (1 = *yes* and 2 = *no*). There were 11 items that assessed sleep problems (negative sleep descriptors) and 3 items that assessed how well a person slept the previous night (positive sleep descriptors). A 15th additional item assessed whether someone slept worse because of participation in the study and was included in the factor analysis of the items. Principal component analysis (PCA) showed that the 12 Sleep Problems items clustered together (first principal component accounted for 31% of the variance in the data) and that the 3 Sleep Quality items clustered on a second factor (which accounted for 11% of the variance). The 12 Sleep Problems items and the 3 Sleep Quality items were summed so that each individual was scored on a problem scale and on a sleep quality scale. Because these scales showed highly skewed distributions, the values were rescaled into 4 ordered categories and genetic analyses were carried out on these ordinal data. The polychoric correlation coefficient between the two scales was –0.82. There were 66 participants who participated twice in the study (average interval was 3 years and 4 months). The test–retest stability (polychoric correlation) was 0.56 for sleep problems and

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0.46 for sleep quality, indicating a moderate degree of stability over a longer interval.

Awakening time was scored as the number of minutes after 24:00 hours. Bedtime was scored as 24 × 60 minutes plus or minus the number of minutes after or before 24:00, depending on whether the event occurred after or before 24:00. Time in bed was scored as the interval between bedtime and awakening time. The test–retest Pearson correlations were 0.51, 0.16 and 0.31 for bedtime, awakening time and time in bed, respectively. To explore the validity of the self-reported sleep and awaking times, we exploited a unique feature of the study. For the majority of subjects a simultaneous recording of heart rate and body movement was available (Kupper et al., 2005a; Kupper et al., 2005b). Interactive scoring of the combined body movement and heart rate signals allowed accurate detection of bedtime and awaking time. These objective measures showed high correlations with the self-report data: for bedtime the correlation was 0.79 (N = 716 Ss) and for awaking time the correlation was 0.91 (N = 478).

For all subjects who participated twice in the study, the data from the first assessment were used in the genetic analyses.

The diary also asked about coffee and alcohol consumption and smoking (yes/no) during the day/evening before the assessment of sleep quality and about subjective assessment of stress on a 3 point scale (0 = *less than average*, 1 = *average* and 2 = *more than average*). As relatively few subjects reported high stress levels, these data were recoded into a dichotomous trait (category 0 vs. 1 and 2).

Data Analysis

PCA was carried out in SPSS (SPSS 13, 2004). For the genetic analyses of the variables sleep problems and sleep quality, the resemblance between relatives was assessed with a liability (threshold) model (Falconer, 1989; Neale & Cardon, 1992) which assumes that many genetic and environmental factors contribute to the liability of a trait. The (small) effects of all these factors add up to an underlying normally distributed liability continuum. If a critical value of liability (the threshold) is reached, a person is affected; otherwise, a person is unaffected. Multiple thresholds can be specified if the trait has more than 2 categories. Both for sleep problems and for sleep quality each trait was modeled to have an underlying continuous distribution with 3 thresholds. The thresholds are inferred from the prevalence. The scale of the unobserved liability can be defined in several ways. Here the variance of the residual (unique environment) variance was constrained at one. The continuous variation in liability was decomposed into genetic and non-genetic components. For the genetic analyses of bedtime, awakening time, and time in bed the continuous data were analyzed.

Genetic models specified variation in each trait to be a function of genotype and environment. The additive genetic factor, denoted 'A', represents the additive effects of alleles at a possibly large number of loci. Two environmental factors were considered: 'C', common environmental influences shared by family members and 'E', environmental influences that are not shared by family members and that include measurement error. The significance of additive genetic and common environmental influences was tested by comparing the fit of an AE or CE model to that of the ACE model. Goodness-of-fit of sub-models was assessed by the Akaike Information Criterion (AIC). The mixed and nlmixed procedures of SAS (SAS Institute Inc., 2004) were used for the analyses. Confidence intervals for heritability estimates h^2 were obtained from the delta method applied either directly to the estimate or, in order to keep the interval bounds between zero and one, to the logit transformation $logit\ (h^2) = log\ [h^2 / (1 - h^2)]$, whose interval bounds were transformed back to the original scale.

Models were first fitted separately to data from men and women. The results of these analyses guided the selection of models that were fitted to data from men and women simultaneously. All models contained a sex specific intercept. Models for the simultaneous analyses of data from both sexes contain effects (A, C or both) that were added to the best fitting models of the separate analyses in order to allow tests for male-female covariance.

Results

Figure 1 contains, for men and women separately, the histograms of the distributions of bedtime, awakening time, time in bed, sleep problems and sleep quality. Bedtime was earlier for women and awakening time later. Consequently, time in bed was higher for women than for men. Women report more sleep problems while men more often score in the highest category for sleep quality.

Table 2 summarizes the best fitting models for males and females, based on separate genetic analyses of the data. Table 3 contains the number of parameters and the AIC values for models fitted to data from males and females simultaneously. The lowest AIC value indicates the model that best describes the data.

For *Sleep Problems*, a genetic model without a C component that allowed for sex differences in thresholds (i.e., sex differences in prevalence) and that specified no sex differences in A and E variance components (i.e., equal heritability in males and females) provided the best model and gave a heritability estimate of 0.20, CI bounds .04–.36 for h^2 and .08–.41 for $logit\ (h^2)$.

For *Sleep Quality*, there was no familial resemblance and a model including only E was the best fitting model.

For *Bedtime*, a genetic model that allowed for quantitative sex differences in the contribution of A and E, best fitted the data and gave heritability estimates of 0.14 in men, CI bounds –.07–.35 for h^2 and

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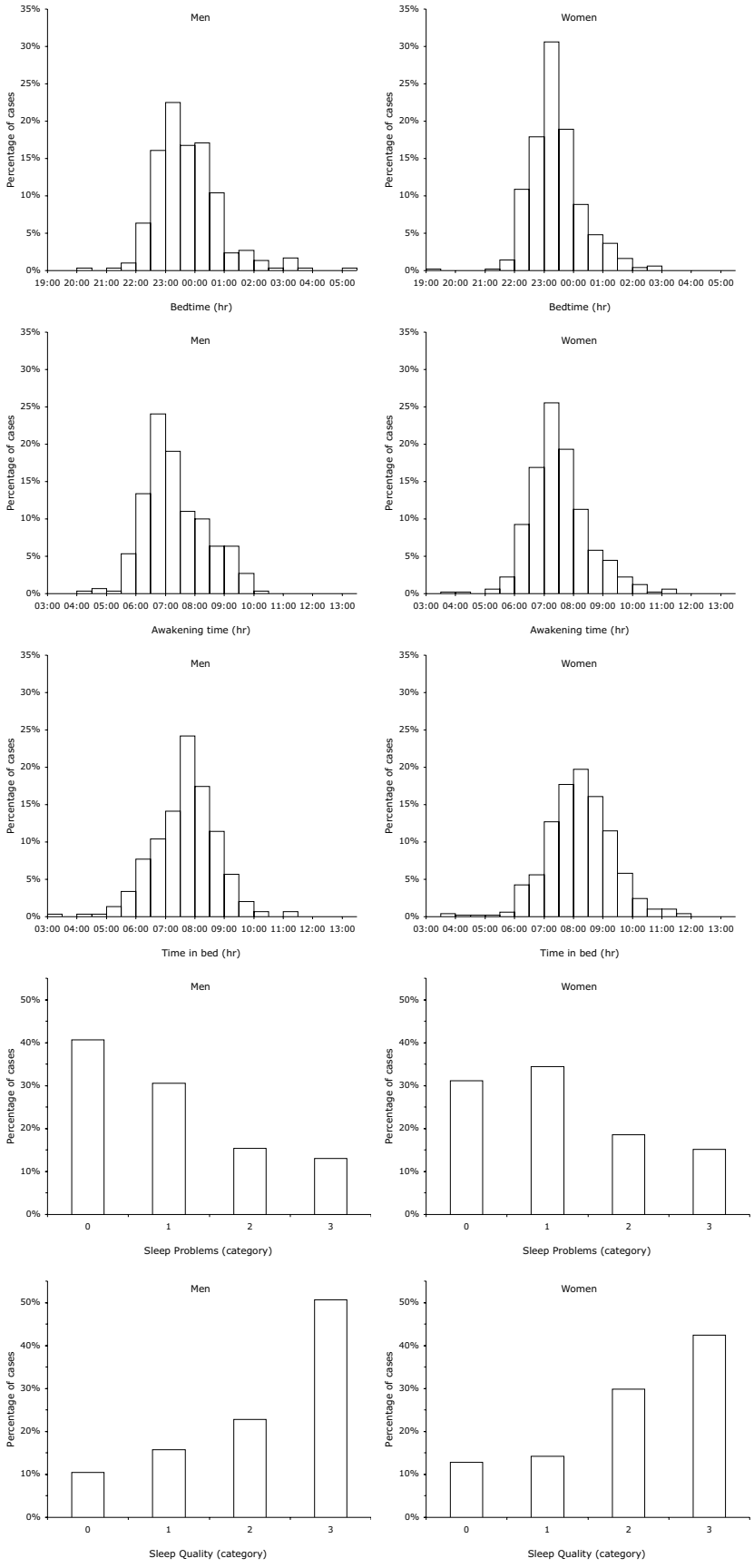

Figure 1

Distributions (in men and women) for bed time, awakening time, time in bed, sleep problems and sleep quality.

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Table 2

Best Fitting Models to Explain Variation in Sleep Quality, Sleep Problems, Bedtime, Awakening Time and Time in Bed in Men and Women

	Sleep quality	Sleep problems	Bedtime	Awakening time	Time in bed
Men	E	E	E	AE	CE
Women	E	AE	AE	CE	CE

Note: E = variation explained by unique environment, A = variation explained by additive genetic effects, C = variation explained by common environment shared by family members. AE or CE indicates a combination of these factors.

.03–.48 for *logit* (h^2), and of 0.34 in women, CI bounds .16–.52 for h^2 and .18–.54 for *logit* (h^2).

For *Awakening Time*, the best model fitted a common C factor for both sexes, sex differences in E and a contribution of A only for males. The male heritability estimate was 0.42, CI bounds .20–.64 for h^2 and .22–.64 for *logit* (h^2). The contribution of C was 0.15 in men and .0.17 in women.

For *Time in Bed*, the best-fitting model included only C and E, indicating zero heritability, both with the same variance for men and women but with C uncorrelated between men and women. The contribution of C accounted for 23% of the variance.

To explore the relatively large contribution of non-genetic factors, we investigated the relation of sleep variables with the use of coffee, nicotine and alcohol the previous night and subjective levels of stress the day before. The number of subjects who had smoked, consumed coffee or alcohol, and who reported experiencing stress are given in Table 4a. The correlation of these variables with sleep quality and timing are given in Table 4b. Coffee use was related to sleep problems and sleep quality. Coffee use was positively related to sleep quality (p = .02) and negatively to sleep problems (p = .04), that is, coffee use (*yes*) was more prevalent in subjects who slept well. For sleep problems, the ratios of the total number of subjects in the two highest sleep problems categories versus the total number of subjects in the two lowest sleep problems categories were .57 for no coffee use and .42 for coffee use. For sleep quality those ratios were 2.18 and 3.07. Nicotine and alcohol use (*yes*) were positively related to Bedtime (p < .001 for both) and to Awakening Time (p = .02 for both); that is, users went to bed later and got up later. Coffee and alcohol use were negatively related to Time in Bed (p = .02 and p < .001, respectively).

Discussion

In spite of considerable night-to-night variation in sleep measures (van Someren, 2007), we show that a moderate part of the variance in sleep measures can still be explained by genetic factors when sleep behav-

Table 3

Goodness-of-Fit (AIC) Values (Upper Part of Table) and Parameter Estimates for the Proportion of Variance Explained by A and/or C

	Sleep quality	Sleep problems	Bedtime	Awakening time	Time in bed
m:ACE; f:ACE (9/-)	—	—	8712.1	8769.0	8929.9
m:AE; f:AE (7/9[e])	2001.4	2107.1	**8706.1**[d]	8769.6	—
AE (-/7[e])	1996.7	**2103.4**			
m:CE ; f: CE (7/9[e])	2002.4	—	8708.2	8772.0	8926.3
m:E; f:A,E (5/-)	—	—	8707.0	—	—
m:E; f:E (4/-)	—	—	8715.3		
m:ACE; f:CE (8/-)	—	—		8769.9	
m:ACE; f:CE (6/-)[f]	—	—		**8765.6**	
m:AE; f:CE (6/-)	—	—		8768.2	
m:CE; f:CE[a] (6/-)	—	—			8924.5
m:CE; f:CE[a, b] (5/-)	—	—			8922.6
m:CE; f:CE (5/-)					8926.9
m:CE; f:CE[a, b, c] (4/-)					**8922.1**
m:E; f:E (-/6[e])	**1996.6**				
Parameter estimates as percentage from best model	A=0 C=0	m:A=0.20	m:A=0.14 f:A=0.34	m:A=0.42 f:A=0 m:C=0.15 f:C=0.17	C=0.23

Note: The lowest AIC value indicates the model that best describes the data (in bold)

[a] r (C_m, C_f) = 0; [b] var (C_m) = var (C_f); [c] var (E_m) = var (E_f); [d] r (A_m, A_f) = .5, Npar = 6; [e] number of parameters for threshold model; [f] common C for males and females

m and *f* refer to effects for males and females.

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Table 4a

Number of Subjects Who Smoked, Consumed Coffee or Alcohol or Reported Stress

	Smoke	Coffee	Alcohol	Stress
No /yes	621 / 178	263 / 537	600 / 197	223 / 512
% yes	22 %	67%	25%	72%

Table 4b

Associations of Nicotine, Coffee and Alcohol Use and Stress Problems the Previous Day With Sleep Problems and Quality (Polychoric Correlations) and With Bedtime, Awakening Time and Bedtime (Pearson correlations)

	Smoke	Coffee	Alcohol	Stress
Sleep problems	–.06	**–.13**	.03	–.04
Sleep quality	–.06	**.14**	–.05	.04
Bedtime	**.13**	**.10**	**.26**	.01
Awakening time	**.09**	–.05	**.06**	–.03
Time in bed	–.04	**–.14**	**–.17**	–.04

Note: Significant values in bold

ior is assessed at a single night. In contrast to previous twin studies, which usually asked for the overall average sleep quality and timing during the last months (Heath et al., 1990; Heath et al., 1998), we specifically assessed the subjective sleep quality and timing of a single night of sleep.

Regarding the timing of sleep, a moderate heritability of 0.34 was found for bedtime in females, but only a marginal heritability of 0.14 in males. On the other hand, a moderate heritability of 0.42 for awakening time was found for men, while no heritability was found in women. Together, these findings suggest a gender-specific contribution of the genetic make-up to sleep timing, which is most marked in the evening for females and most marked in the morning for males. Or, stated differently, if a single night of sleep is assessed in females, variance in the morning rise time is so affected by environmental circumstances, that the genetic contribution to the variance becomes negligible. In contrast, for males, variance in the evening bedtime is so affected by environmental circumstances, that the genetic contribution to the variance becomes negligible. A differential contribution of genes and environment to the sleep timing of males and females has received relatively little attention in previous studies. A gender dissociation may be of interest and warrants further research, given the notion of separate morning ('M') and evening ('E') oscillators in the molecular machinery in the circadian pacemaker in the mammalian suprachiasmatic nucleus (SCN), which is the biological clock of the brain (Daan et al., 2001).

Regarding the subjective evaluation of a single night of sleep, a small proportion of the variance in subjective complaints about sleep (negative sleep descriptors) showed heritability (0.20). No heritability was found in the variance on the sum score of subjective experience of positive sleep descriptors. It is likely that the lack of heritability in the latter factor may be due to the inclusion of only three items in the component Sleep Quality, whereas the negative sleep descriptor component Sleep Problems consisted of the 12 items.

Previous twin studies on the timing of sleep as derived from questions that address the average sleep profile over the last weeks or months report only slightly higher heritability estimates than the present study. Heritability estimates for sleep timing during early development are given in an early report on the Tokyo Twin Cohort Project. Two questions regarded sleeping behavior during the first year of life: its rhythmicity and the time required to fall asleep. Heritability estimates were 0.24 and 0.32 respectively (Ando et al., 2006). Twin studies suggest that the heritability of sleep timing and duration preferences appear to be rather consistent and constant during subsequent development in children, adolescents and younger and older adults, for example, 0.27–0.33 (de Castro, 2002), 0.38–0.45 (Heath et al., 1990), 0.44 (Partinen et al., 1983), 0.45 (Hur, 2007), 0.44–0.48 (Vink et al., 2001) and 0.54 (Hur et al., 1998). Only Klei (2005) found lower heritability estimates, but this was not a twin study but a family study in the closed communion of the Hutterites: a significant 0.12 for Awakening Time and a nonsignificant 0.09 for Bedtime.

Several previous heritability studies also addressed the subjective evaluation of sleep quality. Partinen (1983) reported a heritability for sleep quality of 0.44. De Castro (2002) reported a heritability of 0.39 for sleep latency and of 0.23 for the number of nocturnal awakenings. Heath (1990) studied 3810 twin pairs aged 17 to 88 years and found a h^2 = 0.33 for sleep quality/disturbance. In a family study in the closed communion of the Hutterites, Klei et al. (2005) found heritability of subjective sleep onset latency (0.16) and the time awake after sleep onset (0.20). The genetic contribution to more severely troubled sleep received attention in a few twin studies as well. Watson et al. (2006) studied twin pairs aged 31 years on average and found heritability of insomnia of 0.57. MacCarren et al. (1994) studied sleep problems in Vietnam veteran twins aged 33 to 51 years and found h^2 values ranging from 0.21 to 0.42. These results are consistent with the observation that persons with past or current insomnia are more likely to report a family history of insomnia than good sleepers who never experienced insomnia in the past (39.1% vs 29.0%; Beaulieu-Bonneau et al., 2007).

We found that coffee use was positively related to sleep quality and negatively to sleep problems. This may point to a selection effect: those who sleep badly tend to avoid coffee. Luciano et al. (2007) reported heritability for coffee-attributed sleep disturbance and

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suggestive linkage for coffee-attributed sleep disturbance can be identified on chromosome 2q. Nicotine and alcohol use were not related to sleep quality or problems, but were positively related to bedtime and awakening time, and coffee and alcohol use were negatively to time in bed.

In conclusion, although the heritability estimates of sleep timing and quality are somewhat lower if derived from the evaluation of a single night, the night-to-night variability is not so strong that it completely precludes detection of genetic contribution. By asking about a single night, we revealed that night-to-night variability due to environmental demands affects females mostly regarding their rise time and males mostly regarding their bedtime.

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