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Evidence for Genetic Influences on Sleep Disturbance and Sleep Pattern in Twins

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Summary: The etiologic role of genotype and environment in sleep pattern (daytime napping, habitual bedtime, and sleep duration) and subjective sleep quality and sleep disturbance was examined using a general population sample of 3,810 adult Australian twin pairs, aged 17–88 years. Genetic differences accounted for at least 33% of the variance in sleep quality and sleep disturbance and 40% of the variance in sleep pattern. There was no evidence for a decline in the importance of genetic predisposition with age. Short-term environmental fluctuations accounted for as much as 30% of the variance, and more stable nonfamilial environmental effects accounted for the remainder. No effect of shared family environment on sleep characteristics was found. **Key Words:** Sleep pattern—Sleep quality—Twins—Genetics.

Sleep disturbance is a well-established correlate of psychiatric illness (1–6). It is the second most common symptom of mental distress (7) and, according to some surveys, may afflict as many as one third of the adult population (7–13). It is often a chronic complaint, one study finding that over 40% of those reporting sleep problems have had them for >5 years (10). Compared with the general population, individuals reporting disturbed sleep are more likely to report persistent or recurrent health problems or emotional distress (10). In one major prospective investigation of the effects of insomnia on occupational performance, a longitudinal study of sailors in the Navy, poor sleepers were less effective in their work, less likely to receive promotion, and more likely to be demoted, discharged, or not reenlisted (14). Long sleepers as well as short sleepers have been shown to have an increased risk of mortality (15–19) that cannot be explained by previous history of coronary heart disease, stroke, diabetes, or high blood pressure (17).

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Sleep patterns and subjective sleep disturbance in the general population have been examined in several major epidemiological surveys (7–15,20–24). The prevalence of various forms of sleep disturbance has been found to be greater in women (7–9,11,12,15,20,22,23), in older age cohorts (9–12,15,20–23), and in those with a lower educational level, lower income, or lower socioeconomic status (9,10,20,22). Beyond these gross associations, the determinants of sleep pattern and sleep disturbance in nonclinical populations are not well understood.

Studies of inbred mouse strains have suggested a genetic basis to differences in sleep pattern (25,26). Investigation of the first-degree relatives of probands with clinical disturbances of sleep have shown significant familial aggregation of narcolepsy (27,28), hypersomnia (28,29), insomnia (30), and somnambulism (31,32). Recently, the familial aggregation of narcolepsy has been explained by the discovery of the strongest human-leukocyte-antigen (HLA)–association yet recorded (33–36). In 135 Japanese narcoleptic patients, all were DR2 and DQw1, representing relative risks of 530 and 183, respectively, compared to frequencies of these antigens in control subjects (35).

This dramatic finding raises the question of the extent to which genetic factors may account for variation in sleep pattern and quality in the normal population. Small twin studies of self-reported sleep and dream characteristics (37) and electroencephalogram (EEG) patterns during sleep (38) provided no clear evidence for or against genetic influences. However, a very large study of Finnish twins (39), which included brief items about the duration and quality of sleep in a more general health survey, has suggested a significant genetic effect on both these variables in a general population sample. Using data from an extensive survey of adult twins from the Australian Twin Register (40,41), we have found a significant genetic effect on liability to symptoms of anxiety and depression, including sleep disturbance associated with worrying or feeling miserable (42). Statistical analysis of the genetic and environmental causes of the covariation of symptoms of anxiety and depression has revealed a dimension of genetic liability to sleep disturbance that is independent of genetic liability to anxiety and depression (43). In this article, we present findings on the role of genetic and environmental factors from a more detailed investigation of sleep patterns and sleep difficulties, carried out as part of the same survey.

METHODS

Subjects

A questionnaire, including items about sleep patterns and sleep difficulties, symptoms of anxiety and depression (44), personality (45), drug usage, and general health, was mailed to all adult twins enrolled in the Australian National Health and Medical Research Council (NHMRC) Twin Register (40,41). Questionnaires were mailed to 5,967 twin pairs aged 18 years or more. Ages of respondents ranged from 18 to 88 years. After one or two reminders to nonrespondents, completed questionnaires were returned by both members of 3,810 twin pairs. As a result of missing observations, effective numbers of twin pairs for the analyses to be reported in this article fall within the following ranges: female monozygotic (MZ), 1,165–1,227; male MZ, 544–565; female dizygotic (DZ), 692–748; male DZ, 336–352; unlike-sex DZ, 851–901 pairs. A total of 15 respondents admitted to regular use of "sleeping tablets" or "tranquilizers." Since this number is far too small to have any biasing effect on our genetic analyses, these individuals were not excluded from our sample.

To allow for the possible interaction of age with the determinants of the sleep variables, the total sample was subdivided into four age cohorts: twin pairs aged 18–24, 25–34, 35–48, and 49–88 (see Table 1 for structure of sample by age and zygosity). A two-item zygosity questionnaire was used to determine zygosity for same-sex pairs (40). Such questionnaires have been shown to give 95% agreement with diagnosis based on extensive blood typing (46–50). For a subsample of 96 individuals, responses to an almost identical questionnaire, mailed as part of a pilot study several months before the main mailing, were available. This allowed us to assess the consistency of subjects' responses across time. Unfortunately, this subsample was too small to be subdivided by sex or age, so the reliability of variables will be overestimated if, as is the case with the sleep variables, there are significant mean sex and age differences.

Measures

Items from the sleep questionnaire of Johns et al. (51) and Palmer et al. (52) were selected for this study; this was particularly appropriate since this questionnaire was first developed for use in Australian subjects. Responses to such questions have been shown to give good agreement with laboratory-based EEG measures of sleep (53) and to show good consistency over time (51,54). Measures of subjective sleep quality and sleep disturbance and sleep pattern, and the response alternatives, are listed in Table 2 (names given to variables were chosen purely as a mnemonic device). Also included were two items from the delusions–symptoms–states inventory (44) concerning problems of sleep ("anxious insomnia" and "depressed insomnia" in Table 2). The bedtime, sleep time, sleep latency, and sleep duration items were originally coded as continuous variables. However, when we examined the frequency distribution of responses to these items, they were found to be discontinuous, responses being clustered around hours or 15, 30, or 45 min past 1 h. We therefore recoded these variables as discontinuous five-point scales. For the quality of sleep variable, we collapsed categories 4 and 5 ("poor" and "very poor"), since the frequency of responses falling into category 5 was extremely low.

Data summary

Two-way contingency tables, cross-classifying the response of one twin (designated the first twin on the basis of birth order or at random where this information was lacking) by the response of the co-twin, or second twin, were computed separately for each variable and for each twin group. In the case of unlike-sex pairs, the response of the female twin was cross classified by the response of male twin. Since the sleep variables were discontinuous, the traditional methods of genetic analysis for continuous twin data (55) could not be applied. Instead, we estimated from each two-way contin-

TABLE 1. *Sample size broken down by age/cohort and zygosity group*

	Age cohort, yr				
Zygosity group, pairs	18–24	25–34	35–48	49–88	Total
Monozygotic female	325	376	283	249	1,233
Monozygotic male	168	189	110	100	567
Dizygotic female	194	234	171	152	751
Dizygotic male	136	108	57	51	352
Dizygotic unlike-sex	334	261	171	141	907

TABLE 2. *Sleep quality, sleep disturbance, and sleep pattern variables used in the Australian twin study*

Sleep Quality
Overall quality: "How would you describe the quality of your usual sleep over the last few months? Would it be: (1) very good; (2) good; (3) fair; (4) poor; (5) very poor"
Depth of sleep: "How would you describe the depth of your sleep? Are you: (1) easy to wake; (2) about average; (3) hard to wake?"
Variability of quality: "How much would you say the quality of your sleep varies from one night to the other? Would it be: (1) very much; (2) moderately; (3) slightly; (4) not at all?"
Sleep disturbance
Initial insomnia: "How often does it take you much longer than usual to get off to sleep? (1) less than once a month; (2) 1–4 times per month; (3) more than once a week; (4) most nights?"
Disturbed sleep: "How often do you wake up fully during the night? (1) less than once a month; (2) 1–4 times per month; (3) more than once a week; (4) most nights?"
Anxious insomnia: "Recently worrying has kept me awake at night: (1) not at all; (2) a little; (3) a lot; (4) unbearably"
Depressed insomnia: "Recently I have been so miserable that I have had difficulty with my sleep: (1) not at all; (2) a little; (3) a lot; (4) unbearably"
Sleep delay: "On weekdays, how long do you think it usually takes you to fall asleep from when you first try to go to sleep? (1) 0–9 min; (2) 10–14 min; (3) 15–29min; (4) 30–59 min; (5) 60+ min"
Sleep pattern
Bedtime: "On weekdays, what time do you usually go to bed at night?" (1) 21:45 or before; (2) 21:46–22:29; (3) 22:30–22:59; (4) 23:00; (5) after 23:00"
Sleeptime: "On weekdays after you go to bed, what time do you usually try to get to sleep? (1) 22:00 or before; (2) 22:01–22:30; (3) 22:31–23:00; (4) 23:01–23:30; (5) after 23:30"
Sleep duration: "On weekdays, how much sleep do you usually get at night? (1) less than 7 h; (2) 7–7.49 h; (3) 7.5–7.99 h; (4) 8–8.5 h; (5) > 8.5 h
Daytime napping: "How often do you doze or sleep during the day (including evenings before going to bed and weekends)? (1) less than once a month; (2) 1–4 times per month; (3) more than once a week; (4) most days?"

gency table a polychoric correlation, and its standard error, by the method of maximum likelihood (42,56–60). Estimation of a polychoric correlation (sometimes described as "threshold analysis"; 42) implies the assumptions that each observed variable, though discontinuous, provides a measure of a corresponding latent variable whose distribution is continuous and normal, and that the joint distribution of all the latent variables is multivariate normal. Thus, when we estimate the polychoric correlation between twin pairs for "depth of sleep," we are assuming that this variable provides only an imperfect measure of true sleep depth, which trichotomizes the "true" continuous distribution. The polychoric correlation estimates the correlation between the continuous latent variables (e.g., the "true" sleep depths of twin pairs) rather than the imperfect discontinuous measures.

Model fitting

In our models, the expected correlations between MZ and DZ twins can be expressed as a function of four sources of covariation, two genetic and two environmental.

Expected genetic correlations are based on the assumptions of polygenic inheritance, viz, that genetic variation in the trait is determined by a large number of genes acting independently and of small and equal effect. In fact, the expectations are not greatly altered if there is a smaller number of genes, they are of different effect, and there is some nonindependence between loci (epistasis). In human studies, the best one can do is estimate all the various types of genetic variation with two unknown parameters: VA, the additive genetic variance, results primarily from the additive effects of alleles at

each locus; VD, the dominance variance, results from the nonadditive effects of two alleles at a locus. In twin studies, VD also estimates certain types of epistasis, or interactions between different loci. By the terms "additive" and "nonadditive" we mean the following: suppose variation in a trait is entirely governed by a pair of alleles at a single locus. Then if these alleles act additively, the mean value of offspring from a given pair of individuals should always be the mean of the two parental values. If there is dominance, however, the mean value of offspring will depend on the particular combination of parental genotypes. Environmental effects are divided into two categories: ES, specific environmental variance, is the result of environmental experiences that are unique to the individual and shared with no one else, not even the co-twin or members of the same family; EC, common or familial environmental variance, results from environmental experiences shared by both members of a twin pair.

Three of these parameters (VA, VD, and EC) contribute to the phenotypic similarity between relatives, but since there are only two correlations, only two of them can be estimated. The ES, by definition, is equal to $1 - r_{mz}$. The inferences about sources of variation from various patterns of MZ and DZ correlations are shown in Table 3. Basically, EC increases the DZ correlation above half the MZ correlation and dominance decreases it below this value. Thus, EC and VD are negatively confounded and if both are present, the value of the third parameter estimated additional to ES and VA will depend on the precise relative importance of shared environment and dominance variance. The role of statistical methods is to distinguish between the various inequalities shown in Table 3, so refining the inferences that can be made from twin correlations.

We compared the results of fitting four major types of model: (a) an additive genetic model, which allowed for the effects of additive gene action and nonshared environment (i.e., those environmental influences that make one twin differ from his co-twin) but not shared environmental influences (e.g., family background). (b) A full genetic model allowed for additive and dominance genetic effects plus nonshared environmental effects. (c) An environmental model allowed for both shared and nonshared environmental effects, but not genetic effects. (d) A full model allowed for both additive gene action and shared environmental effects. The effects of genetic dominance and shared environment are confounded in twin data (61,62), so the full genetic and full models will give an identical fit. However, genetic dominance and shared environment

TABLE 3. *Inferences about sources of variation from different patterns of monozygotic and dizygotic correlations*

Observed	Inference
$r_{mz} = r_{dz} = 0$	ES
$r_{mz} = r_{dz} > 0$	ES + EC
$r_{mz} = 2r_{dz} > 0$	ES + VA
$r_{mz} < 2r_{dz} > 0$	ES + VA + EC[a]
$r_{mz} > 2r_{dz} > 0$	ES + VA + VD

ES, specific environmental variance; EC, common or shared familial environmental variance; VA, additive genetic variance; and VD, genetic dominance variance.

[a] If there is correlation between spouses then the estimate of EC may be inflated by extra additive variance due to assortative mating.

have effects that are opposite in direction, the former reducing the DZ twin correlation to below one half the MZ correlation, and the latter inflating the DZ twin correlation to greater than one half the MZ correlation. Thus, negative estimates of the shared environmental variance component, under the full model, indicate genetic dominance, and vice versa.

We also tested for the interaction of genetic and environmental effects with sex. We allowed both for sex differences in the magnitude of genetic and environmental influences on the sleep variables and for the possibility that the correlation between shared environmental effects (r_C) or genetic effects (r_G) in the two sexes was less than unity (55,63). Our purpose in fitting models was to identify the most parsimonious model able to explain the data, and then determine how much of the variance in the sleep variables (strictly, the underlying latent variables) is attributable to genetic factors and to shared environmental and nonshared environmental factors.

For each variable, maximum-likelihood estimates of parameters (42,63,64) were obtained by fitting models directly to the 20 contingency tables for female and male MZ and male, female, and unlike-sex DZ twin pairs from each age cohort. The goodness of the fit of different models was compared by likelihood ratio, χ^2 test (64–66). For each variable, we computed the likelihood ratio χ^2 for testing each simpler model against the full model, which estimates separate correlations for each contingency table. A significant chi-square implies that a model does not fit these data and must be rejected. Since we found little evidence of heterogeneity of twin correlations across age cohorts, models were fitted to the full set of 20 contingency tables for each variable. To test for the interaction of genetic and environmental effects with age, models were also fitted separately for each age cohort. If the χ^2 measure of goodness of fit obtained in the simultaneous analysis of all four cohorts was significantly greater than the sum of the χ^2 obtained from the separate analysis of each cohort, this would indicate that effects were age dependent (67).

RESULTS

Internal validity of categorical variables

In Table 4, we give for each sex mean "sleep delay" and "sleep duration" (measured in hours and decimal fractions of an hour) and "bedtime" and "sleep time" (measured in hours and decimal fractions of an hour since midnight of the previous day), broken down by response to the questions about "initial insomnia," "disturbed sleep," and "daytime napping." Also given is the significance of the F statistic, which tests for differences in mean between response categories. These data provide an important check on the validity of subjective assessments of sleep problems. For example, we see that both men and women who report difficulty falling asleep on most nights of the week also reportedly take an hour longer to fall asleep and sleep for an hour less than those who rarely experience such problems. Those who nap during the day sleep for a shorter duration during the night but do not take any longer to fall asleep than the rest of the sample.

Age and sex differences

Contingency tables were computed, cross classifying the sleep variables by age cohort and sex. Table 5 summarizes the percentage of extreme responses for each cohort, broken down by sex. No percentages are given for the variable "bedtime," since

TABLE 4. *Internal consistency of sleep disturbance items [bedtime, sleep-time (24h clock), sleep delay, and sleep duration (decimal hours)] as a function of response categories for frequency of initial insomnia, sleep disturbance, or daytime napping*

Sleep disturbances	Significance of F	Means			
		< 1/mo	1–4/mo	> 1/wk	Most nights/days
Women					
Initial insomnia					
bedtime	NS	22.37	22.38	22.40	22.30
sleep time	***	22.62	22.74	22.87	23.00
sleep delay, h	***	0.24	0.40	0.78	1.42
sleep duration, h	***	7.89	7.80	7.37	6.76
Disturbed sleep					
bedtime	***	22.42	22.40	22.30	22.23
sleep time	NS	22.70	22.71	22.69	22.65
sleep delay, h	***	0.30	0.36	0.53	0.57
sleep duration, h	***	7.93	7.80	7.66	7.38
Daytime napping					
bedtime	NS	22.36	22.39	22.37	22.31
sleep time	NS	22.68	22.71	22.70	22.62
sleep delay, h	*	0.39	0.35	0.40	0.39
sleep duration, h	***	7.81	7.81	7.71	7.46
Men					
Initial insomnia					
bedtime	*	22.57	22.65	22.71	22.85
sleep time	***	22.78	22.92	23.06	23.25
sleep delay, h	***	0.23	0.34	0.59	1.18
sleep duration, h	***	7.64	7.62	7.34	6.68
Disturbed sleep					
bedtime	***	22.69	22.67	22.47	22.29
sleep time	***	22.92	22.94	22.78	22.54
sleep delay, h	***	0.29	0.32	0.41	0.39
sleep duration, h	***	7.66	7.55	7.56	7.34
Daytime napping					
bedtime	NS	22.62	22.62	22.66	22.54
sleep time	NS	22.88	22.88	22.89	22.76
sleep delay, h	NS	0.32	0.31	0.34	0.30
sleep duration, h	***	7.68	7.58	7.37	7.34

NS, not significant; *, significant at the 5% level; ***, significant at the 0.1% level.

responses to this item were so highly correlated with the item "sleeptime." With the very large sample sizes available in this study, all statistical tests for sex or age differences in endorsement frequency were significant unless otherwise noted.

Consistent with findings in other populations, Australian women reported that they sleep more poorly and more lightly than do their male counterparts, but that the quality of their sleep varies less from night to night. They more frequently have difficulty in falling asleep, have a longer sleep latency, and are more likely to wake up fully during the night. Australian women are also more likely than men to report sleep disturbance because of worrying or feeling miserable. They go to bed earlier and try to get to sleep earlier and sleep longer than Australian men. Unexpectedly, no significant sex difference in frequency of napping during the day was found ($\chi^2_3 = 2.68$, $p = 0.44$).

In both sexes, younger respondents reported that they go to bed later and go to sleep later but sleep longer than older respondents. Predictably, they are less likely to nap during the day, sleep more deeply, and are less likely to wake up fully during the night. Less predictably, in men it is the youngest age cohort who reports most frequently poor quality of sleep, frequent difficulty falling asleep, and long sleep latency. In women, a U-shaped function is found. Fair or poor sleep quality, difficulty falling asleep, and long

TABLE 5. *Percentage of extreme responses as a function of age and sex*

Extreme responses	Women (age range, yr), %				Men (age range, yr), %			
	18–24	25–34	35–48	49+	18–24	25–34	35–48	49+
Quality of sleep: poor/very poor	5.5	6.0	5.0	7.0	5.3	3.8	5.0	2.6
Depth of sleep: easy to wake	29.0	36.2	43.6	49.7	20.6	26.8	34.2	40.3
Variability: very variable	3.3	3.2	1.9	4.0	4.7	4.2	3.08	2.9
Initial insomnia: > 1/wk or most nights	14.1	10.6	13.9	26.2	12.7	9.0	10.4	8.9
Disturbed sleep: most nights	6.6	18.1	17.1	34.8	2.5	10.9	14.8	30.2
Anxious insomnia: a lot/unbearably	6.9	5.9	5.9	6.9	5.4	3.6	3.3	2.6
Depressed insomnia: a lot/unbearably	5.3	4.3	4.8	5.2	3.4	2.2	2.9	1.9
Sleep delay: > 60 min	13.3	8.7	8.3	21.0	10.9	3.9	5.5	6.2
Sleep time: before 22:00	27.3	28.3	27.8	28.6	19.6	18.0	28.8	33.6
after 23:30	14.0	9.4	9.6	11.7	22.5	18.5	10.7	10.6
Sleep duration: < 7 h	7.5	10.5	11.6	21.9	9.1	15.4	21.3	22.2
> 8.5 h	22.4	14.9	12.5	8.5	15.2	6.9	7.0	11.0
Daytime napping: most days	2.7	4.8	6.6	16.6	2.9	3.8	9.2	23.3

sleep latency are all most common in the youngest and the oldest age cohorts. In both sexes, "anxious insomnia" is most frequent in the youngest cohort, while "depressed insomnia" shows no significant differences across age groups ($\chi^2_6 = 11.54$, $p = 0.07$ for women; $\chi^2_6 = 9.97$, $p = 0.13$ for men).

Twin correlations

Polychoric correlations between twin pairs for the sleep variables are summarized in Table 6. Except in the case of "sleep depth," these estimates were obtained by analyzing the full set of 20 twin contingency tables (four cohorts × five twin groups) simultaneously. For the four variables, evidence for heterogeneity of correlations across cohorts was found (initial insomnia, $\chi^2_{15} = 25.66$, $p = 0.04$; disturbed sleep, $\chi^2_{15} = 27.20$, $p = 0.04$; sleep depth, $\chi^2_{15} = 33.84$, $p < 0.01$; bedtime, $\chi^2_{15} = 25.8$, $p = 0.04$), but only in the case of "sleep depth" is the heterogeneity more than marginally significant. For this variable we have also given twin correlations broken down by cohort. These show a progressive increase in the MZ correlations as we go from younger to older cohorts, suggesting that biological influences on sleep depth are becoming more important over the life span. Correlations between the responses of individuals from the reliability subsample on the first and second occasions of measurement are also given in Table 6.

For all variables, correlations between MZ twin pairs were consistently higher than those between DZ twin pairs of the same sex, suggesting that genetic differences contribute to differences in sleep pattern and in susceptibility to sleep disturbance. The correlation between MZ twin pairs provides an estimate of how much of the variance in a variable is attributable to familial (genetic or shared environmental) factors. The

TABLE 6. *Maximum likelihood estimates of twin polychoric correlations*

	MZF[a]	MZM	DZF	DZM	DZX	Reliability
Quality of sleep	0.31	0.31	0.25	0.09	0.15	0.78
Depth of sleep	0.38	0.23	0.06	−0.02	−0.02	0.82
17–24 yr	0.23	0.10	−0.09	−0.04	−0.06	
25–34 yr	0.37	0.28	−0.03	−0.04	−0.02	
35–49 yr	0.41	0.21	0.37	0.05	0.17	
50+ yr	0.56	0.36	0.03	−0.01	−0.18	
Variability	0.21	0.19	0.08	0.11	0.10	0.60
Initial insomnia	0.33	0.31	0.14	0.15	0.16	0.82
Disturbed sleep	0.35	0.30	0.10	0.00	0.04	0.69
Anxious insomnia	0.38	0.28	0.28	0.12	0.09	0.53
Depressed insomnia	0.33	0.31	0.22	0.21	0.11	0.55
Sleep delay	0.43	0.36	0.25	0.10	0.15	0.72
Bedtime	0.45	0.47	0.29	0.30	0.16	0.72
Sleep time	0.37	0.45	0.23	0.25	0.11	0.81
Sleep duration	0.41	0.39	0.09	0.24	0.11	0.74
Daytime napping	0.40	0.39	0.21	0.23	0.14	0.79

[a] MZF, monozygotic female; MZM, monozygotic male; DZF, dizygotic female; DZM, dizygotic male; DZX, dizygotic unlike sex.

highest correlation, that between male MZ twins for "bedtime," was only 0.47, implying that for all variables environmental factors not shared by siblings (including measurement error) account for most of the variance. Monozygotic correlations for the variable "variability of quality" were especially low, implying that almost 80% of the variance in this variable is attributable to short-term and long-term nonshared environmental factors.

Estimates of the reliability of the sleep variables ranged from 53–82%. If we subtract the estimated reliability of a variable from unity, we obtain an approximate estimate of how much of the variance in that variable is attributable to short-term environmental fluctuations, including measurement error. Such short-term effects accounted for 40% of the variance in reported variability of quality of sleep and 45% of the variance in reported anxious and depressed insomnia. For the remaining variables, reliability coefficients were 0.69 or greater, i.e., short-term environmental effects account for less than 31% of the variance. All reliability coefficients were higher than the corresponding MZ twin correlations, implying that stable environmental influences that make one twin differ from his co-twin are also having an important effect, accounting for between 25–50% of the variance.

Twins were asked how often they see and contact each other on a six-point scale. In an analysis of these responses, we have shown that co-twins are highly consistent in reporting their degree of contact and that MZ twin pairs report more frequent contact with each other than did DZ twin pairs (42). It might therefore be objected that the higher polychoric correlations obtained for the MZ pairs are a consequence of their more frequent contact. To test this hypothesis, we computed for each twin group the partial correlations between frequency of contact and absolute within-pair difference in score on each sleep variable, controlling for age. In no case did frequency of contact explain as much as 1.5% of the variance, so we can be confident that the excess MZ twin correlations cannot be explained by the effects of contact on twin resemblance.

Model-fitting analyses

Table 7 summarizes the results of model fitting for each of the sleep quality variables, sleep disturbance variables, and sleep pattern variables. Purely environmental models

TABLE 7. *Results of model fitting: likelihood ratio chi-squares for testing each model against the most general model, estimating separate correlations for each zygosity group, are tabulated*

		Sleep quality			Sleep disturbance					Sleep pattern			
Model	*df*	Quality	Depth	Variability	Initial insomnia	Disturbed sleep	Anxious insomnia	Depressed insomnia	Sleep delay	Bedtime	Sleep time	Sleep duration	Frequency of napping
Full[a]	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Full[b]	1	0.30	9.08[d]	0.01	0.06	10.65[d]	0.17	0.49	1.42	1.65	2.07	2.44	0.40
Environmental[a]	2	9.31[d]	40.06[d]	6.83[c]	14.87[d]	29.26[d]	3.48	3.68	28.94[d]	20.30[d]	16.53[d]	49.18[d]	13.74[d]
Environmental[b]	3	15.78[d]	49.10[d]	8.89[c]	18.14[d]	40.62[d]	9.28[d]	12.18[d]	40.10[d]	55.95[d]	46.84[d]	71.43[d]	27.89[d]
Genetic[a]	2	6.02[c]	11.33[d]	0.42	0.34	5.61	2.07	1.37	2.31	3.97	1.17	8.50[c]	0.41
Genetic[b]	3	6.09	20.64[d]	0.43	0.34	10.63[c]	3.39	2.48	3.29	7.63	7.09	13.75[d]	2.01
Full	3	6.00	7.60	0.41	0.22	2.13	6.78	2.61	7.86[c]	7.59	8.38[c]	5.55	1.93
Environmental	4	19.70[d]	77.09[d]	9.05	18.35[d]	45.82[d]	17.20[d]	13.30[d]	54.97[d]	56.61[d]	46.96[d]	71.53[d]	28.38[d]
Genetic	4	6.57	30.75[d]	0.53	0.38	12.64[c]	6.78	2.65	8.86	7.67	8.80	13.80[d]	2.04

The "full" model includes additive gene effects and shared and unique environmental effects; the "environmental" model includes shared and unique environmental influences (but no genes); the "genetic" model includes additive genes and unique environmental influences (but no shared environment).

[a] The correlation between gene effects in the two sexes (r_G) was allowed to take values less than unity.

[b] Parameters were allowed to vary with sex.

[c] The model gives a significantly worse fit than the most general model at the 5% significance level.

[d] The model gives a significantly worse fit than the most general model at the 1% significance level.

could be rejected for all except the "variability of quality" and "anxious insomnia" and "depressed insomnia" variables. In the case of "sleep variability," a purely environmental model that makes no allowance for sex differences (model 8) gave a fit that was not significantly worse than that of the most general model ($\chi^2_4 = 9.05$, $0.1 > p > 0.05$), though nearly so. However, since model 8 gave a significantly worse fit than model 7 ($\chi^2_1 = 8.64$, $p < 0.01$), which allowed for sex-independent genetic and familial environmental effects, but model 9 (under which family resemblance is entirely genetic in origin) did not give a significantly worse fit than model 8 ($\chi^2_1 = 0.14$, $p > 0.05$), we were still able to reject the purely environmental model. In the case of "anxious insomnia" and "depressed insomnia," both a simple genetic model (model 9) and a purely environmental model, which assumes that different features of family background predispose to sleep disturbance in the two sexes (model 3), gave equally good fits.

With the exception of "sleep depth," "disturbed sleep," and "sleep duration," in all cases an additive genetic model that made no allowance for the effects of shared environment was able to account for the observed data. For these three variables, the full model with no sex-dependent effects (model 7) is the simplest model consistent with the data. Negative estimates of the familial environmental parameter were obtained, however, implying that the failure of the simple additive genetic model occurs because of genetical nonadditivity (probably dominance) for these variables (61,62). There is thus little evidence that family background predisposes to sleep disturbance. Full genetic models including a genetic dominance parameter were therefore refitted to these data.

For two variables, "sleep time" and "sleep delay," we found significant evidence for sex-dependent gene action. In the case of "sleep time," a model allowing for a correlation between gene effects (r_G) in the two sexes less than unity (model 5) gave a significantly better fit than models that either ignored sex-dependent gene action (model

9) or allowed only for differences in the magnitude of genetic effects but assumed r_G = 1 (model 6). For "sleep delay," we found evidence for sex-dependent gene action, but allowing r_G to take values less than unity did not lead to a significant improvement in fit.

Estimates of the proportions of variance explained by genetic factors and by nonshared environment are summarized in Table 8. The nonshared environmental variance has been subdivided into that due to short-term environmental effects including measurement error and that due to more long-term effects, using the reliability estimates from Table 6. For the three variables where we found evidence of genetical nonadditivity (sleep depth, disturbed sleep, and sleep duration), the estimate of the dominance component of variance is given in addition to the additive genetic component. For these three variables, the estimate of VA is very small and negative in the case of "sleep depth" and "sleep duration." This reflects the difficulty of obtaining precise estimates of additive gene action and dominance, since these two parameters are strongly negatively correlated in twin data (61,62). The only adequate summary of the importance of genetic influences will therefore be the "broad heritability" of these variables, which may be derived as the sum of the additive and dominance genetic components, since the total variance for each variable is scaled to unity.

Estimates of the importance of genetic effects, accounting for 32–36% of the variance, are remarkably similar for the sleep quality and disturbance variables "sleep quality," "sleep depth," "initial insomnia," "sleep latency" (at least in women), "disturbed sleep," "anxious insomnia," and "depressed insomnia" (if we take the parameter estimates obtained under the simple genetic model for the latter two variables). In the case of "variability of quality," only 20% of the variance is attributable to genetic factors. For the sleep pattern variables (bedtime, sleep time, sleep duration,

TABLE 8. *Proportions of variance explained by additive and dominance genetic and nonshared environmental effects under best-fitting models: r_G gives the correlation between gene effects in the two sexes*

	Variance components, (%)				
	Genetic		Nonshared environment		Genetic correlation,
Variable	Additive	Dominance	Long term	Short term	r_G
Sleep quality	32		46	22	1.00
Sleep variability	20		40	40	1.00
Sleep depth	−28	61	49	18	1.00
Initial insomnia	32		50	18	1.00
Sleep delay					
Men	44		28	28	1.00
Women	32		40	28	1.00
Disturbed sleep	−9	42	36	31	1.00
Anxious insomnia	36		17	47	1.00
Depressed insomnia	33		22	45	1.00
Bedtime	46		26	28	1.00
Sleep time					
Men	38		43	19	0.53
Women	45		36	19	0.53
Sleep duration	9	31	34	26	1.00
Daytime dozing	39		40	21	1.00

and daytime dozing) and also sleep delay in men, we find that genetic differences account for a substantial 40% of the variance.

DISCUSSION

The validity of self-report data

Our research has relied entirely on self-report assessments of the usual quality and timing of sleep. This is inevitable, since the very large sample sizes required for genetic research (62) could not be achieved in a sleep laboratory-based study (38). When subjective estimates of sleep have been validated against EEG recordings in the sleep laboratory, poor sleepers have regularly been found to overestimate sleep latency and underestimate total sleep duration but also to underestimate how often they awaken fully from sleep (14,68–70). Such studies are usually able to confirm the existence of sleep difficulties, even if they have been exaggerated. Normal sleepers are able to give a more accurate report of their sleep latency (14).

The questionnaire measures of sleep pattern and sleep disturbance used in this research have previously been validated against laboratory-based EEG measures of sleep (53). An important feature of the study is that it combines multiple self-report measures of sleep disturbance and sleep quality with estimates of sleep latency. This provides one check on the validity of the self-report measures, that of internal consistency (Table 4). The estimates of the heritability of these different measures of sleep quality and sleep disturbance also show a pleasing consistency (Table 8).

The sex and age differences in endorsement frequencies for the sleep variables confirm that the sleep pattern items are assessing something rather different than the sleep quality and sleep disturbance items. Female twins reported sleeping for longer than the men but reported more sleep problems. Younger twins likewise complained of as many or more sleep problems as their older twins but slept for longer. Broad heritability estimates of the sleep pattern variables are again remarkably consistent (38–46%) and somewhat higher than observed for the sleep quality and sleep disturbance variables.

Representatives of the sample

Our sample is unselected for anything except volunteering to enroll on the Australian Twin Registry and willingness to return our questionnaire. It is not obvious that this should lead to sample bias in reporting sleep characteristics, but it would be reassuring to know that the distribution of responses from our large sample was similar to that from normative studies. The only normative data on sleep patterns in Australia to which the present data can be compared come from the original study of Australian medical students of Johns et al. (51), in which the items of our questionnaire were first used. Of his sample of 249 (predominantly male) students (mean age, 21), 5% complained of moderately bad to very bad sleep quality. This is very close to the 5.5% of women and 5.3% of men in the 18–24 cohort who gave the same response in our study (Table 5). Enrollment in the Australian NHMRC Twin Register was voluntary, a disproportionate number of volunteers being young, female, and from MZ twin pairs (40,41). We have, however, subdivided our sample into age cohorts and tested for the interaction of genetic and environmental effects with age and sex. For most sleep variables, no evidence for such interactions was found. We know that this sample does not differ from the general population of Australia with respect to its personality characteristics (41) or the prevalence of symptoms of anxiety and depression (42). It seems

unlikely, therefore, that the unrepresentativeness of the sample will have seriously biased the distribution of responses concerning sleep.

If nonresponse to a questionnaire is a function of one of the variables being measured, then the estimated MZ and DZ correlations will be differentially biased and so will our conclusions about the relative importance of genetic and environmental factors (71). However, we have no evidence that the decision to respond to our survey was influenced by sleep characteristics per se or by traits strongly correlated with them, so we may be reasonably confident of the generality of our conclusions about the broad causes of sleep disturbance.

Interpretation of twin data

Our conclusion that genetic differences have a significant effect on sleep pattern and sleep disturbance rests ultimately on the finding that for all the sleep variables, the correlation between MZ twin pairs is greater than that for DZ twin pairs. It is commonly objected that this arises because of the greater "environmental" correlation between MZ twin pairs. What evidence exists suggests that any excess "environmental" correlation of MZ pairs compared to DZ pairs arises because MZ twin pairs, being genetically identical, behave more similarly and therefore create for themselves more similar environments (63,72). For most of the sleep variables, we found no evidence for heterogeneity of twin correlations as a function of age. Many of the younger twins in the sample were still cohabiting at the time of the study, but very few older twin pairs will have been cohabiting. This makes it unlikely that an excess environmental correlation between MZ pairs compared to DZ pairs could explain our findings, since we would expect such a correlation to decline when the twins were living apart. In the one case where there was striking evidence for an age-dependent change in correlations, for "depth of sleep," correlations were actually higher in the older cohorts!

Partinen and colleagues (39) examined correlations for sleep length and sleep quality as a function of cohabitation and age cohort in their very large Finnish twin study. For sleep length, correlations in the 18–24 cohort were larger for both MZ and DZ twins living together than apart, consistent with a contribution of shared environment in the cohabiting twins. However, in the young women, the difference in MZ and DZ correlations was greater in the pairs living apart, consistent with a higher heritability. There was an insufficient number of older cohabiting twins to make the same comparison. Among pairs living apart, heritabilities were slightly higher in twins $\geq$25 years of age than in the younger cohort. Similarly, the Finnish correlations for sleep quality do not suggest significant effects for age or cohabitation on heritability and do not support the notion of a serious flaw in the fundamental assumption of the twin method.

An alternative environmental interpretation of these data might be that MZ twin pairs, because they have more frequent social contact than DZ pairs (42), would be more likely to experience the same environmental events. They would be subjected to more similar strains and, insofar as these influence the pattern and quality of sleep, would be expected to be more similar. However, we were able to show that differences in frequency of contact could explain less than 1.5% of the variation within pairs in the sleep variables, far too small a proportion to explain the significant differences in correlation between MZ and DZ pairs. This is consistent with our findings elsewhere of negligible correlations between contact frequency and MZ similarity for psychiatric symptoms (42), social attitudes (73), and alcohol consumption (74). The most reason-

able interpretation of the greater MZ than DZ correlation is that variation in sleep disturbance and sleep pattern between individuals is partly genetic in origin.

The genetic basis of sleep pattern and sleep disturbance

Our results suggest that the time at which an individual chooses to go to bed or to sleep, how frequently he or she takes naps during the day, and how long the individual sleeps at night are all influenced by that individual's genotype. If we consider only that component of sleep pattern that is stable over time, ignoring short-term environmental fluctuations, then genetic effects account for roughly one half the variance in sleep pattern. For subjective sleep quality ("quality," "variability," and "depth") too, genetic influences, though less important than in the case of sleep pattern, are still having a major impact, accounting for between 33–46% of the variance that is stable over time. For sleep disturbance related to affective problems ("anxious insomnia" and "depressed insomnia") and for sleep latency in men, genetic effects have an even greater impact on the stability of problems over time than in the case of sleep patterns, accounting for over 60% of the stable variance. For other sleep disturbance measures ("initial insomnia," "disturbed sleep," and "sleep delay" in women), genetic effects account for 39–48% of the stable variance.

In principle, the classical twin design provides a powerful way of detecting sex differences in gene expression or environmental effects (55,63). However, with twin correlations as low as in this study, quite large sex differences could remain undetected. Thus, the fact that we found sex-dependent gene expression only for "sleep delay" and "sleep time" does not preclude the possibility that such effects would also be found for other aspects of sleep, using larger samples.

Our failure to find evidence for age dependence of genetic effects on sleep may also reflect a problem of statistical power. We would expect to detect major changes in gene expression, such as might occur if genetic predisposition to "disturbed sleep" or an inherited tendency to "daytime napping" became important only in older age cohorts. The absence of such changes may suggest that genetic influences on sleep pattern and sleep disturbance are acting with remarkable constancy throughout the individual's life span. Alternatively, the fact that our oldest age cohort mainly contains subjects in their fifties, with progressively fewer in their sixties, seventies, and eighties, causes us to suspect that we simply lack the power to detect changes in genetic architecture that we might reasonably expect to occur.

The role of the environment

It is sometimes forgotten that the study of MZ and DZ twin pairs can be used to detect effects of family background as well as effects of genotype on differences between individuals (55,61,62). Indeed, the effects of family background can be detected with greater statistical power than the effects of genotype when twin pairs are used (62). Our failure to find any evidence for effects of shared environment on sleep disturbance may therefore come as a surprise to some. Small effects of family background ($< 10\%$ of total variance) could, however, remain undetected against a background of additive genetic variation, even with our extremely large sample sizes (62). We have shown elsewhere that data on symptoms of anxiety and depression on the same sample are consistent with a purely genetic model for the familial aggregation of these symptoms (31,32). Other studies of phobias (75) and obsessions and compulsions (76,77) in clinically unselected populations have had similar conclusions. If family background does

have a substantial effect on any symptoms of mental distress in the general population, the symptoms that are affected have yet to be identified.

Our findings do indicate the importance of nonshared environmental effects, i.e., those short-term and long-term influences that make one twin differ from his or her co-twin. Together these account for over half the variance in each of the sleep variables. With the exception of two items specifically related to affective causes of sleep disturbance ("anxious insomnia" and "depressed insomnia"), the importance of long-term environmental effects was found to be at least as great as that of short-term effects. Such long-term effects may reflect exposure to stable situational features (e.g., external noise) that disturb sleep.

We cannot yet exclude the possibility that the impact of environmental factors on sleep is modified by genetic differences in liability to sleep disturbance and sleep pattern. Any such "genotype × environment interaction" would be confounded with nonshared environmental effects in twin data, if the environmental influences are uncorrelated over twin pairs (78). We have not yet attempted the more subtle analyses incorporating measured environmental risk factors that would permit such genotype × environment interactions to be detected (74). If there is significant genotype × environment interaction, the role of genetic factors in sleep disturbance and sleep pattern may prove to be even greater than we have suggested.

Having found evidence for genetic influences on a number of different aspects of sleep disturbance and sleep pattern, the important question arises as to whether it is the same genes influencing all these variables, and this question will be explored in a future article.

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