Heritability of sleep quality in a middle-aged twin sample from Spain

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Abstract

Study objectives: Sleep quality is associated with health throughout the life span, which is particularly salient in middle-age and older adulthood. Sleep quality appears to be influenced by both genetic and environmental factors. However, there is still limited information about genetic influences on sleep quality in middle-aged adults, and particularly in those from certain geographical locations. We estimated the magnitude of genetic and environmental influences on sleep quality in a representative sample of middle-aged Spanish twins.

Methods: The sample comprised 2150 individuals born between 1939 and 1966, who participate in the Murcia Twin Registry. In order to estimate the heritability of sleep quality variables we performed univariate analyses for the global score on the Pittsburgh sleep quality index and for each of its components.

Results: We found moderate but significant heritability (34%) for sleep quality. The genetic variance of the components of the Pittsburgh index ranged from 30% to 45%, except for sleep efficiency for which no genetic influence could be detected. In summary, there was a moderate genetic influence on most dimensions of sleep quality in a sample of adult male and female twins. Shared environment influences were not found.

Conclusions: This study adds new information regarding the underlying determinants of sleep quality by providing heritability estimates in a middle-aged population-based representative sample from a geographical location that has not been included in studies of this type previously. This could provide a reference point for future research regarding sleep research in middle-age.

Keywords: adult, dizygotic, heritability, monozygotic, sleep duration, sleep quality, twins.

Statement of significance: Twin studies indicate that both genetic and environmental factors are important in explaining individual differences in sleep quality. However, heritability is a population statistic, meaning that the magnitude of genetic influences may vary depending on the specific population under investigation. There is a paucity of information focusing on middle aged twins, and those from Southern Europe (where cultural habits concerning sleep differ from those in countries typically focused on in twin studies). This study examines the role of genetic and environmental influences in sleep quality in a sample of middle-aged Spanish twins of both sexes; thus, allowing for sex comparison and providing estimates for an age period when poor sleep quality is common. We found no evidence of sex differences and report similar estimates to those found when focusing on samples from other locations.

Introduction

Sleep quality is a concept that incorporates different aspects of our sleep, including total sleep time, sleep latency, sleep efficiency, or sleep disturbances.[1] It is well known that poor sleep quality is associated with general health and wellbeing.[2] Sleeping poorly has been associated with a wide array of problems including psychological disorders, chronic pain and higher BMI.[3-6] Sleep quality often worsens with age[7] and shows a gender disequilibrium. Thus, middle-aged women as compared to men have a higher predisposition to suffer sleep problems, like insomnia[8] and poorer sleep quality[8,9]. Moreover, age contributes progressively to poorer sleep quality in men and women.[7,9] Altogether, middle-age adulthood seems to be a sensitive period in which to develop sleep problems for both, women and men.

Sleep parameters are influenced by both genetic and environmental factors.[10,11] There is a wealth of literature on twin studies estimating genetic and environmental influences on sleep. However, most of it focuses on sleep duration, which is just one of the

components of sleep quality and heritability estimates of sleep duration between .17 to .63 have been reported.[11-17] These estimates, however, have been inconsistent. Thus, Butkovic et al.[16] reported a heritability of .63 in a sample of young adults, while Barclay et al.[18] did not find genetic influence for sleep duration in those aged 18-27 years. Other aspects of sleep have also been investigated using twin studies. For example, heritability estimates have been reported between .29 and .38 for sleepiness, .39 for daytime sleep duration (i.e. siesta), and .22 for bedtime.[12,15,19]

A similar picture appears related to insomnia, the most common sleep disorder with a prevalence between 6% and 33% depending on the criterion used.[20-23] Heritability values for insomnia vary from .14 to .55.[10,24-26]

All of the aforementioned papers focus on a specific aspect of sleep. On the other hand, sleep quality, as a global index, encompasses different aspects of sleep providing a more complete and valid image of the subjective experience of sleep. Such an index has also been studied from a quantitative genetics perspective. For example, a pioneering study by Partinen and colleagues[13] found a heritability for sleep quality of .44. In another study, using a large sample of twins measured at 2 different time points, reported heritabilities were .33 and .39 for men and .53 and .39 for women.[2] Similarly, Heath et al.[27] found a heritability of .33. A limitation of all of these studies is that they used a very simple measure (i.e. one question) to assess sleep quality. More recent studies have used psychometrically adequate measures, like the Pittsburgh Sleep Quality Index (PSQI), and have reported a heritability of .43 in young adults[28] or .34 in middle-aged males,[17] with a wide variation between specific components of the PSQI questionnaire in both studies. For example Barclay et al.[18] did not find genetic influences on sleep duration while Genderson et al.[17] reported a heritability of .29. Such discrepancies reinforce the need to consider specific features of the population under investigation,

such as age and sex, and cultural environment as well, when we are estimating the heritability of sleep quality and its components.

To the best of our knowledge, no study to date has analyzed the genetic architecture of the PSQI index and its components in a sample including middle-aged women. Given that they seem to be a group at risk of poor sleep quality, this information has the potential to be of great value. It allows a better understanding of the genetic underpinnings of sleep difficulties and increases knowledge about possible age and gender effects on the heritability of sleep quality. Additionally, heritability is a population statistic.

Therefore, it seemed important to analyze data from a southern European country where several social characteristics and cultural habits differ from those of previously reported twin samples. In particular, the use of Central European Time in Spain, means that sunset is at a later hour than would be expected according to its geographical location, the practice of daytime naps or siestas, late bedtimes, commercial opening hours, and prime time television hours create a specific milieu in Spain which could influence the relative impact of genetic and environmental underpinnings of sleep. We conducted a classical twin study of the PSQI index and its components in a population-based sample of middle-aged Spanish twins of both sexes.

Method

Participants

The sample comprised 2150 subjects from a population-based registry in the Region of Murcia, South East of Spain (Murcia Twin Registry, MTR). Description about MTR, recruitment procedures and data collection is provided elsewhere.[29,30] There were 975 males (45.3%) and 1175 females (54.7%). The sample comprised twins that were 32.7%

monozygotic (MZ), 31% same-sex dizygotic (DZ-SS) and 31.7% opposite sex dizygotic (DZ-OS). Mean age was 53.7 (SD=7.4; Range: 41-73) (table 1). Altogether the sample is representative of the general population in the region.[30]

The MTR protocols and instruments, as well as the data collection procedures and the analysis derivatives thereof, have been approved by the Research Ethics Committee of the University of Murcia and meet the legal requirements of confidentiality and protection of personal data. Participants provided written informed consent when interviewed in person or oral consent when a telephone interview was used.

Measures

Zygosity assessment

Twin zygosity was assessed by DNA in 338 pairs of twins. When this was not possible, a 12-item questionnaire focusing on the degree of similarity and mistaken identity between twins was used. This questionnaire-based zygosity corresponds well with zygosity as determined by DNA testing with an agreement in nearly 96% of the cases.[29]

Sleep quality

Sleep quality was measured through the Spanish version of the PSQI .The PSQI is a widely used self-report questionnaire, comprising 7 subscales 1) subjective sleep quality, 2) sleep latency, 3) sleep duration, 4) habitual sleep efficiency, 5) sleep disturbances, 6) use of sleeping medication and 7) daytime dysfunction.[31] The components scores range from 0 to 3 (where a higher score represents poorer sleep quality). These seven partial scores add up to a global index ranging from 0 to 21. The questionnaire has been validated in its Spanish version[32] and has also shown adequate reliability and validity.[33] In the current sample Cronbach's alpha for the global score was 0.73. Additionally, the questionnaire allows for an estimation of average sleep

hours during the last month based on self-report of usual time to go to bed and awakening.

Data analysis

The global PSQI score was log-transformed because of positive skewness (0.92 before and -0.34 after log transformation) and treated as a continuous variable in the analyses. Since scores of the PSQI components range from 0 to 3, they were treated as ordinal variables.

Data from the MZ and DZ twin pairs were analyzed using structural equation modelling, with the Open MX software package in R,[34] to estimate the contribution of genetic and environmental factors to phenotypic variability. The ordinal variables were analyzed using a liability threshold model. In order to apply variance component genetic models to categorical twin data, it is assumed that the categories reflect an imprecise measurement of an underlying normal distribution of liability, which would have one or more thresholds to discriminate between the categories.[35] This liability may be influenced by genetic and environmental factors and is normally distributed with a mean value of zero and a variance of one. Twins' similarity can be estimated by the correlation for the liability scale, called a polychoric correlation.

Assumptions of the twin design (i.e., equal variances and means for MZ and DZ twins as well as for co-twins) and possible age effects were tested by comparing twin models to saturated models. Next, we tested whether MZ twin intra-pair correlations were higher than DZ twin correlations for each of the phenotypes, which would suggest a genetic influence on individual differences for such trait. Genetic influences found in the measured parameters were estimated by fitting genetic structural equation models in which the observed phenotypic variance is decomposed into genetic and environmental components.[36] Observed MZ and DZ twin correlations generally show a combination of

additive (A; i.e., summed allelic effects across multiple genes) and non-additive (D; i.e., genetic dominance, possibly including epistasis) genetic factors, as well as shared (C; i.e., environmental influences that act so as to make family members more alike) and individual (E; i.e., environmental influences that make those within a family less alike, including measurement error) environmental factors. It is not possible to estimate C and D simultaneously, because C and D are negatively correlated and the choice of modelling C or D depends on the pattern of MZ and DZ correlations; usually C is estimated if the DZ twin correlation is greater than half of the MZ twin correlation, and D is estimated if the DZ twin correlation is less than half of the MZ correlation.[37,38] Structural equation modelling determines the combination that best matches the observed data.[39] We fitted both ACE and ADE models to the data. Since the goodness-of-fit of a model is distributed as a chi-square (χ^2), by testing the change in chi-square ($\Delta\chi^2$) against the change in degrees of freedom (Δdf), we can test whether dropping or equating specific model parameters significantly worsens the model fit, and following the principle of parsimony, select the simplest model among those that are not statistically different. The best-fitting model was chosen in each case by deducting the residual deviance of the compared models and by comparing Akaike's information criterion (AIC).

In addition, as a checking analysis, possible sex differences in the distribution of variance were explored through the comparison of the magnitude of the DZ-SS and DZ-OS twin pair correlations. Higher DZ-SS correlations than DZ-OS correlations, would suggest that different genes or shared environmental factors could influence individual differences in the trait.[40] A saturated model was used to estimate means and variances (for men and women separately) as well as five twin correlations (MZm and DZm for males; MZf and DZf for females; and DZ-OS for opposite-sex pairs) for the PSQI

global score. The subsequent models tested were 1-variances; 2-correlations of DZm and DZf pairs; and 3-correlations of DZ-SS and DZ-OS pairs, were constrained to be equal. If the constraints in the nested models do not cause a significant deterioration in model fit, correlation difference is non-significant and no suggestion of sex differences in the genetic or common-environment architecture is implied.

Results

Mean PSQI index was 5.14 (SD=3.96). Females reported greater sleep problems than males [$\overline{X}$=5.74 (SD=4.15) and $\overline{X}$=4.37 (SD=3.57) respectively]. This pattern was similar for all the components of the questionnaire except for average sleep hours, where the mean scores were almost identical, 6.43 (SD=1.41) for women and 6.42 (SD=1.37) for men.

Testing for sex differences

Correlations for the global PSQI score in the different zygosity groups were, as expected, higher for MZ twins than for DZ twins (r_{MZM}=0.28, 95%CI 0.08, 0.46; r_{MZF}=0.39, 95%CI 0.26, 0.50; r_{DZM}=0.09, 95%CI 0.0, 0.26; r_{DZF}=0.21, 95%CI 0.06, 0.36; $r_{DZ\text{-}OS}$=0.07, 95%CI 0.0, 0.22). No suggestion of sex differences was found since correlations for male, female and opposite-sex DZ pairs could be equated without significant deterioration of fit ($p>.05$). Consequently, we proceeded with the univariate analyses taking the complete sample as a whole.

Heritability PSQI global score and its components

The univariate analysis for the global PSQI score showed an important contribution of genetic factors and non-shared environmental effects. When we compared the ADE model versus more restricted models, an AE model was selected as the best fitting model. Estimated parameters were .34 for genetic influences and .66 for non-shared environmental influences (table 2).

Regarding the PSQI components, all correlations ranged from 0.17 to 0.47 for MZ and .0 to .26 for DZ twins (table 3). Six of the seven components showed an important genetic influence, regardless of whether an ACE or ADE model was fitted according to the correlations structure. AE models showed the best fit for subjective sleep quality, sleep latency, sleep duration, sleep disturbances and use of sleeping medication, with estimates of heritability ranging from .30 to .40 (table 2). However, nested models showed a significantly worse fit in the case of daytime dysfunction, probably due to the low frequency of problems in this dimension. Additionally, the best fitting model for sleep efficiency was a CE model, where E represented an important percentage of variance (.80).

Sensitivity analyses were conducted, whereby we fitted models for raw data rather than for the ordinal PSQI scales for those dimensions in which quantitative data were available (i.e. duration, latency and efficiency). So, for example, for sleep efficiency scores we focused on scores which could theoretically range from 0-100 (rather than the scaled scores of 0-3). Heritability estimates obtained from the raw data were similar to those of the scales, albeit of a lesser magnitude, in two of these dimensions. Thus, heritability lowered from 0.30 to 0.25 (duration) and from 0.20 to 0.16 (efficiency). For latency, the best fitting model changed to a CE model in this case.

Discussion

The objective of this study was to analyze the relative genetic and environmental contributions to sleep quality and its components, in a sample of middle-age twins. We focused on both sexes from a geographical location (Southern Europe) which has not been explored previously. We expected to shed light on the genetic architecture of sleep quality during a time of life when sleep can deteriorate and within a specific environment with distinct cultural habits regarding sleep.

We first showed that DZ correlations from same-sex and opposite-sex pairs were not significantly different, suggesting that the same genes related to sleep quality seem to be operating in middle-aged men and women. In our sample, the heritability of sleep quality was estimated at .34. This result is consistent with previous studies with more limited samples. For example, Genderson et al.[17] found exactly the same heritability estimate, although their sample comprised only male adults twins (mean age =55.4). Heritability estimates appear to be roughly similar regardless of age or measurement method, as other studies have reported values ranging from .33 to .53. [2,13,27,28] Interestingly, our estimate is at the lower end of the range meaning that the largest part of the variance is due to unique environmental factors. While in this study, we partitioned genetic and environmental influences (as is standard in twin analyses) in reality, there was likely gene-environment interplay, whereby exposure or sensitivity to the environment is based in part on genetic propensities. Middle-age men and women, can have specific age-related circumstances that produce difficulties and interruptions of sleep. For instance, among those in our current sample reporting sleep disturbances, men usually mentioned shift working (32.6%) or the emergence of age-related diseases (e.g. respiratory or prostatic) (26.8%) as sleep disrupters. In turn, women, mentioned partner snoring/noises (7.4%) or a care-giver role (children or elder people) (13.6%) as important sources of sleep disturbance. Moreover, worries or anxiety were present in 46.3% of those females, but only in 16.3% of males. There are other age-related factors that could affect sleep differently between sexes. Menopause has been repeatedly mentioned in the literature as related to sleep disruption[41] however not all work supports this, and a previous analysis with the current sample showed that age, and not menopausal status, was associated to a decline in sleep quality.[9] In spite of all this, we have not been able to detect significant sex-related differences in common

environmental factors, which is likely due to lack of power in our sample for this analysis. Larger samples and longitudinal studies are needed to better determine the age and other covariate effects, if any, on the heritability of sleep quality.

Genetic influences on the PSQI components were also analyzed. The genetic variance estimates of 6 of the 7 PSQI components in our study ranged from .30 to .45. These results are also consistent with findings of other studies that reported heritability for PSQI components ranging from .21 to .47[18] and from .23 to .34.[17] In contrast, we did not find genetic influences for sleep efficiency, while a heritability of .30 and .34 respectively was estimated in the above cited studies. Sample differences or power issues might be behind this discrepancy and these results need to be replicated before we can be confident that environmental influences are key in explaining sleep efficiency in this age group and cultural context. An additional difference relates to "use of sleeping medication", which fitted an AE model in our sample, whilst a CE model fitted best in Genderson et al.[17] study. A possible explanation for this discrepancy could be the sex of the sample, for ours includes males and females, and the prevalence for using sleeping medication was higher in women (24.9%) than men (9.4%). Again, replication is necessary before strong conclusions should be drawn about this point.

Our estimates are, in general, consistent with those in the literature, despite the differences in the sleep-related social and cultural habits in Spain in comparison to countries from Northern Europe and North America, where most of the previously reported samples come from. Spain uses Central European Time, which involves a delayed schedule (due to later sunset) as compared to what might be expected based on geographical location. This results in a delay in commercial hours, with closing times of malls usually later than 21:00, late evening meals, and with a TV prime time between 21:00 and 00:00. It has been suggested that societal factors may trump biological cues

around the end of the day resulting in a late bedtime [42] and, in fact, in a Spanish sample heritability has been reported to be higher for traits earlier on in the day than for those later on in the day.[15] All in all, these factors result in a late bedtime in Spain as compared to other countries which predicts shorter sleep duration.[42] Indeed, our sample reported an average night-time sleep duration of 6.43 hours, which is shorter than that noted in other samples of European origin,[43,44] but largely consistent with the results of the Spanish National Health Survey (2011-12) of ≈7.15 hours (which included time spent sleeping during the day), for same age subsamples.[45] Short night-time sleep duration has also been related to the practice of midday naps, which might be a method to compensate for insufficient sleep at night. However, this compensatory hypothesis appears too simple to explain this phenomenon as both homeostatic pressure and circadian rhythmicity are important in understanding night-time and nap sleep architecture.[46] Actually, siesta is less common in Spain than is sometimes assumed to be the case (about 40- 60% of the Spanish population never takes siesta). [47,48] Furthermore, siesta has been found to be more frequent among people sleeping 7-8 hours at night than among those sleeping <5 hours.[48] It has been suggested that siesta might be associated with some of the parameters of sleep quality (e.g., daytime sleepiness), but not others (e.g., sleep duration).[49,50] Moreover, a recent twin study in a subsample of the Spanish twins participating in the MTR, found a 45% heritability for siesta even after controlling for night-time sleep duration.[15] The results of the current study might imply that all of these variations between countries/samples regarding duration and timing of sleep do not have a strong impact on the genetic architecture of sleep quality. However, the complexity of the factors involved means that further research is required to elucidate possible interactions between genetic influences and the social environment.

These results provide valuable information about the etiological influences on overall sleep quality and its components, and highlight the need for multivariate and longitudinal studies to characterize the changing relative impact of genetics and the environment on the experience of sleep. This might be particularly useful when focusing on global sleep quality, which is a broader measure of sleep that just sleep duration and may be better able to capture certain associations.[51]

Additionally, quantitative genetic twin studies can guide future genetic molecular studies to identify specific genes.[52] Molecular studies have already shown that sleep is genetically related to depression, schizophrenia and other health variables.[53-56] Future research in this area will be informative regarding more precise diagnostic and treatment alternatives and there has already been a pilot/ feasibility study conducted with the aim of understanding more about genetic and environmental predictors of outcome to treatment aimed at reducing insomnia symptoms.[57]

This study has several strengths. For example, our sample is quite large, representative of the general population in the region[30] and comprises middle-aged males and females. The inclusion of females of this age is critical because they usually have poorer sleep quality as compared to males or to participants of other age groups. Despite strengths there are also limitations. Besides the classical assumptions (e.g., equal environment) required for the twin method, there are other issues that advise for caution in interpreting our results. For example, conclusions are limited by the use of self-report measures of sleep. Objective measures such as polysomnography or actigraphy would provide valuable additional information. However, the PSQI questionnaire has repeatedly show adequate psychometric properties and sleep quality is a subjective phenotype with specific interest *per se*. Moreover, a large proportion of twins were classified as MZ/DZ based on responses to a questionnaire rather than using a DNA

test. This could have resulted in misclassification in certain cases. However, our questionnaire has been validated with data from our own sample showing a high agreement with genetic screening.[29] Therefore, the possible impact of this limitation for our results is considered negligible.

In summary, this study adds to the literature by providing heritability estimates of sleep quality in middle-aged subjects of both sexes. Its results point to the need for longitudinal studies to provide information about the changes in sleep patterns and the genetic contribution to such variation. Future research may focus on gene x environment studies in order to understand the interplay between genes and the environment in bringing about poor sleep quality. Finally, molecular and bivariate genetic studies between sleep and other relevant variables may contribute to our understanding of the important relations between sleep disruption and health.

Abbreviations list

PSQI: Pittsburgh Sleep Quality Index

MZ: Monozygotic

DZ: Dizygotic

MZf: Monozygotic female

MZm: Monozygotic male

DZf: Dizygotic female

DZm: Dizygotic male

DZ-SS: Dizygotic same-sex

DZ-OS: Dizygotic opposite-sex

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