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SCIENTIFIC INVESTIGATIONS

Sleep quality and chronic neck pain: a cotwin study

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Study Objectives: Sleep quality and chronic neck pain (NP) are associated. However, the genetic influences on this association have not been explored. This study investigated the genetic and environmental influences on the association between sleep quality and chronic NP.

Methods: The sample comprised 2,328 individual twins from the Murcia Twin Registry (Spain). A bidirectional cotwin logistic regression analysis was performed (sleep quality assessed as the exposure and chronic NP as the outcome and vice versa). Analysis included 2 sequential stages: total sample analysis and within-pair twin case–control analysis.

Results: Sleep quality was significantly associated with chronic NP in the total sample analysis (adjusted odds ratio [OR]: 1.09; 95% confidence interval [CI]: 1.06, 1.12; $P < .001$); in the cotwin case-control analysis, including both monozygotic and dizygotic twin pairs (adjusted OR: 1.10; 95% CI: 1.04, 1.17; $P = .001$); in dizygotic pairs (Adjusted OR: 1.11; 95% CI: 1.03, 1.19; $P = .005$); but not in monozygotic pairs (adjusted OR: 1.08; 95% CI: 0.98, 1.19; $P = .118$). Chronic NP was significantly associated with poor sleep quality in the total sample analysis (adjusted OR: 1.80; 95% CI: 1.43, 2.26; $P < .001$); in the cotwin case-control analysis, including both monozygotic and dizygotic twin pairs (Adjusted OR: 1.63; 95% CI: 1.07, 2.47; $P = .023$); in dizygotic pairs (Adjusted OR: 1.80; 95% CI: 1.05, 3.09; $P = .031$), but not in monozygotic pairs (adjusted OR: 1.67; 95% CI: 0.80, 3.48; $P = .170$).

Conclusions: The association between sleep quality and chronic NP is partially confounded by genetic factors.

Keywords: chronic neck pain, Murcia Twin Registry, sleep quality

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Despite previous research investigating the effect of environmental factors on both sleep and neck pain, no study has yet assessed the potential genetic influences on this association. This study investigated the genetic and environmental influence on this association in a cohort of adult Spanish twins.

Study Impact: Results suggest that the association is partially confounded by genetic factors. If these findings are confirmed by further research, the next step would be the identification of the genetic variants potentially associated with both sleep and chronic neck pain.

INTRODUCTION

Neck pain (NP) is common, with a 37.2% 1-year prevalence[1] and a 5% lifetime prevalence for chronic NP.[2] The condition has been ranked as the most important contributor of disability in Spain in 2016, together with low back pain.[3] NP can affect the life of individuals, with significant limitations on daily activities and psychological consequences.[4,5] NP is also a costly condition, with both direct (eg, medication, therapies) and indirect (eg, number of work days lost, productivity loss) associated economic costs.[6] Together with low back pain, NP accounts for the third highest amount of spending at $87.6 billion in the United States between 1996 and 2013, also showing the second highest increase, only after diabetes, over that period.[7] A factor that has been significantly associated with NP is sleep quality.[8–10] Many adults experience sleep difficulties, with a 16.6% (range 3.9–40.0%) estimated prevalence of sleep difficulties reported in a study that assessed the sleep quality of more than 40,000 adults from 8 different countries.[11] In a previous study carried out with the same sample that will be used in this study, the prevalence of poor sleep quality was high (38.2%).[12] Many individuals with pain also report concurrent sleep difficulties, and experiencing sleep difficulties can exacerbate musculoskeletal pain by lowering the pain threshold and perpetuating the cycle of chronic pain.[10,13] The association between poor sleep quality and pain is thought to be bidirectional,[10,14] although recent evidence suggests that poor sleep is more likely to precede pain in contrast to pain as a predictor of poor sleep.[14] However, the nature of such association is still unclear and could be the result of unidirectional or bidirectional causation as well as the consequence of the simultaneous effect on NP and sleep of other factors, including environmental and possibly genetic influences.[15] Previous studies reported on the role of lifestyle-related factors such as physical activity,[8,16] anxiety/depression,[8,17] or smoking,[8,18,19] on both sleep and NP. In addition, for other pain

conditions such as low back pain, common genetic factors with sleep were previously identified.[20] Therefore, it may be hypothesized that genetic factors play a role also in the concomitant experience of disturbed sleep and NP. A moderate heritability for both the occurrence of NP and sleep quality has been reported. A 24–58% heritability estimate for NP has been observed in adult populations from the United Kingdom, Sweden, and Denmark,[8,21] although one study reported no heritability in older Danish participants.[22] Other studies carried out in adult populations from the United Kingdom, Vietnam, Spain, and the United States showed a 33–44% heritability estimate for sleep quality.[23–26] Therefore, the phenotypic association between NP and poor sleep quality could in part be confounded by common genetic factors. However, to our knowledge, the possible role of genetic and environmental factors in the relationship between sleep and NP has not yet been investigated. The cotwin control design provides a method for analysis of this association, controlling for the effects of genetic and common environmental factors. In this design, by using discordant twin pairs (ie, one member of the pair shows the outcome, or the exposure, while the other member does not), cases and controls can be matched not only by age, sex, and other covariates but, importantly, by early shared environmental and genetic factors. This offers the possibility to approach true causality between variables by discarding important confounding factors.[27–29] Both discordant dizygotic (DZ) and monozygotic (MZ) twin pairs control for the effect of early environmental factors shared by the siblings. Additionally, they control partially (DZ twins) or completely (MZ twins) for genetic factors. Consequently, if genetic influences act as a confounding variable, the association between exposure and outcome should be attenuated in discordant DZ twins and disappear in discordant MZ twins. In other words, a nonsignificant relationship between exposure and outcome within discordant MZ pairs would not be consistent with a causal relationship between them and would suggest that genetic confounding instead of true causation is responsible for the association. This study aimed to investigate the relationship between sleep quality and NP using 2 parallel, within pair case-control analyses, which allow us to control genetic and early shared environmental influences in the association between those variables. A bidirectional analysis will be performed. First, the relationship between sleep quality (exposure) and NP (outcome) will be investigated, followed by the investigation of the relationship between NP (exposure) and sleep quality (outcome).

METHODS

Cross-sectional observational study with a within-pair twin case–control design.

Study sample

The study population of this cross-sectional study was drawn from the Murcia Twin Registry (MTR), a population-based registry of adult twins born between 1940 and 1966 in the region of Murcia, Southeast Spain. Data for this study were collected during the second wave of data collection of the registry. This was the only time when data about sleep quality and neck pain were collected together. Characteristics and recruitment procedures of the MTR were previously described elsewhere.[30,31] All registry and data collection procedures involved in this study were approved by the Murcia University Ethics Committee and informed consent was obtained from all twins.

Assessment of neck pain

Lifetime prevalence of NP was assessed through a dichotomous self-reported question derived from the Spanish National Health Survey.[32] Participants were required to answer the following question: "Have you ever suffered from chronic neck pain?" and answers were dichotomized into 2 categories, yes or no. Chronic NP was explained to participants as pain in the neck that lasted for at least 6 months (including seasonal or recurrent episodes).

Assessment of sleep quality

Self-reported sleep quality of participants was assessed through the Pittsburgh Sleep Quality Index (PSQI), Spanish version.[33] The PSQI is a self-report questionnaire that consists of 18 items for the assessment of 7 different domains of sleep disturbances in the last month: self-reported sleep quality, sleep latency (the time one takes to fall asleep), sleep duration, habitual sleep efficiency (the ratio of total sleep time to time spent in bed), sleep disturbances, use of sleeping medication, and daytime dysfunction. By summing the scores of these 7 domains, a total score is obtained (range from 0 to 21). The total PSQI score was entered as the exposure variable in the analysis of the association between sleep quality and chronic NP (outcome). Higher total PSQI scores indicate a worse sleep quality. A cutoff point of more than 5 points was used to define individuals with poor sleep quality.[34] A PSQI dichotomous variable (good sleep quality: PSQI total score ≤ 5; poor sleep quality: PSQI total score > 5) was created and entered as an outcome in the analysis of the association between chronic NP (exposure) and poor sleep quality (outcome).[34]

Assessment of potential covariates

Sex, age, anxiety/depression, body mass index (BMI), alcohol use, educational level, smoking, and engagement in leisure time and daily physical activity were considered as potential confounding variables. Anxiety/depression was assessed with the corresponding dimension of the EuroQol (EQ-5D) health questionnaire, which is a quality of life instrument that requires participants to respond to 5 health domains (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression).[35] Participants had to answer a single question and indicate how they felt that day ("I am not anxious or depressed," "I am moderately anxious or depressed," or "I am extremely anxious or depressed"). The participants' answers were dichotomized into "I am not anxious or depressed" or "I am moderately/extremely anxious or depressed." Information on weight and height was assessed through self-reported measures from all male participants and 39% of the female participants and for the remaining female participants by means of standardized anthropometric measurements collected by a research assistant blinded to the study. BMI was calculated by dividing the individuals' body weight in kilograms by the square of their height in meters. Educational level was self-reported, ranging from illiterate to university high degree

levels following the guidelines of the Spanish National Statistic Institute.[36] Information on smoking, alcohol use, and physical activity was collected through the corresponding items of the Spanish National Health Survey questionnaire.[32] Participants were questioned regarding smoking habits, and the answers were dichotomized as ex/never smoker versus current smoker. Frequency of alcohol use was assessed by an 8-level ordinal scale ranging from never to daily. Answers were also dichotomized as weekly/nonweekly drinkers. Participants were required to report their engagement in leisure physical activity, with 4 potential options available: (1) "I do not practice exercise. My leisure time is mostly sedentary (reading, watching TV, movies, etc)," (2) "Some sport or physical activity occasionally (walking, gardening, soft gym, light efforts, etc)," (3) "Regular physical activity several times a month (tennis, jogging, swimming, cycling, team sports, etc)," and (4) "Physical training several times a week." Similarly, 4 options were available for the assessment of engagement in daily physical activity: (1) "Sitting most of the time," (2) "Standing. No big movements or efforts," (3) "Walking, carrying light weights, moving but no big effort," (4) "Tasks that require physical effort". Leisure physical activity engagement was dichotomized into no physical activity or low/moderate/vigorous physical activity, while daily physical activity engagement was dichotomized into low/no engagement in work-related physical activity (mainly sitting or light physical efforts) or moderate/vigorous physical activity engagement (doing tasks that require a strong physical effort).

Statistical analysis

Descriptive statistics were conducted for all variables. The association between sleep quality and chronic NP was investigated by means of 2 separate analyses. In the first analysis, the outcome variable investigated was lifetime prevalence of chronic NP, and the exposure variable was sleep quality (total score of the PSQI). In the second parallel analysis, the outcome variable investigated was sleep quality (PSQI score dichotomized), and the exposure variable was lifetime prevalence of chronic NP. Each analysis was performed in 2 sequential stages: total sample analysis and within-pair twin case–control analysis (**Figure 1**), which in turn included 3 stages: total discordant pairs, DZ discordant pairs, and MZ discordant pairs. To select confounding variables that should be included in each of the multivariable models, univariate logistic regression analysis between potential confounding variables and NP or sleep quality was performed. Variables with P values <.20 for associations in univariate models were included as confounders in the multivariate logistic regression model of the total sample analysis and retained in all subsequent analytical phases if significant (P value <.20). In the within-pair twin case–control multivariate models, age was excluded as twins were of the same age and sex was included only when relevant (ie, in DZ but not MZ analysis). All the analyses were performed with STATA version 14 (Stata Corp., College Station, TX) and SPSS v22.0 (IBM Corp., Armonk, NY).

Total sample analysis

The association between sleep quality (exposure) and chronic NP (outcome) was investigated by means of logistic regression including the whole sample (total sample analysis). Complete or incomplete twin pairs regardless of the concordance or discordance status for chronic NP were used, with the twins being analyzed as single individuals rather than pairs. The total sample analysis was repeated to assess the association between chronic NP (exposure) and PSQI score dichotomized (outcome) by means of logistic regression analysis using complete or incomplete twin pairs regardless of the concordance or discordance status for sleep quality. Since the analysis with individuals from the same family produces dependence on data, regression analyses were performed by adjusting the estimates of standard error using the robust method in STATA.

Within-pair twin case–control analyses

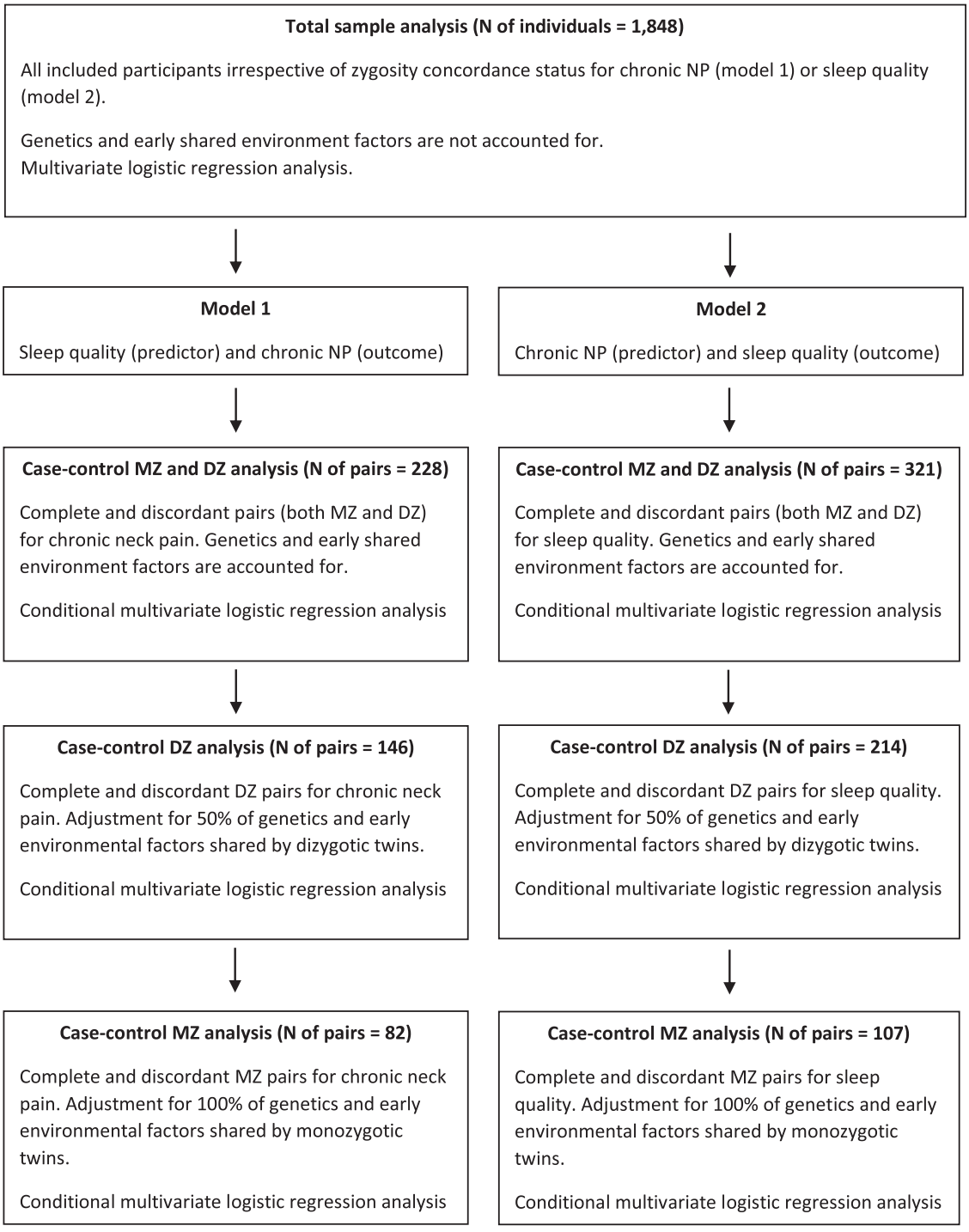
Within-pair twin case–control analyses were used to investigate the association between sleep quality (exposure) and chronic NP (outcome), adjusting for genetic and early shared environment influences. The use of this method involves an increase in the level of adjustment for confounding factors with increasing analytical stages. First, conditional logistic regression was performed to investigate the association between sleep quality and chronic NP, including all complete MZ and DZ twin pairs discordant for chronic NP (ie, twin pairs in which one twin reported chronic NP and the cotwin reported no chronic NP).[37] Subsequently, a within-pair twin case–control analysis was performed separately for DZ and MZ twin pairs (model 1). All analytical phases of the within-pair twin case–control analyses were repeated with MZ and DZ twin pairs discordant for sleep quality using the PSQI score dichotomized (ie, twin pairs in which one twin reported good sleep quality and the cotwin reported poor sleep quality) to assess the association between chronic NP and sleep quality (conditional logistic regression analysis) (model 2). This sequential analysis is based on the knowledge that twins in a pair are optimally matched on age, sex, genetics (MZ 100% and DZ on average 50%) and shared (early family) environmental factors (100%) if they grow up together.[37] Therefore, this procedure allows for more precise estimates of the association between variables and to assess whether the association is consistent with a possible causation path between variables by sequentially eliminating genetic and familial confounding.[37] For example, if the association between sleep quality and chronic NP is confounded by both genetic factors and family background, the association will exist in the analyses of the total sample but not in discordant twin pairs. Conversely, if the association is confounded by genetic factors, it would be attenuated within MZ twin pairs but not within DZ twin pairs.[37] In presence of familial confounding from shared (family) environment, the association would be attenuated in both MZ and DZ discordant pairs. Finally, when it is independent from familial effects, the association is present in all analytical stages.[37]

RESULTS

Sample characteristics

Overall, 2,328 individuals (58.0% women) were included in the sample at the time of data collection, and the mean age was 53.7 years (standard deviation = 7.4) (**Table 1**). Data regarding chronic NP and sleep quality were provided by 2,148 and 1,952

Figure 1—Description of the stages of analysis applied in the study.



DZ = dizygotic, MZ = monozygotic, NP = neck pain.

individuals, of which approximately 28% and 39% reported having chronic NP and poor sleep quality, respectively. The percentage of individuals who were moderately/extremely anxious or depressed was approximately 22%, while 61% and 59% were classified as alcohol users and smokers, respectively. Approximately 54% of individuals engaged in leisure time physical activity and 19% in daily physical activity; 22% had higher education levels (superior secondary education or university). Twins were 66.4% DZ and 33.6% MZ.

Association between sleep quality (exposure) and chronic NP (outcome)

In the unadjusted total sample analysis (Table 2), the PSQI total score was significantly associated with chronic NP (OR: 1.12;

Table 1—Study sample characteristics.

Variable	n	Mean (± SD)
Age, y	2,157	53.7 (± 7.4)
Body mass index	2,097	27.4 (± 4.5)
Variable	**n**	**%**
Chronic neck pain		
Yes	610	28.4%
Sleep quality		
Good	1,193	61.1%
Poor	759	38.9%
Sex		
Male	977	42.0
Female	1,351	58.0
Anxiety/depression		
Not anxious or depressed	1,675	78.2
Moderately/extremely anxious or depressed	468	21.8
Alcohol use		
Nothing/some times a month	828	38.7
Once a week/daily	1,311	61.3
Educational level		
Illiterate/primary education	1,042	45.5
Secondary education	747	32.6
Superior secondary education/University	501	21.9
Smoking		
Ex/never smoker	882	41.1
Current smoker	1,263	58.9
Engagement in leisure time physical activity		
No	980	45.6
Low/moderate/vigorous	1,167	54.4
Engagement in daily physical activity		
No/low engagement	1,739	81.2
Moderate/vigorous	402	18.8
Zygosity		
Monozygotic twins	782	33.6
Dizygotic twins	1,546	66.4

95% CI: 1.09, 1.15; $P < .001$); the association remained significant and was only slightly attenuated after adjustment for sex, age, daily physical activity, leisure time physical activity, BMI, smoking, alcohol use, anxiety/depression, and educational level (adjusted OR: 1.09; 95% CI: 1.06, 1.12; $P < .001$). A total of 228 MZ and DZ twin pairs were discordant for chronic NP, and the cotwin case-control analysis, including both MZ and DZ, twin pairs showed a statistically significant association between PSQI total score and chronic NP (adjusted OR: 1.10; 95% CI: 1.04, 1.17; $P = .001$). The association remained statistically significant in DZ pairs (adjusted OR: 1.11; 95% CI: 1.03, 1.19; $P = .005$), but not in MZ pairs (adjusted OR: 1.08; 95% CI: 0.98, 1.19; $P = .118$). Furthermore, none of the covariates showed a clear significant trend in the cotwin analyses (**Table 2**).

Table 2—Total sample analyses and within-pair twin case–control analysis of the association between PSQI and chronic NP.

Total sample analysis (n = 1,950)	Chronic NP	
	Unadjusted OR (95% CI)	***P***
PSQI (total score)	1.12 (1.09, 1.15)	< .001
Total sample analysis (n = 1,848)	**Adjusted OR (95% CI)**	***P***
PSQI (total score)	1.09 (1.06, 1.12)	< .001
Sex	2.85 (2.21, 3.70)	< .001
Age	0.98 (0.96, 0.99)	.008
Daily physical activity	0.63 (0.46, 0.87)	.005
Leisure time physical activity	1.03 (0.82, 1.28)	.811
BMI	1.02 (1.00, 1.05)	.056
Smoking	0.86 (0.67, 1.09)	.209
Alcohol use	0.97 (0.77, 1.23)	.825
Anxiety/depression	1.56 (1.19, 2.06)	.001
Educational level	0.73 (0.62, 0.87)	< .001
MZ and DZ pairs (n = 228)		
PSQI (total score)	1.10 (1.04, 1.17)	.001
Sex	1.22 (0.68, 2.19)	.507
Daily physical activity	0.56 (0.32, 0.98)	.041
BMI	1.01 (0.96, 1.07)	.732
Anxiety/depression	1.62 (0.94, 2.78)	.080
Educational level	0.97 (0.66, 1.42)	.862
DZ pairs (n = 146)		
PSQI (total score)	1.11 (1.03, 1.19)	.005
Sex	1.21 (0.66, 2.22)	.533
Daily physical activity	0.59 (0.30, 1.16)	.126
BMI	1.04 (0.98, 1.12)	.209
Anxiety/depression	1.73 (0.88, 3.42)	.114
Educational level	0.91 (0.59, 1.41)	.678
MZ pairs (n = 82)		
PSQI (total score)	1.08 (0.98, 1.19)	.118
Daily physical activity	0.63 (0.23, 1.72)	.366
BMI	0.91 (0.80, 1.03)	.123
Anxiety/depression	1.48 (0.59, 3.70)	.406
Educational level	1.02 (0.42, 2.44)	.971

Analysis adjusted for sex, age, daily physical activity, leisure time physical activity, BMI, smoking, alcohol use, anxiety/depression and educational level. BMI = body mass index, CI = confidence interval, DZ = dizygotic, MZ = monozygotic, n = number of participants in each analysis stage, OR = odds ratio, PSQI = Pittsburgh Sleep Quality Index.

Association between chronic NP (exposure) and sleep quality (outcome)

In the unadjusted total sample analysis (**Table 3**), chronic NP was significantly associated with poor sleep quality (OR: 2,24; 95% CI: 1.82, 2.77; $P < .001$); the association remained significant after adjustment for sex, age, daily physical activity, leisure time physical activity, BMI, smoking, alcohol use, anxiety/depression, and educational level (adjusted

Table 3—Total sample analyses and within-pair twin case–control analysis of the association between chronic NP and sleep quality.

Total sample analysis (n = 1,950)	PSQI (dichotomized)	
	Unadjusted OR (95% CI)	*P*
Chronic NP	2.24 (1.82, 2.77)	< .001
Total sample analysis (n = 1,848)	**Adjusted OR (95% CI)**	***P***
Chronic NP	1.80 (1.43, 2.26)	< .001
Sex	1.29 (1.02, 1.62)	.031
Age	1.04 (1.03, 1.06)	< .001
Daily physical activity	0.96 (0.74, 1.26)	.773
Leisure time physical activity	0.75 (0.61, 0.92)	.005
BMI	1.01 (0.99, 1.04)	.366
Smoking	0.78 (0.62, 0.97)	.029
Alcohol use	1.02 (0.82, 1.27)	.853
Anxiety/depression	2.76 (2.15, 3.53)	< .001
Educational level	1.00 (0.86, 1.16)	.994
MZ and DZ pairs (n = 321)		
Chronic NP	1.63 (1.07, 2.47)	.023
Sex	1.63 (0.99, 2.67)	.053
Leisure time physical activity	0.62 (0.43, 0.90)	.011
Smoking	0.75 (0.48, 1.17)	.209
Anxiety/depression	3.94 (2.32, 6.69)	< .001
DZ pairs (n = 214)		
Chronic NP	1.80 (1.05, 3.09)	.031
Sex	1.71 (1.04, 2.83)	.036
Leisure time physical activity	0.61 (0.40, 0.95)	.030
Smoking	0.99 (0.59, 1.65)	.964
Anxiety/depression	4.32 (2.20, 8.47)	< .001
MZ pairs (n = 107)		
Chronic NP	1.67 (0.80, 3.48)	.170
Leisure time physical activity	0.64 (0.32, 1.27)	.200
Smoking	0.30 (0.11, 0.86)	.025
Anxiety/depression	3.74 (1.52, 9.19)	.004

Analysis adjusted for sex, age, daily physical activity, leisure time physical activity, BMI, smoking, alcohol use, anxiety/depression and educational level. BMI = body mass index, CI = confidence interval, DZ = dizygotic, MZ = monozygotic, n = number of participants in each analysis stage, NP = neck pain, OR = odds ratio.

OR: 1.80; 95% CI: 1.43, 2.26; $P < .001$). The cotwin case-control analysis, including both MZ and DZ twin pairs (total n = 321), showed a statistically significant association between chronic NP and poor sleep quality (adjusted OR: 1.63; 95% CI: 1.07, 2.47; $P = .023$). The association was stronger and still statistically significant in DZ pairs (adjusted OR: 1.80; 95% CI: 1.05, 3.09; $P = .031$), but was smaller and nonsignificant in MZ pairs (adjusted OR: 1.67; 95% CI: 0.80, 3.48; $P = .170$). Interestingly, in this case, anxiety/depression remained significantly associated with poor sleep quality after controlling for genetics and common environment and regardless of NP status and other covariables (**Table 3**).

DISCUSSION

The aim of this study was to investigate the association between sleep quality and chronic NP, controlling for potential genetic and early shared environmental effects. Analysis of the total sample showed a statistically significant association between sleep quality (PSQI total score) and chronic NP. This association remained significant in the within-pair twin case–control analysis that included all complete MZ and DZ twin pairs discordant for chronic NP and in the analysis that included DZ twins, but not in the analysis carried out only in MZ twins. Similar results were observed in the reversed analysis, when sleep quality (PSQI score dichotomized) was considered as the outcome. Statistically significant associations were found in the total sample analysis, in the within-pair twin case–control analysis of all complete MZ and DZ twin pairs discordant for sleep quality, and in the analysis that included DZ twins. However, the effect was smaller and not significant in the analysis carried out only in MZ twins. These findings suggest that the association between sleep quality and chronic NP is partly confounded by genetic factors. Our results also highlight the relevant association between anxiety/depression and sleep quality, regardless of NP or other covariates, including genetics. Such association showed a lesser and nonsignificant magnitude when the analyses were performed on discordant pairs for NP. This would be compatible with a causal effect of anxiety/depression on sleep quality, but not on NP. More specific analyses, including the possible moderating or mediating role of psychological distress in the relationship between pain and sleep would be needed to shed light on this question.

Comparison with previous studies and interpretation of the findings

The genetic and environmental basis of the association between sleep and pain has been explored in previous studies.[20,38,39] In one study,[38] a statistically significant association between sleep problems and fibromyalgia was found in the total sample analysis, but was not present in any of the within-pair twin case–control analysis, suggesting that the association might be confounded by familial factors. Other studies investigated the association between sleep and back pain, and reported that genetic factors accounted for 42.5% of the covariance between sleep quality and low back pain,[20] as well as independent genetic correlations between back pain and sleep disturbance,[40] suggesting that genetic factors play an important role on this association. These results agree with those of another study,[39] where a comparison of the cross-trait correlations between pain and sleep showed stronger associations among offspring–father pairs and offspring–mother pairs compared to father–mother pairs. The coefficient of correlation accounted by genetic components for phenotypic associations between sleep and pain was also stronger than the coefficient accounted by environmental components (not statistically significant), suggesting a role of genetic factors. These latter results are supported by the findings of another study that showed a stronger influence of genetic factors compared with environmental factors on the

relationship between physical workload and NP.[41] In addition, other studies showed a higher genetic influence for the co-occurrence of NP and musculoskeletal pain in other body sites (eg, back, elbow, knee, thigh, hand, and foot) compared with NP in isolation, suggesting that there might be a common genetic factor accounting for the prevalence of general musculoskeletal pain rather than NP only.[42–44]

Outside the specific area of twin studies, the relationship between sleep and chronic musculoskeletal pain in the literature has often been described as bidirectional,[10,14,39] although evidence suggests that the temporal effect of sleep on the onset or exacerbation of musculoskeletal pain is stronger compared with the effect of pain on subsequent sleep.[14] Several mechanisms have been suggested in the literature to explain the association between sleep and pain. For example, a modification of the opiodergic or serotoninergic neurotransmission systems, which are involved in the regulation of sleep and pain, might decrease the pain threshold.[14,45] Also, genetic factors might be involved. Genes for the catechol-*O*-methyltransferase, the serotonin transporter, and the D4 neurotransmitter receptor gene have been proposed as potentially associated to both chronic pain and sleep.[25,39,46] The array of genes (at least 358) that might be associated with pain or analgesia is wide,[47] and some candidates for specific pain locations were recently proposed (eg, loci at SOX5, CCDC26/GSDMC, DCC, SPOCK2, and CHST3 associated with chronic back pain[40,48]). The mechanism responsible for the heritability of pain may include an alteration of pain processing, which would result from genetic factors.[21,40,49] Other individual or environmental factors are possibly associated with both low sleep quality and musculoskeletal pain, such as anxiety and depression symptoms,[39,45] low levels of physical activity,[16,45] and smoking.[8,19] However, these factors have been controlled for in the analysis of our current study.

Strengths and limitations

This study has several strengths. First, it is based on a large and representative sample of Spanish adult twins.[30] Second, a within-pair case–control analysis was performed. This is a suitable method to control for the genetic and early shared environment influences on the association between sleep quality and chronic NP. Another strength of this study is that sleep quality was assessed through the PSQI (Spanish version), which has been shown to be a proper instrument for the assessment of sleep quality in adults.[33] This study also includes some limitations. First, the assessment of chronic NP may be somewhat restricted, as it did not include a clinical evaluation of the severity, impact (eg, care-seeking behavior), and disability associated with NP. Therefore, these results need to be viewed with caution when translated to the clinical setting. In addition, the question used on the assessment of NP may have been affected from "recall bias,"[50] as participants who experienced NP a long time ago may have had problems in recalling the actual duration of pain. Second, anxiety and depression were assessed with a combined measure that does not allow for identification of the individual effect of anxiety and depression on the relationship between sleep and chronic NP. Therefore, future studies should collect individual measures of anxiety and depression to assess the individual impact of these factors on this relationship. Third, the cross-sectional nature of this study limits the inference of causality on the association between sleep quality and chronic NP. However, analyses were performed in both directions (sleep quality as the exposure and chronic NP as the outcome variable and vice versa) and results are consistent with the bidirectional relationship between sleep and pain reported in the literature.[14] Future longitudinal studies may be carried out to elucidate the direction of causality of this association. Fourth, despite the reliability of the within-pair case–control method used, results of the analysis carried out only in MZ twins might have been affected by the reduced sample size of the MZ twin groups (82 and 107 twin pairs in model 1 and model 2, respectively). In addition, residual confounding may have influenced the explored association.

Implication for research and clinical practice

This study found that the association between sleep quality and chronic NP is partially confounded by genetic factors. However, to date it is not known which specific genes may underlie the association between sleep and NP. In addition, previous studies have shown that the genetic contribution to the occurrence of NP gradually decreases with increasing age, being replaced by an increased effect of environmental factors accumulated during the lifetime.[21,22,51,52] This suggests that, especially in adults and older adults, efforts should aim at limiting the exposure to certain environmental factors that may cause or worsen NP and sleep, such as those related to the work environment (eg, sedentary work postures, work-related psychosocial factors, having shifts at work, and irregular work hours).[53,54] Potential effective strategies to target environmental factors could be the implementation of fitness training at the work place, exercise, and promoting sleep hygiene.[53,54] In addition, in individuals with chronic NP or sleep problems, or when a sleep-chronic pain reciprocal relationship is established, medications might be prescribed to improve pain and consequently sleep or to improve sleep directly.[10,53,55] However, potential issues with medications, such as polypharmacy because of concurrent comorbidities (especially in older individuals), concerns about tolerance and addiction, and the limited long-term effects of sleep and pain medications should be considered.[10,55] Alternatively, sleep problems and pain might be managed through nonpharmaceutical approaches such as cognitive-behavioral therapy.[10,53,56] However, genetic and environmental factors interact in the occurrence of diseases. For example, genetic factors may be activated only after the exposure to certain environmental factors, or specific environmental factors may produce an effect only among those individuals with a specific genetic variant.[22,52] Therefore, the issue of a potential genetic basis underlying the association between sleep and chronic NP remains, and further research that investigates the genetic and environmental influences on this association is needed. More specific data, including extensive information on particular sleep dimensions and severity of sleep and NP problems across individuals of different age-ranges,[51] should be collected to enable the assessment of potential different effects depending on the variability of outcomes and exposures. If a genetic contribution on the relationship between sleep and NP is confirmed by future studies, the next step might be the

investigation of genes associated both with sleep and NP and whether there is a common genetic variant underlying the occurrence of NP and musculoskeletal pain in other body sites.[42,43] In addition, further research should focus more specifically on the type of sleep problem (eg, insomnia, obstructive sleep apnea) associated with chronic NP as well as exploring psychosocial factors that impact both sleep and chronic NP.

CONCLUSIONS

Poor sleep quality and chronic NP are linked, and this link appears to be partially confounded by genetic factors. Further research is needed to confirm these findings in groups of different age ranges and to subsequently identify the genetic variants potentially associated with both sleep and NP.

ABBREVIATIONS

BMI, body mass index
CI, confidence interval
DZ, dizygotic
MTR, Murcia Twin Registry
MZ, monozygotic
NP, neck pain
OR, odds ratio
PSQI, Pittsburgh Sleep Quality Index

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