Functional somatic symptoms in adolescence and young adulthood

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Chapter 3|
sleep problems and pain: a longitudinal cohort study in emerging adults

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Abstract

Background: Sleep and pain are thought to be bidirectional related on a daily basis in adolescents with chronic pain complaints. In addition, sleep problems have been shown to predict the long-term onset of musculoskeletal pain in middle-aged adults. Yet, the long-term effects of sleep problems on pain duration and different types of pain severity in emerging adults (aged 18-25) are unknown. This study investigated the cross-sectional and longitudinal relations between sleep problems and chronic pain, and musculoskeletal pain, headache, and abdominal pain severity in a general population of emerging adults. We studied whether these relations were moderated by sex, and if symptoms of anxiety and depression, fatigue, or physical inactivity mediated these effects.

Methods: Data of participants from the longitudinal Dutch TRacking Adolescents' Individual Lives Survey were used. Follow-up data were collected in 1753 participants who participated in the fourth (*N*=1668, mean age: 19.0 years [*SD*=0.6]) and/or fifth (*N*=1501, mean age: 22.3 years [*SD*=0.6]) assessment wave. Autoregressive cross-lagged models were used for analyses.

Results: Sleep problems were associated with chronic pain, musculoskeletal pain, headache and abdominal pain severity, and predicted chronic pain and an increase in musculoskeletal pain severity at three years follow up. This prospective effect was stronger in females than in males, and was mediated by fatigue but not by symptoms of anxiety and depression or physical inactivity. Only abdominal pain had a small long-term effect on sleep problems.

Conclusion: Our results suggest that sleep problems may be an additional target for treatment in female emerging adults with musculoskeletal pain complaints.

Introduction

Emerging adulthood (i.e. the period between 18-25 years old) is characterized by psychosocial and behavioral changes, such as altered sleep patterns (1,2). In emerging adulthood sleep habits change, problems with maintaining sleep increase, and around 30% of the emerging adults experience at least one sleep problem (3). Moreover, approximately 14% of the emerging adults suffer from chronic pain, females more often than males (4,5). Emerging adulthood could therefore be considered a unique developmental period to examine the effects of sleep problems on the course of pain complaints.

Sleep and pain have been shown to interact in a bidirectional manner on a daily basis in adolescents with chronic pain (6-9). Pain is thought to cause sleep problems in the short run through arousal caused by physical discomfort or catastrophizing thoughts. Yet, recent findings indicate that the long-term effects of pain on sleep are minor (10). Sleep problems on the other hand may not only be a short-term but also a long-term risk factor for pain increase through altered pain thresholds, emotional disturbances or behavioral changes (11,12). Although some longitudinal population studies have focused on the role of sleep in the onset of musculoskeletal pain in adolescents and adults (10), it is unclear if, and to what extent, sleep problems predict the long-term duration and severity of pain in the general emerging adult population. Eventually, more insight herein could contribute to the development of effective prevention strategies for pain in young people.

It is unknown whether the association between sleep problems and pain is symptom- or gender-specific (10,11) Sleep problems have been associated with musculoskeletal pain, headaches, and abdominal pain in cross-sectional studies (13-15). Yet, almost all longitudinal studies concerned musculoskeletal pain (10,16,17). Further, there is evidence that sleep and pain are stronger related in adult females than males (18), but it is not known whether emerging woman are also more vulnerable for the longitudinal effect of sleep problems on pain.

Another gap in the literature concerns the pathways via which sleep problems lead to pain. Empirical research on this topic is scarce. However, the three factors that have been suggested to mediate this association, are symptoms of anxiety and depression, fatigue, and physical inactivity (10). These factors have been found to be a result of sleep problems (19-21), and predictors of pain in adolescents and/or adults (22-25).

The main aim of this study was to investigate how sleep problems affects chronic pain and the severity of three commonly experienced pain types in a population cohort of emerging adults. We hypothesized that: 1) Sleep problems are associated with chronic pain and three types of pain severity; 2) The long-term relation between sleep and pain is bidirectional; 3) The effect of sleep problems on pain is stronger in females than in males; 4) Symptoms of anxiety and depression, fatigue, and physical inactivity mediate the effect of sleep problems on pain severity.

Methods

Design and participants

The sample consisted of participants of the TRacking Adolescents' Individual Lives Survey (TRAILS), a Dutch population-based cohort. The main objective of TRAILS is to investigate the etiology, underlying mechanisms, and course of mental and physical health during adolescence and young adulthood. After approval by the Dutch Central Committee on Research Involving Human Subjects, all primary schools in five municipalities in the North of the Netherlands (n=135) were informed about the study. In total, 122 schools agreed to participate. Subsequently, recruitment of participants (N=3145) subscribed to these schools was started, depending on their date of birth. Parents/guardians and children were informed about the study. Parents (T1-T3) and adolescents (T2-T5) had to provide written informed consent for inclusion. Exclusion criteria were inability of the child to participate due to a mental or physical handicap, or no Dutch, Turkish or Moroccan speaking parent/guardian (excluded: n=210). After extensive recruitment efforts (reminder letters, calls, home visits), 2230 children and their parents/guardians were included at baseline measurements which started in 2001 (mean age: 11.1 [SD: 0.6]; 50.8% girls) (26). More information about the population characteristics, non-response bias and recruitment efforts can be found elsewhere (26-28).

In this study, data from the fourth (T4) and fifth (T5) assessment waves (T4: N=1668, mean age 19.1 [SD: 0.6]; T5 N=1501, mean age 22.3 [SD:0.7], mean duration to follow up: three years) were used. Eleven percent of the participants attending one or both of these waves suffered from a chronic disease or handicap (as indicated by the parents at T4). See Table 1 for more details of the study sample.

Measures

Sleep problems. Sleep problems were obtained with the sleep scale of the Nottingham Health Profile (NHP) at T4, a well validated questionnaire for identifying health problems in adults (29). The NHP sleep scale was in previous research moderately related to the reported frequency of sleep disturbances ranging from hardly ever to every day (Spearman Rho = 0.3, $p < 0.05$) (30), and strongly related to the Pittsburg Sleep Questionnaire Index (PSQI) in adults (Spearman Rho 0.61, $p < 0.001$) (31). The five sleep items of this questionnaire refer to the overall experience of sleep problems: 'I take pills to help me sleep', 'I am waking up in the early hours of the morning', 'I lie awake for most of the night', 'It takes me a long time to get to sleep' and 'I sleep badly at night'. These questions were answered with 'yes' or 'no'. The scale score for sleep problems (i.e. the number of sleep problems experienced by the participant, range 0-5) was used (Cronbach's Alpha = 0.65), since exploration of the data revealed a linear relation between the number of sleep problems and pain severity.

Pain. Pain was assessed at T4 and T5, with a questionnaire previously developed for pain research in adolescent populations (32,33). This questionnaire includes a Numeric Rating Scale, which is a recommended pain measure also validated in young adults (34,35). Participants were asked in three subsequent questions if they had experienced one of the following pain types more than one day in the preceding 12 months; musculoskeletal pain (in legs, arms, back, neck or shoulder), headache or migraine, or abdominal pain. It was clearly stated that the questions did not refer to, for instance, muscle pain after sport activities or incidental headaches of short duration. When participants filled in 'yes', they additionally indicated to what extent they had suffered from that particular pain on a 10 point Likert scale (1=very mild pain-10=unbearable pain). Participants who filled in that they had *not* experienced a certain pain type on any day in the previous twelve months were assumed to have experienced a pain severity of '0'. Additional pain indicators were also available. Participants reported how long the pain had lasted ('less than four weeks', 'between four weeks and three months', 'more than three months'), how often they had experienced the pain in the preceding three months ('less than once a month', 'once a month', 'two to three times a month', 'once a week, 'two to six times a week' or 'every day'), to what extent their pain had interfered with their daily activities (T4) or their work (T5) in the previous month ('not at all', 'a little bit', 'a lot' or 'very much'), and how often they used pain medication ('almost never', 'less often than once a month', 'at least once a month but not weekly', 'weekly' or 'daily'). In line with previous research in adolescents, chronic pain was defined as having experienced at least one type of pain, with a mean severity of more than 5, at least weekly for more than three months (33,36). In addition, we constructed a pain severity scale (range: 0 'no pain at all'- 10 'unbearable pain') for each of the three pain variables separately. The pain severity ratings were given independently of the frequency and chronicity ratings of the pain complaints. The information about the interference of daily life by the pain complaints and the use of pain medication were used to describe our sample and for cross-sectional analyses at T4.

Potential mediators. *Symptoms of anxiety and depression* were assessed at T4 using the Anxious/Depressed scale of the Adult Self-report (ASR) a well validated and reliable questionnaire for adults (37). This scale consists of 18 items which can be rated to have occurred 0 = 'never', 1 = 'sometimes or a bit', or 2 = 'often or a lot', during the past six months. The scale showed good internal consistency in our sample (α = 0.91). *Fatigue* was assessed with two items of the ASR at T4. One item referred to fatigue without an obvious reason ("I feel tired without an obvious reason") and the other referred to having low energy ("I experience low energy") during the past six months. These items could be rated to have occurred 0 = 'never', 1 = 'sometimes or a bit', or 2 = 'often or a lot'. We computed the mean score on these two items. *Physical inactivity* was derived from one item at T4 asking how many days in the past week (range 0-7) the participant was involved in physical activities for more than 60 minutes. Participants had to count all activities which raised breathing rate or heart rate, including sports, walking and bicycling. This single-item physical activity measure has been shown to be a reliable and valid measure of physical activity in adolescents and adults (38,39).

Statistical analyses

Descriptive statistics were performed in SPSS 22.0. Subsequent analysis were performed in Mplus 5.2. First, the cross-sectional relations of sleep problems with chronic pain, musculoskeletal pain, headache and abdominal pain severity, interference of pain in daily life and the use of pain medication at T4, were studied in a covariance matrix. Second, the bidirectional relations of sleep problems at T4 and T5 with chronic pain, and musculoskeletal pain, headache and abdominal pain severity, at T4 and T5 were studied in four autoregressive cross-lagged models, adjusted for sex. The relations between sleep problems and pain severity were analyzed in all participants, and not only in participants with any pain or chronic pain. To test our third hypothesis that sleep problems have a stronger effect on pain in females, the product of the centered variable 'Sleep problems at T4' and the centered variable 'Sex' was entered into the cross-lagged models. Additional analyses stratified by sex were only performed when this interaction term was significant. To study if symptoms of anxiety and depression, fatigue, or physical inactivity at T4 mediated the effect of sleep problems at T4 on the severity of the three pain types at T5, mediation analyses were performed. The potential mediators were not entered simultaneously to avoid multicollinearity between fatigue and symptoms of anxiety and depression ($R=0.56$). Kappa squared (K^2) effect sizes were calculated for significant indirect effects.

Missing values on any of the included variables, beyond attrition, were less than 2%. Participation in T4 or T5 (instead of attending both waves) was predicted by sex, age, parental socioeconomic position and sleep problems at T4, but not related to any of the pain variables at T4 or T5, sleep problems at T5 or the potential mediators at T4. Therefore, missing values were assumed to be missing at random (MAR) and handled with maximum likelihood estimation. Age and socioeconomic position were not related to the dependent variables and thus not included in the model. Since none of the variables were normally distributed in the sample, bias corrected bootstrapping was performed (10.000 per analyses) (40). Statistical significance was defined as a 95% CI not including zero.

Results

Descriptive statistics

The study cohort consisted of 1753 (79% of baseline enrollment) TRAILS participants attending T4 and/or T5. In total, 1668 participants were included at T4, whereof 1416 also attended T5. Additionally, 85 participants who did not attend T4 attended T5. The characteristics of these participants are shown in Table 1. Of the participants with at least one sleep problem at T4, 53% also suffered from sleep problems at T5. The severity, frequency and duration of the musculoskeletal pain, headache, and abdominal pain experienced by participants are described in more detail in Table 2.

Table 3.1. Sample characteristics.

	T4	T5
Subjects, *N*	1668	1501
Female subjects, *n* (%)	918 (55%)	847 (56%)
Age, *M* years (*SD*)	19.0 (0.6)	22.3 (0.6)
Low educated*, *n* (%)	774 (46%)	172 (11%)
Subjects in school/college, *n* (%)	1439 (86%)	993 (66%)
Any sleep problems, *N* (%)	617 (37%)	580 (52%)
Sleep problems, *M* (*SD*)	0.6 (1.0)	0.7 (1.1)
Difficulties falling asleep, *n* (%)	465 (28%)	376 (25%)
Sleeping badly, *n* (%)	235 (14%)	230 (15%)
Waking up early, *n* (%)	172 (10%)	239 (16%)
Lying awake, *n* (%)	158 (9%)	126 (8%)
Using sleep medication, *n* (%)	34 (2%)	44 (3%)
Any pain, *n* (%)	1275 (76%)	1118 (74%)
Pain(s) ≥1/week, *n* (%)	345 (21%)	345 (23%)
Pain(s) ≥3 months, *n* (%)	260 (16%)	269 (18%)
Chronic pain, *n (%)*	192 (12%)	212 (14%)
Interference, *n* (%)	179 (11%)	147 (10%)
Pain medication ≥1/week, *n (%)*	169 (10%)	143 (10%)

Note. *Only finished elementary school or lower tracks of secondary education. Chronic pain = weekly pain with a severity > 5 for ≥ 3 months. Interference=interference of pain with daily activities (T4) or work (T5) ≥ a lot.

The bidirectional relation of sleep with pain

Sleep problems at T4 were significantly associated with the presence of chronic pain (B = 0.04, 95% CI [0.02, 0.06]), musculoskeletal pain severity (B = 0.48, 95% CI [0.33, 0.66]), headache severity (B = 0.52, 95% CI [0.35, 0.69]) and abdominal pain severity (B = 0.65, 95% CI [0.50, 0.80]) at T4.

Sleep problems at T4 significantly increased the probability of chronic pain at T5 three years later (Figure 1). Of the 1415 participants attending both waves, 9% (n=124) reported chronic pain at T5 but not at T4 (i.e., new onset chronic pain). Twelve percent of the participants (n=165) reported chronic pain at T4, whereof 6% (n=80) also reported pain at T5 (i.e., persistent chronic pain), and 6% (n=85) reported no pain at T5 (i.e., remitted chronic pain). Post-hoc analyses revealed that sleep problems predicted both the onset (*B* = 0.15, 95% CI [0.06, 0.24]) and persistence vs remittance of chronic pain (*B* = 0.15, 95% CI [0.03, 0.027]). Sleep problems at T4 increased musculoskeletal pain severity (Figure 2) at T5 three years later. When a participant experienced all sleep problems at T4 compared to experiencing no sleep problems at T4, the probability of chronic pain at T5 increased from 14% to 38%, corresponding with an odds ratio of 3.8. The experience of all five sleep problems at T4 predicted an increase of 1.3 (scale 0-10) in musculoskeletal pain severity at T5. Sleep problems at T4 had no effect on the level of headache or abdominal pain severity at T5 (Figure 3 and 4).

Abdominal pain severity at T4 had a small effect on sleep problems at T5 (Figure 4): suffering from unbearable pain (a score of 10) resulted in a 0.3 increase of sleep problems. Chronic pain, musculoskeletal pain severity and headache severity had no significant effect on sleep problems (Figure 1, 2 and 3).

Table 3.2. Musculoskeletal pain headache and abdominal pain severity at T4 and T5.

T4	Musculoskeletal pain *N* = 1668	Headache/Migraine *N* = 1668	Abdominal pain *N* = 1668
Pain, *n* (%)	768 (46%)	816 (49%)	734 (44%)
Females, *n* (% Pain)	458 (60%)	548 (67%)	545 (74%)
Pain severity (0-10), *M* (*SD*)	2.4 (3.0)	2.5 (2.9)	2.3 (2.9)
Pain severity (1-10)*, *M* (*SD*)*	5.3 (2.0)	5.1 (2.0)	5.3 (2.0)
Frequency ≥1/week, *n* (% Pain)*	326 (42%)	178 (22%)	136 (19%)
Duration ≥3 months, *n* (% Pain)*	176 (23%)	57 (7%)	62 (8%)
T5	Musculoskeletal pain *N* = 1501	Headache/Migraine *N* = 1501	Abdominal pain *N* = 1501
Pain, *n* (%)	726 (48%)	714 (48%)	614 (41%)
Females, *n* (% Pain)	457 (63%)	513 (72%)	490 (80%)
Pain severity (0-10), *M* (*SD*)	2.8 (3.2)	2.6 (3.1)	2.3 (3.0)
Pain severity (1-10), *M* (*SD*)*	5.7 (2.0)	5.6 (2.0)	5.7 (2.0)
Frequency ≥1/week, *n* (% Pain)*	332 (46%)	151 (21%)	114 (19%)
Duration ≥3 months, *n* (% Pain)*	202 (28%)	51 (7%)	66 (11%)

Note. *These values were based on only those participants reporting pain.

The moderating role of sex in the effect of sleep problems on pain

Sex affected the influence of sleep problems on chronic pain (*B* = -1.81, 95% CI [-2.37, -1.18]), musculoskeletal pain (*B* = -0.37, 95% CI [-0.73, -0.07]) and abdominal pain (*B* = -0.32, 95% CI [-0.63, -0.01]), but not on headache severity at T5 (*B* = -0.05, 95% CI [-0.33, 0.24]). Subsequent stratified models showed that the significant effects of sleep problems at T4 on pain at T5 did only hold for females (chronic pain: *B* = 0.18, 95% CI [0.09, 0.25]; musculoskeletal pain: *B* = 0.38, 95% CI [0.17, 0.59]), and not for males (chronic pain: *B* = 0.06, 95% CI [-0.12, 0.19]; musculoskeletal pain: *B* = 0.06, 95% CI [-0.18, 0.31]). In addition, sleep problems at T4 predicted an increase of abdominal pain severity at T5 in females (*B* = 0.22, 95% CI [0.01, 0.43]) and not in males (*B* = -0.03, 95% CI [-0.23, 0.19]). Since sex did not moderate the effect of sleep problems on headache severity, no subgroup analyses were performed for this pain variable.

The mediating role of symptoms of anxiety and depression, fatigue and physical inactivity

The mean score on the symptoms of depression and anxiety scale was 0.32 [*SD*=0.33, range 0-2], and the mean score on the fatigue scale was 0.47 [*SD*=0.58, range 0-2] at T4. The mean number of days that participants were more than 60 minutes physical active at T4 was 3 [*SD*=2, range 0-7]. The associations between these three potential mediating variables at T4, sleep problems at T4 and pain variables at T4 are shown in Table 3. Higher fatigue levels and higher levels of anxiety and depression symptoms at T4 were associated with more sleep problems and more pain at T4, while physical inactivity at T4 was only associated with musculoskeletal pain severity at T4, and not with other pain severities.

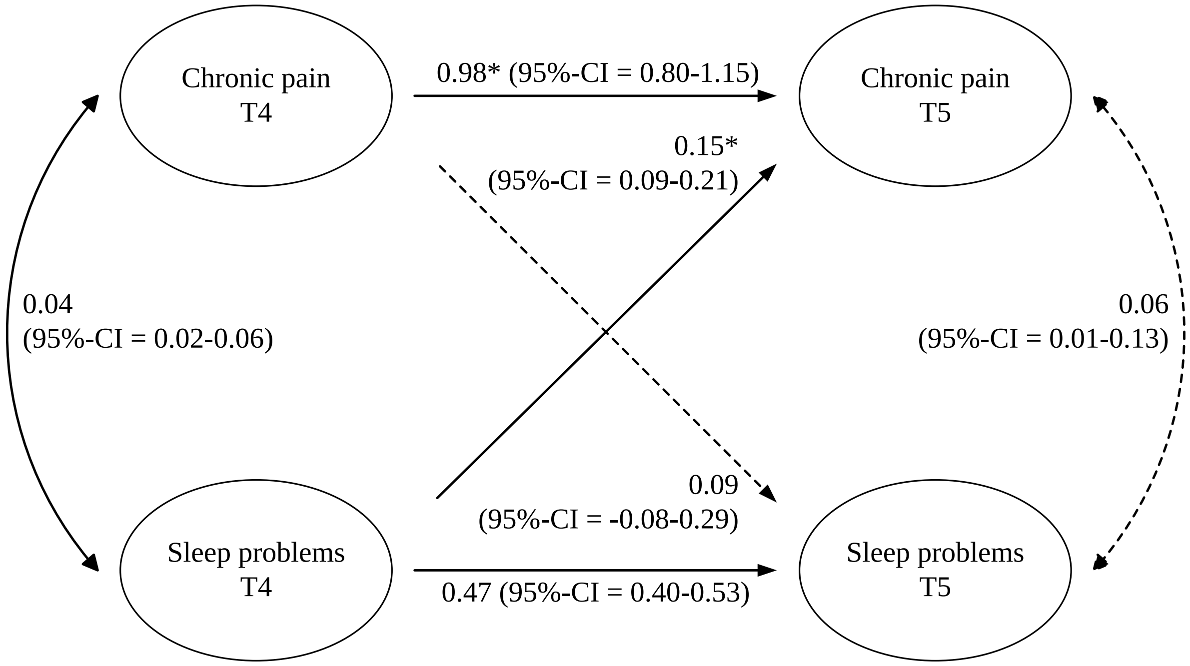
Table 3.3. The associations between potential mediators, sleep problems and pain variables at T4

	Sleep problems	Musculoskeletal pain severity	Headache severity	Abdominal pain severity
	Estimate, 95% CI	Estimate, 95% CI	Estimate, 95% CI	Estimate, 95% CI
Anx/Dep	0.10 [0.08, 0.12]	0.18 [0.13, 0.22]	0.19 [0.15, 0.25]	0.19 [0.15, 0.24]
Fatigue	0.18 [0.14, 0.21]	0.28 [0.20, 0.37]	0.37 [0.29, 0.46]	0.31 [0.22, 0.40]
Physical activity	0.03 [-0.08, 0.13]	0.40 [0.08, 0.72]	-0.06 [-0.36, 0.23]	0.17 [-0.13, 0.46]
Interference	0.11 [0.07, 0.15]	1.12 [1.00, 1.24]	0.40 [0.31, 0.51]	0.29 [0.19, 0.39]

Note. The found estimates are unstandardized and adjusted for sex. Bias corrected 95% CI are displayed. Interference = interference of pain with daily life. Medication = medication for pain relieve. Anx/Dep = symptoms of anxiety and depression.

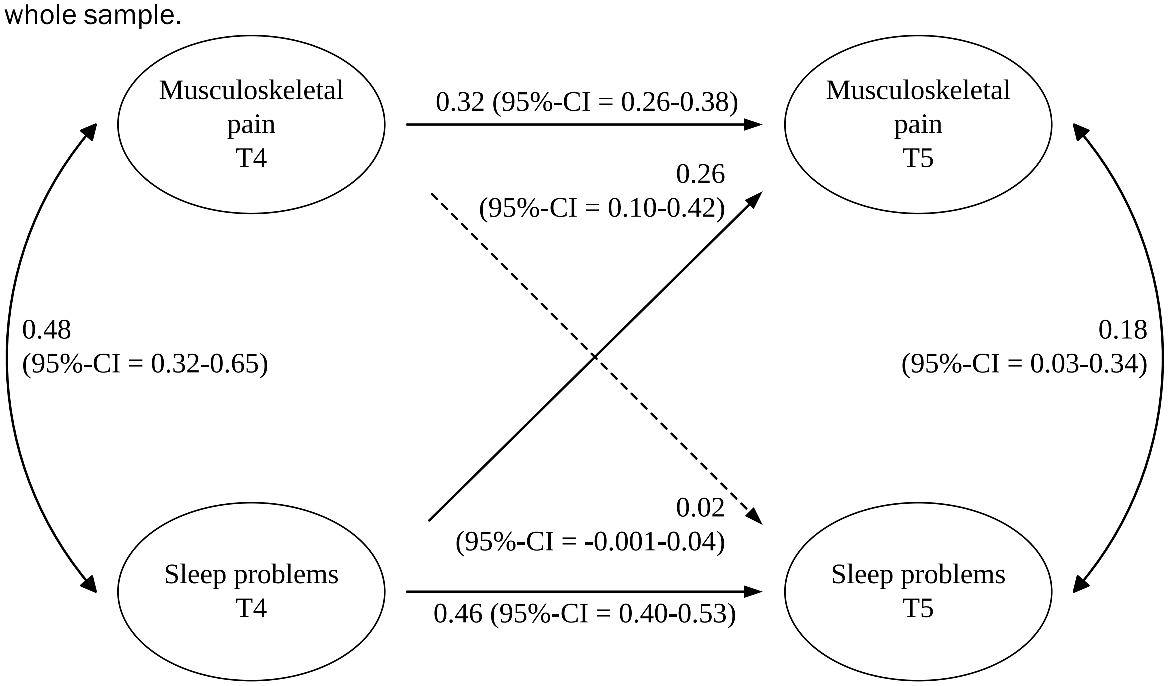
We tested if symptoms of anxiety and depression, fatigue or physical inactivity mediated the effect of sleep problems at T4 on pain severity at T5. Sleep problems only had an indirect effect on musculoskeletal pain severity through symptoms of fatigue (B = 0.05, 95% CI [0.01, 0.10], K^2 = 0.06), and on abdominal pain severity through anxiety and depression (B = 0.05, 95% CI [0.01, 0.09], K^2 = 0.06) and fatigue (B = 0.06, 95%-CI [0.02, 0.10], K^2 = 0.07)

Figure 3.1. The bidirectional relation of sleep problems with chronic pain.



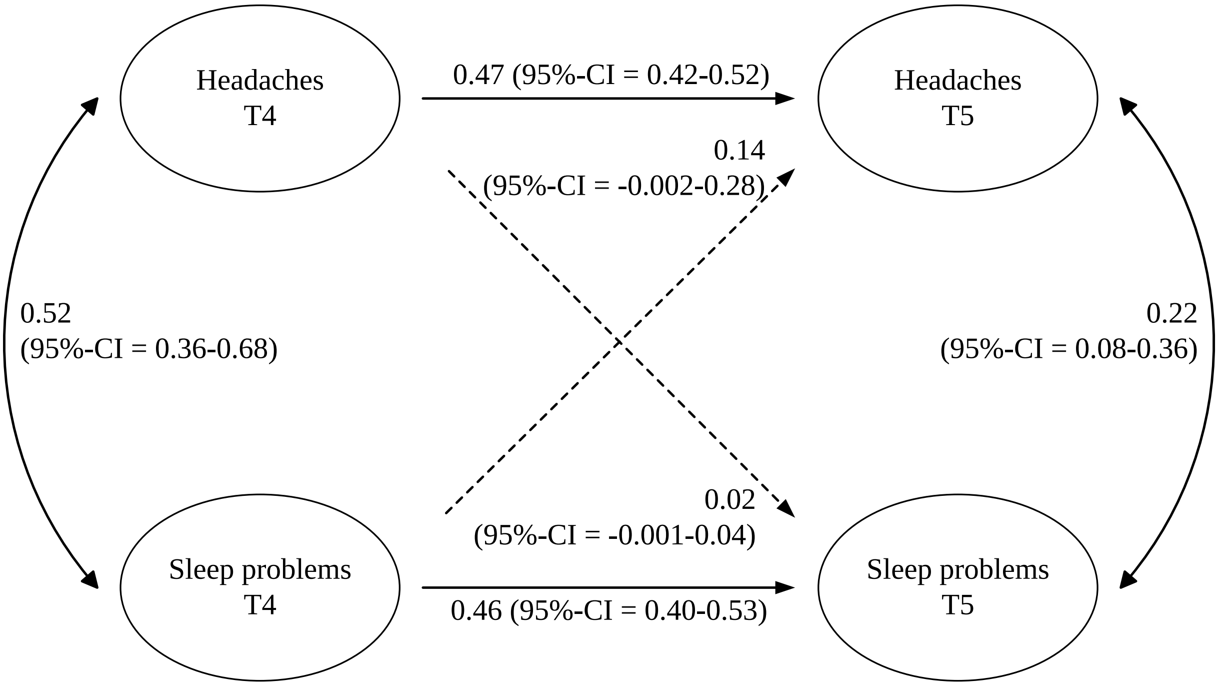
Note. Estimates are unstandardized. *probit regression coefficient. Chronic pain = at least one pain complaint at least once a week for longer than three months. Solid lines denote significant and dotted lines denote insignificant paths.

Figure 3.2. The bidirectional relation of sleep problems with musculoskeletal pain severity in the whole sample.



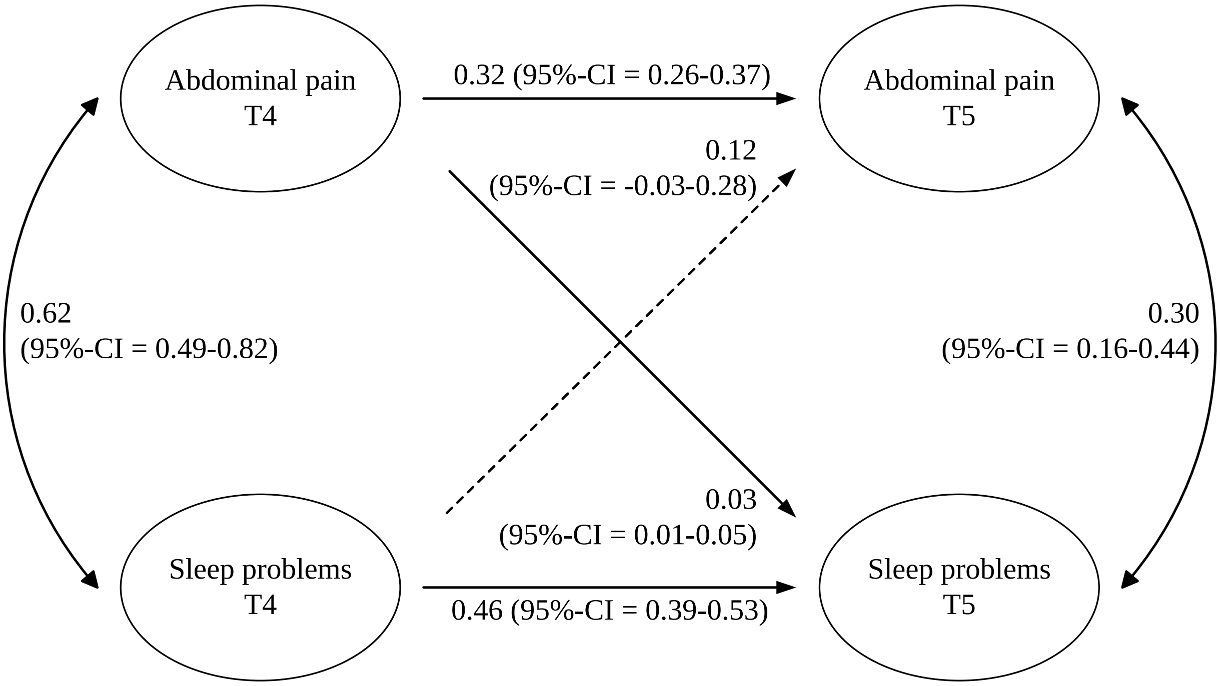
Note. Estimates are unstandardized. Pain severity range = 0-10. Solid lines denote significant and dotted lines denote insignificant paths.

Figure 3.3. The bidirectional relation of sleep problems with headache severity in the whole sample.



Note. Estimates are unstandardized. Pain severity range = 0-10. Solid lines denote significant and dotted lines denote insignificant paths.

Figure 3.4. The bidirectional relation of sleep problems with abdominal pain severity in the whole sample.



Note. Estimates are unstandardized. Pain severity range = 0-10. Solid lines denote significant and dotted lines denote insignificant paths.

Discussion

We found that sleep problems were associated with chronic pain, and musculoskeletal pain, headache and abdominal pain severity in emerging adults (aged 19-22 years). Sleep problems also predicted (persistent) chronic pain, and an increase of musculoskeletal pain severity over three years. These effects were stronger for females than for males. Sleep problems were only predictive of abdominal pain severity in females, and did neither predict headache severity in females nor in males. Only abdominal pain had a small long-term effect on sleep problems.

In line with our findings, a study in adolescents aged 15-17 years showed that impaired sleep predicted suffering from chronic musculoskeletal pain two years later (41). Findings in middle aged adults led to the same conclusion (10), and therefore sleep problems seem to predict the onset of chronic pain independent of life stage. Our research complements these studies by confirming an effect of sleep problems on the level of musculoskeletal pain severity, when adjusting for baseline pain. Our findings indicate that sleep problems are not only a precursor for pain, but actually predict the persistence of chronic pain and an increase in pain levels. In agreement with studies in clinical populations (10), our findings partly argue against a long-term bidirectional relation between sleep problems and pain. Previous micro-longitudinal research also revealed a stronger effect of sleep on daily pain compared with the effect of pain on sleep in adolescents and adults (6,42). Only abdominal pain had a small effect on sleep problems three years later in our study. This could indicate that the effect of sleep on pain runs through different mechanisms than the effect of pain on sleep, such as neurobiological alterations.

One might expect sleep problems to influence different pain types in a similar manner, when general mechanisms such as emotional disturbances would be responsible for the effect of sleep on pain. However, we only found effects of sleep problems on chronic and musculoskeletal pain. In agreement with the only other study on sleep problems and headaches in young people (aged 16-21 years) (43), sleep problems did not increase the level of headache severity in our study. We did also not find a long-term effect of sleep problems on abdominal pain. To our knowledge this relation was not previously investigated. Altered opiodergic and dopaminergic signaling due to impaired sleep are thought to play an important role in experiencing chronic pain by lowering pain thresholds (10,11). We found that musculoskeletal pain is more often chronic than headaches or abdominal pain, which may be the reason that sleep problems predicted a long-term increase of musculoskeletal pain severity in particular. Headaches and abdominal pain were often non-chronic problems, and therefore these pain types might be better predicted by day to day fluctuations in sleep than by a history of sleep problems (44,45). It could also be that sleep impairment is a specific risk factor for musculoskeletal pain. Sleep impairment was found to cause spontaneous muscle pain, fibromyalgia-like symptoms, and increased muscle tension in some experimental studies (10,11). Moreover, increased muscle tension may induce muscle fatigue, impair postural performances and increase the musculoskeletal requirements (46), and could therefore further increase the risk of minor injuries, muscle fatigue and related muscle pain.

We further found a stronger effect of sleep problems on pain in females than in males. This finding is in agreement with previous research in adults, but not with a study in 14 years old adolescents (18). This may suggest that the sex differences in the effect of sleep on pain start around older adolescence/emerging adulthood. It is not well known why sleep would impact pain particularly in females. Chronic musculoskeletal pain was in line with earlier studies more common in females (4,5), and chronic abdominal pain was even very rare in males. As mentioned earlier, this might be a reason why sleep problems predicted these pains in females but not in males. Another possibility is that there are biological (i.e. hormonal and gene driven) sex differences in how pain is modulated and that sleep problems lead to different functional neurological changes in females versus males (47).

Previous research already showed that sleep problems, pain and depressive symptoms are cross-sectionally related (10,48). The effect of sleep on physical activity was not previously investigated in adolescents, but a recent study found that impaired sleep predicted lower levels of physical activity the following day in adults (21). In addition, lower levels of physical activity were reported to be related to higher levels of pain symptoms in adolescents and adults (17,23,24). Therefore, the effect of sleep problems on pain levels might run through physical inactivity, but we did not find support for this mediation effect in our study. Fatigue has previously been shown to predict pain in adolescents and adults (16,25), and is obviously a potential consequence of sleep problems. Our findings indicate that the presence of fatigue in emerging adults with sleep problems may be responsible for a small increase in musculoskeletal pain severity, even over a period of three years' time. Emotional disturbances did not play a role in how sleep influences pain over time.

Our study has some limitations that should be kept in mind when interpreting the results. First, we had no detailed information about sleep problems with regard to their severity, their frequency, or their impact on daily life, since only the NHP sleep subscale was available. Therefore, our measure of sleep problems only reflected a limited number of sleep problems. Although the NHP sleep subscale highly correlated to the PSQI in a previous study (31), the internal consistency of the scale was only moderate in our sample. In addition, some important sleep problems for young adults such as nightmares and insufficient sleep length have not been captured in the NHP. A more extensive assessment of sleep problems could have shed more light on which specific aspects of sleep problems are related to pain. The same holds for our measures of fatigue and physical activity which were assessed with only a few items.

The use of variables with few items may have introduced contamination of the investigated constructs and measurement errors (49). The findings of our mediation analyses should therefore be interpreted with caution. More important, the potential mediating variables were assessed during the same wave as the predictor, and it can thus not be assured that they are in fact a consequence of sleep problems. Therefore, the found mediation effect could also be reversed with fatigue predicting pain levels through sleep problems. Second, because we studied pain severity as experienced in the general population, our overall pain levels were low due to a substantial amount of participants not experiencing any pain, thus reducing the power to find an effect of sleep problems on pain levels. Third, we asked the participants to report fatigue not explained by an obvious reason or medical cause. Participants who considered being fatigued as an obvious result of their sleep problems may therefore not have reported this complaint, which may account for the only small to moderate indirect effects of fatigue. Finally, the clinical relevance of the small to moderate mediation effects of fatigue could be questioned.

The main strength of this study is that we analyzed the longitudinal relations between sleep and pain using a cross-lagged panel model, which enabled us to control for baseline levels of pain and sleep problems. In addition, we were the first to study the relation between sleep and pain in emerging adults, an often overlooked life period known for its high prevalence of sleep problems and pain complaints (1,4). Further, the associations of sleep problems with these three pain types were studied in a population cohort which makes it more likely that our findings are generalizable to the young adult population. Finally, because we studied pain severity as an outcome (instead of labelling pain as present or not present) we reduced the loss of information.

In conclusion, our findings suggest that sleep problems may be an additional target for treatment and prevention strategies in female emerging adults with chronic pain and musculoskeletal pain. Although the found effect of sleep problems on chronic pain and musculoskeletal pain severity was small, it was previously established that a change of 30% in pain severity could be considered a relevant change in clinical settings (50). Hence, the increase of more than one point in severity due to sleep problems in our study may be seen as clinically relevant in emerging adults suffering from low and moderate pain levels, while this one point increase is probably not of clinical relevance in emerging adults already suffering from severe pain. This underlines the importance of managing sleep problems at an early stage. In future research it would be interesting to focus on the question why impaired sleep predicts change in musculoskeletal pain, and not headache and abdominal pain, and why only in females. Finally, it could be valuable to study more indirect pathways through which sleep can affect pain, such as worrying, functional neurological alterations, (neuro)endocrine changes, or inflammation (10,11).

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