Individual Differences in Concurrent Developmental Trajectories of Pain and Insomnia in Adolescents Are Predicted by Chronotype and Arousal-causing Pre-sleep Behaviors.

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Research Article

Keywords: Chronic pain, insomnia, concurrent developmental trajectories, adolescents, chronotype, arousal-causing, pre-sleep behaviors

Posted Date: November 1st, 2021

DOI: https://doi.org/10.21203/rs.3.rs-1016845/v1

Abstract

The onset of both chronic pain and insomnia is high during adolescence. Although a bidirectional relationship between pain and insomnia has support, how pain and sleep co-develop throughout adolescence remains unknown. Both sleep-wake patterns and pre-sleep behaviors that cause arousal may influence the co-development of pain and insomnia. Four waves of longitudinal self-report data were used ($N^{baseline}$ = 2767, $Age^{baseline}$ M = 13.65 years, SD = 0.65). Multidimensional growth mixture modeling was used to identify four subgroups of adolescents with different concurrent trajectories of pain and insomnia. The trajectories followed each other across time in all classes: one class of consistently low pain and insomnia (68.7 %), one class with persistent high symptoms (4.9 %), as well as one class of increasing (13.9 %), and one of decreasing (12.5 %), trajectories. Later sleep-wake patterns and more pre-sleep behaviors causing cognitive-emotional arousal predicted both increasing and decreasing trajectories of concurrent pain and insomnia. The current study showed that developmental trajectories of pain and insomnia follow each other within adolescents and across adolescence. Both sleep-phase focused interventions as well as psychological interventions that focus on pre-sleep behaviors causing cognitive-emotional arousal may prove beneficial for adolescents with comorbid pain and insomnia.

1. Introduction

Chronic pain is a leading cause of years lived with disability worldwide [1]. Insomnia appears to be a considerable driver of pain [2,3], also during adolescence [4], which has been identified as a critical period for their co-development [5]. The incidence and onset of both chronic pain [6] and insomnia [7] is high across adolescence. About 50 % of adolescents who suffer from chronic pain also have insomnia [8,9], and this comorbidity may be more disabling than each condition on its own [9].

Evidence supporting an association between pain and insomnia continues to grow. Yet, little is known about how pain and insomnia co-develop over time. Which co-developmental trajectories of pain and insomnia can be distinguished, and what factors predict these different patterns? It is known that adolescents who develop chronic pain [10] or insomnia [11] are at high risk of maintaining these conditions into adulthood. A better understanding of how pain and insomnia co-develop throughout adolescence may not only reveal specific targets for intervention for adolescents with comorbid insomnia and chronic pain but is also needed to develop effective strategies to prevent the maintenance and exacerbation of chronic pain and sleep conditions.

We are not aware of any studies that specifically have addressed heterogeneity and individual differences in longitudinal co-development of insomnia and pain. Several critical questions remain unanswered. For example, how do insomnia and pain continuously and concurrently develop throughout adolescence? Beyond the 50 % clinical comorbidity [8,12], how do insomnia and pain relate at sub-clinical levels? Are there subgroups of adolescents with only insomnia or pain problems? Can the mixed findings on the reciprocal relationship between sleep disturbance and pain [2] be attributed to (unobserved) subgroups in

the general population of adolescents who show a weak sleep-pain relationship? A recent review established that a change towards poorer sleep can predict a future increase in pain, but it remains unclear whether an improvement in sleep quality can predict a decrease in pain [13]. The authors hypothesized that this inconsistency may be due to considerable heterogeneity in the results of the included studies [13]. Previous research has shown that some pediatric subpopulations are particularly vulnerable to comorbid sleep and pain problems, such as youth with sickle-cell disease, intellectual or developmental disabilities or juvenile idiopathic arthritis [8,14]. Questions remain whether this may also be true for other, unobserved subgroups among adolescents that are not as readily predefined. Such subgroups may explain heterogeneity of results in previous studies.

Applying a person-oriented framework [15] may address such gaps in the literature. Strengths with a person-oriented framework are that it allows for exploring how pain and insomnia co-develop within the same individual over time (in addition to differences between individuals), unobserved heterogeneity of developmental trajectories, and if predictors differ in salience depending on subgroup [16]. A person-oriented perspective also allows for an exploration of factors that explain and predict different co-developing patterns of pain and insomnia. Relatively little is known of such predictors or risk factors, but potential candidates include female gender, older age, depression and anxiety, stress, low socioeconomic status (SES), and immigrant background [8,14,17]. Moreover, since insomnia has been found to be a stronger predictor of future pain than vice versa, a focus on sleep-related risk factors has been proposed when examining comorbid pain and insomnia [8]. Yet, it is not known whether risk factors for insomnia predict how both pain and insomnia co-develop over time.

The increasing prevalence of pain and insomnia during adolescence temporally coincides with both pubertal development and a pronounced delay in sleep-wake patterns [18], the latter mainly driven by a reduced build-up of sleep pressure and a delayed circadian rhythm [5]. Therefore, the concurrent increases of pain and insomnia in adolescents have been explained in terms of developmental changes associated with puberty or by factors specifically related to the delay in sleep-wake patterns [5,12], such as melatonin. For example, delayed dim light melatonin onset is apparently associated with delayed sleep-wake patterns in adolescents [7,19] as well as with pain [20].

One manifestation of a delay in sleep-wake patterns is a late *chronotype* [18], commonly operationalized as the midpoint of sleep on days without sleep restriction [21]. In cross-sectional studies, a late chronotype has been associated with insomnia and negative mood in adolescents [22,23] and pain in adults [24,25]. There is also broad evidence for a bidirectional relationship between pain and circadian rhythms [26]. However, no longitudinal studies to date have explored the effect of a late chronotype on concurrent pain and insomnia.

Besides biological circadian factors, late night pre-sleep behaviors, such as chatting with friends or worrying, may play a role in concurrent pain and insomnia. Pre-sleep arousal and poor sleep hygiene habits have been shown to predict insomnia in adolescents with comorbid pain [9,12]. Moreover, cognitive

and physiological hyperarousal has been found to be a main etiological factor in the pathogenesis of insomnia [7], and has been associated both with pain generally [20], as well as the interaction between sleep and pain specifically [5]. The question of whether and how these risk factors simultaneously influence pain, beyond the indirect effect through insomnia, still remains unclear. To what extent pre-sleep behaviors that cause arousal may influence the co-development of insomnia and pain is a question that warrants further investigation.

The purpose of the current study was threefold: First, to identify subgroups of adolescents with unique co-developmental patterns of pain and insomnia by using a person-oriented multidimensional growth mixture modeling approach in a large longitudinal community sample of adolescents (N=2767) spanning from early to later adolescence (13/14 to 16/17 years old). Second, to describe the subgroups on demographic and mental health variables. Third, to explore the predictive effects of a late chronotype and pre-sleep habits causing either cognitive-emotional arousal (e.g., worry, rumination) or behavioral arousal (e.g., chatting with friends), on longitudinal growth trajectories of concurrent pain and insomnia. The resulting insights may prove useful in uniquely adapting interventions for adolescents with comorbid chronic pain and insomnia.

2. Method

2.1. Participants and procedure

This study is part of the Three Cities Study, a 5-year longitudinal study in Sweden that sought to better understand risk factors and mechanisms underlying mental health problems among adolescents. The procedure of the data collection is described in detail elsewhere [4,27]. To reduce risks for sampling bias, the Three Cities Study used passive consent from the parents and active consent from adolescents. The parents to 122 adolescents (3.7%) returned a prepaid letter where they declined participation, and, additionally, 447 adolescents (13.4%) either declined participation or were absent on the day of the first data collection. This resulted in a baseline sample of N=2767 (82.9 % of the N = 3336 target population: M_{age} =13.65 (SD = 0.65). The analyses reported in this article included the first four data waves since data on the predictor variables were not collected in the fifth wave of data collection. All cases that had any data on the main pain and insomnia variables at baseline were included in the analyses. This resulted in an analytic sample of N= 2755 participants (82.6 % of baseline target population, 99.6 % of baseline sample). 1384 adolescents (50 % of baseline sample) participated in all four measurement occasions, 2167 (78.3 %) adolescents participated in at least three, 2619 (94.7%) in at least two, and 148 (5.3 %) only participated at baseline. The study was approved by the regional Ethical Board in Uppsala (No 2013/384).

To investigate whether attrition across the four yearly measurement occasions (T1 to T4) was influenced by any systematic bias, we regressed attrition (number of missed measurement occasions, ranging from 1 to 3) on the baseline demographic characteristics of the adolescents (gender, age, SES and immigrant background) and all the other study variables (insomnia, sleep duration, chronotype depression, anxiety,

pain frequency, pain intensity, pain interference, sleep-related behaviors). Older adolescents (Wald $\chi^2(1) = 28.57$, $p < .001$), adolescents not born in Sweden or whose parents were not born in Sweden (Wald $\chi^2(1) = 23.31$, $p < .001$), or with a later chronotype (Wald $\chi^2(1) = 8.23$, $p = .004$) were more likely to drop out from the study.

2.2. Measures

2.2.1 Descriptive measures at baseline

Age, gender, SES, immigrant background, stress, depression, anxiety, sleep duration, insomnia, pain intensity, pain frequency, and pain interference were assessed at baseline (T1). *Age* was measured by asking the respondents to indicate their chronological age in years. *Gender* was measured by the respondent indicating “boy” or “girl” on one dichotomous item. *SES* was assessed using the four items of the *Family Affluence Scale, version 2 (FAS-II)*, from WHO’s Health Behavior in School-aged Children (HBSC) – survey [28]. The respondent was instructed to indicate whether they had their own bedroom in the household, how many cars the household had, how many computers the household currently owned, and how many times the household went on a holiday during the last 12 months. The mean on FAS-II in the Swedish HBSC-survey (N=23088) was $M = 6.28$ ($SD = 1.67$). The cut-off for *low SES* was set at 4.61, one standard deviation below the population mean [28]. *Immigrant status* was assessed by the respondent indicating whether they were born in Sweden and where either of their parents were born (Sweden, Scandinavia, Europe or outside of Europe). Immigrant background was defined as being born in Sweden or having one parent being born in Sweden (i.e., non-immigrant background), or being born outside of Sweden or having both parents being born outside of Sweden (i.e. immigrant background), according to the official definition of Statistics Sweden [29]. *Depressive symptoms* were assessed with the Center for Epidemiology Studies Depression Scale for Children (CES-DC). CES-DC is a 20-item Likert scale with possible responses ranging from 0 (“not at all”) to 3 (“a lot”), resulting in a total score ranging from 0-60 [30] At T1, possible responses ranged from 1 to 5 and were adjusted to the original scaling using a POMP method. CES-DC has shown good reliability and validity when applied on a sample of Swedish adolescents [30], and the cut-off for clinical depression was set at a total score of at least 24 [30]. In the current sample, the internal consistency of the scale at T1 was Cronbach’s $\alpha = .84$. *Anxiety* was assessed with the Overall Anxiety Severity and Impairment Scale (OASIS). OASIS includes five Likert scale items assessing the degree of anxiety and impairment due to anxiety experienced during the last week. Possible responses range from 0 (“no”/”none”/”not at all”) to 4 (“constant”/”extreme”/”all the time”), resulting in a total score ranging from 0 to 20 [31]. The cutoff for clinical anxiety problems is 8 [31], and the scale has previously shown good psychometric properties [31]. Cronbach’s alpha at T1 in the current study was $\alpha = .87$. *Stress* was assessed with the Adolescent Stress Questionnaire, Short version [32]. Adolescents indicated how much stress from various social domains they have experienced in the past six months, on a 27 item, five-point Likert scale, ranging from 0 = not at all stressful to 4 = very stressful. The internal consistency at timepoint 1 was $\alpha = .87$.

2.2.2. Pain measures

Pain intensity, pain frequency, and pain interference were measured separately for the three most common pain types in adolescents [6]: abdominal pain, headache, and musculoskeletal pain (i.e., pain in the neck, shoulders or back).

Pain intensity was measured by one item where the participants rated their average pain intensity during the last 6 months on a 10-point scale ranging from 0 ("not at all") to 9 ("very painful") [33]. In T3, the intensity measures for headache and abdominal pain asked for the average pain during *the last 2 months* instead for *the last 6 months*. To assess the potential impact of this, we fitted a longitudinal confirmatory factor analysis including the pain intensity measures for the three pain types across the four measurement occasions and tested for measurement invariance. The model met the assumption of strong measurement invariance, indicating that the meaning of the measures remained constant across the four measurement occasions, and that the deviation in T3 was inconsequential. For more details on these analyses, see the **Supplementary Information**.

Pain frequency; how often the participant had experienced pain, on average, during the last 6 months, was assessed with one item from the HBSC Symptom Checklist [34], with the possible answers on a five-point Likert scale being "rarely or never" (0), "about every month" (1), "about every week" (2), "more than once per week" (3), and "about every day" (4).

Pain interference: how much the pain severely interfered with three life domains - school work, friend relationships and leisure activities. Possible responses were "no", scored as 2, "yes, a bit", scored as 1, and "yes, definitely", scored as 0. The scores were reversed and summed across the three domains into a total score, ranging from 0 to 6. The measure was adapted from the Social Phobia Screening Questionnaire [35] for the purpose of the Three Cities Study and has been used in previously published studies [4,27].

Pain grades. A composite "pain grade" was constructed based on the above-mentioned facets of the pain experience (pain intensity, pain frequency, and pain interference) [17,27], as described in Table 1. We calculated separate pain grades for musculoskeletal pain, abdominal pain, and headache. An average pain grade was calculated by averaging the pain grades across these three pain types, for each individual and per measurement occasion. In the rest of this paper, pain grade refers to this average pain grade.

Table 1. Operationalization of the chronic pain grade scale in the current study.

	Pain grade				
	0	1	2	3	4
Pain frequency [0-4]	[0]	[1-4]	[1-4]	[1-4]	[1-4]
Pain intensity [0-9]	-	[0-4]	[5-9]	[5-9]	[5-9]
Pain interference [0-6]	-	[0-2]	[0-2]	[3-4]	[5-6]

The pain grade measure can be taken to capture the degree of problematic pain, which is defined as having a high pain intensity associated with either significant distress or disability, or being experienced as multiple types of pain [36]. A pain grade of at least 2 on all three pain types can be taken to reflect generalized, problematic pain [36].

2.2.3. Sleep

Insomnia symptoms were measured with the Insomnia Severity Index (ISI) [37], from T1 to T4. It consists of seven items regarding sleep problems during the last six months, each with ratings from 0 (“no problems at all”) to 4 (“very much”). Total scores range from 0 to 28. It has been used on a sample of Swedish youths with chronic pain [38], and it has shown significant correlations with other measures of sleep quality, such as the Pittsburgh Sleep Quality Index, sleep diaries, and polysomnography [39]. A total score of 9 has been suggested as an appropriate cut-off for insomnia in adolescents [40]. The internal consistency in the current sample was α = .85 for T1, α = .84 for T2, α = .86 for T3, α = .87 for T4.

Arousal-causing pre-sleep behaviors were measured from T1 to T4 by using two subscales of the Adolescent Sleep Hygiene Scale, revised version (ASHS-R) [41]. ASHS is a questionnaire including 28 items with possible responses on Likert scales ranging from 0 (“Always”) to 5 (“Never”). The 6-item *cognitive-emotional sub-scale* [0-30] measures cognitive-emotional arousal-causing pre-sleep behaviors (CEA-PSB) and includes items assessing worrying or ruminating in bed or feeling strong emotions in proximity to bedtime. The 3-item *behavioral arousal subscale* [0-15] measures behavioral arousal-causing pre-sleep behaviors (BA-PSB) and includes items assessing behavior before going to bed, or in bed, that increase physiological arousal and keeps you awake, such as talking on the phone or playing video games (3 items). The internal consistency in the current sample for the cognitive-emotional subscale was: .83 for T1, .83 for T2, .85 for T3, and .85 for T4; for the behavioral arousal subscale, the internal consistency was: .63 for T1, .67 for T2, .67 for T3, and .65 for T4. To represent change, we calculated the difference between pre-sleep behaviors at T1 and T4 (T4-value minus T1-value) and used it as a predictor of the trajectories of pain grade and insomnia symptoms. From here on, cognitive-emotional arousal-causing pre-sleep behaviors will be referred to as *CEA pre-sleep behaviors*, and behavioral arousal-causing pre-sleep behaviors will be referred to as *BA pre-sleep behaviors*.

Sleep duration was measured by using the School Sleep Habits Survey for adolescents (SSHS) [42], where the respondent is asked to estimate when they usually went to bed, how long time they usually took to fall asleep, and at what time they usually woke up, on average weekdays and average weekend days, during the last two weeks. In the current study, we included the average sleep time on weekdays and the average sleep time on weekends separately. Sleep duration was measured by calculating the time from bedtime to wake time, subtracting the reported time it took to fall asleep.

C*hronotype* was also assessed with the SSHS [42], operationalized as hours and minutes between midnight and sleep midpoint (the mid-point between sleep onset and wake time) on weekend days [21]. However, most adolescents' biological clocks are out of sync with school times, resulting in a general lack of sleep and accumulated sleep debt during weekdays for which they then compensate by sleeping in on weekends [51]. To adjust chronotype for this confounder *sleep debt*, we utilized the correction that is used in the Munich Chronotype Questionnaire: In individuals who sleep longer on weekends than on weekdays, half the difference of sleep time during weekdays and sleep time during weekends is subtracted from the chronotype-value [21].

Shift in chronotype was operationalized as change in adjusted chronotype between T1 and T4 (T4-value minus T1-value), measured in minutes.

2.3. Statistical analyses

Management of the raw data was handled in SPSS, version 24, and all subsequent analyses were conducted in Mplus, version 8.1. We applied multidimensional growth mixture modelling (GMM) following previously proposed guidelines [16,43,44]. GMM is a person-oriented analysis that extends latent growth curve modelling by incorporating a latent class variable that accounts for between-individual heterogeneity [16]. It assigns individuals to latent classes based on similar patterns of growth curves. A probability distribution decides what class the individual is most likely to belong to [43].

To assess model fit, we put substantive value on meaningful, theoretical interpretability of the class solution [16,44]. We also used two types of statistical indices: the sample size – adjusted Bayesian Information Criteria (SSA-BIC) and the adjusted Lo-Mendell-Rubin likelihood ratio test (LMR-LRT) [16]. In addition, we considered entropy, as opted for the model with the least restrictions on model parameters, while also encountering the least convergence problems[15]: First, separate growth models were constructed on insomnia symptoms and pain grade. Low model fit and significant variance factors indicate heterogeneity in growth trajectories [16]. Secondly, a multidimensional growth mixture model was constructed on these two growth models simultaneously. We opted for an explorative approach [43] and fitted latent class growth analyses (LCGA) with 2 to 7 classes, to establish the optimal number of classes. We then utilized Wald χ^2 -tests to compare a zero-variance model (LCGA) to a model with class-invariant variances (GMM-CI), as well as to explore whether equal variances across the classes fitted the data as well as class-varying variances (GMM-CV). As a general rule, the preferred model is as freely estimated as possible while not encountering convergence problems [16]. Convergence problems indicate that the model is inadequate, that it may be overparameterized, and that a more parsimonious model is preferred [43]. Thereafter, we successively freed parameters – first class-invariant parameters, then class-varying parameters, until the optimal model was established. Since freeing parameters may change what number of classes is optimal [16], we continuously tested 2 to 7 classes for both the class-invariant, and the class-varying models.

For incorporating the predictors (chronotype, CEA pre-sleep behaviors and PA pre-sleep behaviors, as well as change scores of those measures) into the GMM, we utilized the “three-step approach”, consisting of: 1) estimating an unconditional GMM, 2) assigning individuals to latent classes while accounting for uncertainty of class membership, and 3) including predictors of the class-variable and within-class growth factors. Benefits of this approach is that the parameters of the mixture model are not influenced by the auxiliary predictor variable, while still accounting for uncertainty rate in class membership [44]. Three sets of analyses were done: First, differences among the classes on selected baseline variables were compared via Wald χ^2 – tests. Secondly, a multinomial regression analysis was done to assess if baseline chronotype and arousal-causing pre-sleep behaviors could predict class membership. Third, we examined the effect of sleep-related predictors on within-class growth factors (intercept and slope) of insomnia symptoms and pain grade. More information on statistical indices and criteria can be found in the **Supplementary Information**.

For handling missing data, we used full information maximum likelihood estimation (FIML) [45].

3. Results

3.1. Estimation of the best fitting multidimensional growth mixture model

First, we established that latent basis growth curves fitted the data best. Second, we opted for a CI-GMM as the best-fitting model, since it fitted the data better than the LCGA while not encountering convergence problems (which the GMM-CV did), and it yielded theoretically meaningful classes that facilitated interpretation. Third, we found that a four-class solution of a GMM with class-invariant variances fitted the data best, when comparing theoretical meaningfulness and model fit indices of 2 to 7 classes. Details on model fit indices are described in Table 2. For more detailed information on these analyses, see the **Supplementary information**.

Table 2
Comparison of growth mixture models on insomnia symptoms and pain grade, on selected fit statistics (total N = 2755).

Fit statistics	2 Classes	3 Classes	4 Classes	5 Classes	6 Classes	7 Classes
LCGA						
LL (no. of parameters)	-71665.31	-71405.11	**-71168.38**	-71051.37	-70993.83	-70857.36
SSABIC	143477.68	142980.99	**142531.26**	14230.96	142109.60	141980.37
Entropy	0.796	0.754	**0.778**	0.785	0.757	0.764
Adj. LMR-LRT (*p*)	2489.90 (<.001)	507.59 (.027)	**461.79 (.014)**	228.26 (.201)	229.29 (.108)	149.18 (.375)
Class sizes in %	73.6 – 26.4	60.8 – 9.9	**58.1 – 8.1**	58.8 – 7.4	51.8 – 5.0	50.0 – 3.0
GMM-CI						
LL (no. of parameters)	-71074.35	-70970.12	**-70884.83**	*-70817.40*	*-70755.91*	*-70707.20*
SSABIC	142343.20	142158.46	**142011.60**	*141900.46*	*141801.19*	*141727.49*
Entropy	0.850	0.776	**0.786**	*0.794*	*0.778*	*0.786*
Adj. LMR-LRT (*p*)	600.68 (<.001)	203.32 (<.001)	**166.38 (.048)**	*131.54 (.059)*	*119.96 (.690)*	*101.53 (.173)*
Class sizes in %	84.3 – 15.7	74.0 – 11.7	**68.7 – 4.9**	*65.0 – 2.9*	*61.0 – 3.0*	*60.2 – 1.3*
GMM-CV*						
LL (no. of parameters)	-70529.12	-70673.47	**-70567.67**	-70502.04	*-70421.09*	*-70378.90*
SSABIC	141266.97	141598.37	**141438.95**	141359.86	*141250.16*	*141217.96*
Entropy	0.682	0.657	**0.683**	0.687	*0.719*	*0.742*
Adj. LMR-LRT (*p*)	1679.80 (<.001)	579.38 (<.001)	**174.62 (0.067)**	129.79 (.751)	*141.73 (.409)*	*83.42 (.158)*
Class sizes in %	53.2 – 46.8	50.5 – 14.6	**48.9 – 7.6**	48.6 – 7.6	*46.8 – 2.6*	*45.7 – 1.4*

Fit statistics	2 Classes	3 Classes	4 Classes	5 Classes	6 Classes	7 Classes

Note: The columns in bold text represent the optimal class number. The columns in italics represent models that encountered convergence problems.

LCGA= Latent Class Growth Analysis. GMM-CI = Growth Mixture model with class-invariant variances and covariances. GMM-CV = Growth Mixture model with class-varying variances and covariances. Columns in italics represent inadmissible solutions. Columns in bold represent the optimal solution.

LL = Loglikelihood.

SSABIC = Sample size adjusted Bayesian information criteria.

Adj. LMR-LRT = Adjusted Lo-Mendell-Rubin likelihood ratio test.

* For the class-varying models to properly converge, the variance of the intercept factors had to be constrained to be equal across classes, and the slope variances in the largest class had to be constrained to zero.

3.2 Class characteristics

3.2.1 Class descriptions

Figure 1 shows the conjoint trajectories of pain grade and insomnia symptoms of the four classes. Class 1 (n = 1893; 68.7 % of total sample) was primarily characterized by consistently low levels of pain grade and insomnia, although both trajectories increased slightly. This class was labeled “Low pain and insomnia”. Class 2 (n = 134; 4.9 %) was characterized by high levels of pain grade and insomnia symptoms throughout the measured period, although the trajectory of insomnia symptoms increased slightly. This class was labeled “High pain and insomnia”. Class 3 (n = 383; 13.9 %) was characterized by increasing trajectories of both pain grade and insomnia symptoms. We labeled this class “Increasing pain and insomnia”. Class 4 (n = 345; 12.5 %) was characterized by decreasing trajectories of pain grade and insomnia symptoms, although the decrease in pain grade was modest. This class was labeled “Decreasing pain and insomnia.

3.2.2 Baseline characteristics of classes.

Table 3 compares the classes on baseline variables. All variables, except for low SES and chronotype shift, differed depending on class. Class 2 (high pain and insomnia) consistently reported a more severe profile than the other classes. About two thirds (68.7 %) of the class-members were girls. This class reported the highest levels of arousal-causing pre-sleep behaviors. About half of the class-members fulfilled the criteria for clinical anxiety and clinical depression. Furthermore, class 2 reported the shortest average sleep times and the latest chronotype. Compared to class 1 (low pain and insomnia), class 2 reported a more than thirteenfold prevalence of generalized problematic pain. Class 3 (increasing pain and insomnia) generally showed low symptoms at baseline, but reported a large shift towards a later chronotype and the most profound deterioration of CEA pre-sleep behaviors. Class 4 (decreasing pain and

insomnia) showed the second highest symptom levels on most variables at baseline, but also the smallest shift in chronotype and was the only class to show an improvement in CEA pre-sleep behaviors.

Table 3
Sociodemographic data (mean (SD) or percentage) and differences of classes at baseline (T1).

	Class 1 (n=1893)	Class 2 (n=134)	Class 3 (n=383)	Class 4 (n=345)	Total (n=2755)	*Wald* χ^2 ($p < .05$)
Class probability	0.919	0.860	0.805	0.770		---
Demographic variables						
Age	13.63[a]	13.76[bc]	13.68[abd]	13.73[cd]	13.66	**11.93***
Gender, proportion girls	41.8%	68.7 %[a]	54.8 %	63.1 %[a]	47.6 %	**95.97***
Immigrant background	28.4 %[ab]	40.3 %[c]	30.0 %[ad]	32.3 %[bcd]	29.7 %	**8.91***
Low SES	9.2 %	14.2 %	9.4 %	11.8 %	9.8 %	4.29
Clinical anxiety	5.5 %	45.1%	13.9 %	31.4 %	11.9 %	**184.66***
Clinical depression	6.4 %	50.0 %	18.5 %	32.9 %	13.6%	**218.21***
Stress	16.81	41.73	25.25	34.89	21.40	**415.6***
Pain variables						
Average pain grade [0-4]	0.64	1.87	0.91	1.54	0.85	**396.40***
Generalized problematic pain	1.7 %[a]	22.4 %	2.9 %[a]	11.8 %	4.1 %	**63.98***
Musculoskeletal pain frequency [0-4]	0.67	2.16	1.02	2.16	0.91	**185.91***
Headache frequency [0-4]	0.66	2.12	0.92	1.77	0.91	**191.85***
Abdominal pain frequency [0-4]	0.49	1.71[a]	0.84	1.63[a]	0.77	**190.68***
Musculoskeletal pain intensity [0-9]	1.34	4.06	2.25	3.34	1.86	**189.72***
Headache intensity [0-9]	1.92	4.75	2.47	4.75	2.42	**363.23***
Abdominal pain intensity [0-9]	1.52	4.23	2.25	3.59	2.02	**247.14***
Musculoskeletal pain interference [0-6]	0.39[ac]	1.79[b]	0.82[c]	1.79[ab]	0.73	**32.53***
Headache interference [0-6]	0.55	2.09[a]	0.87	2.43[a]	0.95	**355.07***
Abdominal pain interference [0-6]	0.40	1.88[a]	0.80	2.14[a]	0.79	**253.51***

	Class 1 (n=1893)	Class 2 (n=134)	Class 3 (n=383)	Class 4 (n=345)	Total (n=2755)	*Wald* χ^2 ($p < .05$)
Sleep variables						
Insomnia symptoms [0-28]	3.32	17.26	5.91	12.74	5.57	**4356.94***
Sleep duration week (hours:minutes)	8:15	6:39	7:48	7:16	7:59	**269.75***
Sleep duration weekend (hours:minutes)	9:37	8:39[a]	9:32	9:16[a]	9:31	**32.52***
Chronotype (hours: minutes)	4:39	5:45	5:00[a]	5:10[a]	4:49	**84.82***
Chronotype change (hours:minutes)	00:24	-00:03	00:23	00:08	00:21	6.45
CEA-PSB [0-30]	6.31	16.22	9.37	13.27	8.1	**516.71***
CEA-PSB change	2.00[a]	0.88[ab]	5.17	-0.54[b]	2.20	**57.5***
BA-PSB [0-15]	7.62	9.75	8.80[a]	9.42[a]	8.12	**115.08***
BA-PSB change	2.84[a]	1.13[b]	2.61[a]	1.48[b]	2.59	**22.22***

Note. The variables with the post-script “change” refer to the change score of the variables value at T4 minus the value at T1. Pairwise comparisons, based on Wald χ^2 tests, were done between all classes on all variables. Since most comparisons were significant, the superscripts represent specifically the class comparisons that did not significantly differ; all class comparisons without superscript differed at $p < .05$ level. Note that pairwise comparisons were not done on variables with non-significant overall tests.

* $p < .05$.

CEA-PSB = Cognitive-emotional arousal-causing pre-sleep behaviors.

BA-PSB =Behavioral arousal-causing pre-sleep behaviors.

3.3. Sleep-related predictors of longitudinal trajectories and change.

3.3.1. Chronotype and pre-sleep behaviors that cause cognitive-emotional arousal predict diverging trajectories of

pain grade and insomnia symptoms.

To explore whether chronotype and arousal-causing pre-sleep behaviors at baseline could predict diverging concurrent trajectories of pain grade and insomnia symptoms, we conducted a multinomial regression analysis and focused on comparing the “Low pain and insomnia” class (1) with the “Increasing pain and insomnia” class (2), and the “High pain and insomnia” class (3) with the “Decreasing pain and insomnia” class (4). Note that all classes were compared, but that for clarity only the above-mentioned comparisons are presented here. See the **Supplementary Information** for the full set of analyses. As can be seen in Table 4, a later chronotype and higher ratings on CEA (but not BA) pre-sleep behaviors at baseline predicted increased insomnia symptoms and pain grade. An earlier chronotype and less CEA pre-sleep behaviors at baseline predicted reduced pain grade and insomnia symptoms.

Table 4
The influence of chronotype and arousal-causing pre-sleep behaviors on class membership, using multinomial logit regressions. Displayed are the predictors’ effects on the increasing Class 3, with the low Class 1 as reference, and the decreasing Class 4, with the high Class 2 as reference.

	Low (Class 1) versus Increasing (Class 3)	High (Class 2) versus Decreasing (Class 4)
Chronotype	**0.003***	**-0.004***
CEA-PSB	**0.101***	**-0.062***
BA-PSB	0.016^{ns}	-0.001^{ns}

Note. Unstandardized coefficients are shown. The predictors are measured at baseline (T1).

*p<.05.

^{ns} = non-significant at p < .05 level.

CEA-PSB = Cognitive-emotional arousal-causing pre-sleep behaviors.

BA-PSB = Behavioral arousal-causing pre-sleep behaviors.

3.3.2. Chronotype and pre-sleep behaviors that cause arousal predict within-class change of insomnia symptoms and pain grade.

To assess whether chronotype, CEA pre-sleep behaviors and BA pre-sleep behaviors could predict initial levels and longitudinal change in pain grade and insomnia symptoms, we regressed the intercepts and slopes of pain grade and insomnia symptoms on the predictors at baseline, as well as on their change

scores, in a multivariate regression analysis. Table 5 depicts the results of these analyses. CEA pre-sleep behaviors predicted levels of both pain grade and insomnia symptoms, a later chronotype predicted more insomnia symptoms, and BA pre-sleep predicted more insomnia symptoms as well as a slighter increase in insomnia symptoms. A greater shift to a later chronotype and a larger increase in reported CEA pre-sleep behaviors predicted a steeper longitudinal increase in insomnia symptoms, whereas only a greater increase of CEA pre-sleep behaviors predicted a steeper longitudinal increase of pain grade.

Table 5
The predictive effects of sleep-related factors on within-class change (intercept and slope factors) in pain grade and insomnia symptoms.

	Insomnia intercept (*p*)	**Insomnia slope (*p*)**	**Pain intercept (*p*)**	**Pain slope (*p*)**
Chronotype at baseline	**0.005 (.051)**	0.001 (.436)	0.003 (.527)	-0.002 (.588)
Chronotype change	—	**0.003 (.021)**	—	-0.003 (.289)
CEA-PSB at baseline	**0.496 (<.001)**	0.043 (.098)	**1.006 (<.001)**	0.093 (.054)
CEA-PSB change	—	**0.216 (<.001)**	—	**0.485 (<.001)**
BA-PSB at baseline	**0.125 (.015)**	**-0.076 (.033)**	0.101 (.335)	-0.125 (.058)
BA-PSB Change	—	-0.019 (.531)	—	0.018 (.764)

Note. Coefficients in bold are significant at $p < .05$ level. “Change” refers to a change score, where the value at T1 is subtracted from the value at T4.

CEA-PSB = Cognitive-emotional arousal-causing pre-sleep behaviors.

BA-PSB = Behavioral arousal-causing pre-sleep behaviors.

4. Discussion

The current study examined the co-development of pain and insomnia throughout adolescence. We identified four subgroups with different concurrent developmental trajectories of pain and insomnia symptoms. The results suggest that adolescents with consistently high pain and insomnia may constitute a unique subgroup that is particularly vulnerable. Furthermore, the study established that both

a late chronotype and pre-sleep behaviors causing cognitive-emotional (but not behavioral) arousal predicted pain and insomnia symptoms.

The current results show that trajectories of pain and insomnia co-occur to a high degree in all subgroups, regardless of the direction of the trajectories. We saw no indication that there were adolescents with only pain problems or insomnia, with no symptoms of the other condition. Given the substantial variability in the trajectories, however, there may be adolescents with high symptoms levels of either pain or insomnia included. This finding also indicates that previous lack of such relationship is not due to pain and insomnia being unrelated in some subgroups. Rather, previous study samples might have included subgroups with both increasing and decreasing trajectories, resulting in a null result when looking at grand means. By utilizing a person-oriented approach, we were able to show that there is a relationship between pain and insomnia in all unobserved subgroups in the general adolescent population. We are not aware of any previous study that has explored heterogeneity in longitudinal trajectories of co-developmental pain and insomnia. Previous studies have primarily focused on associations between variable means, for example that mean levels of insomnia symptoms at one timepoint can predict mean levels of pain at a later timepoint. Such an approach fails to capture continuity of trajectories over time and cannot demonstrate that pain and insomnia continuously co-change within individuals. Previous findings of established longitudinal stability of insomnia in adolescents with chronic pain [9] are in line with the current results.

In line with previous work [2,3,46], we were able to demonstrate a strong relationship between pain and insomnia. Notably, the trajectories in the decreasing pain and insomnia class do not follow each other as well as in the stable or increasing subgroups, as can be seen in Fig. 1. This fits the hypothesis that pain and insomnia follow each other on an upward, but not downward, trajectory [13]. Insomnia appears to have an important role in the development of pain in adolescents, but it remains uncertain if also a decrease in insomnia may predict a subsequent decrease in pain.

Most of the adolescents in the current sample had consistently low pain and insomnia levels throughout the measured period (Class 1, 68.7 %), which is to be expected in a sample derived from the general population. About 14 percent of the sample (Class 3, 13.9 %) was characterized by increasing levels of both pain and insomnia symptoms. Although there were no clear-cut characteristics at baseline to discern this subgroup, they showed the largest shift towards a later chronotype and the largest increase in pre-sleep behaviors causing cognitive-emotional arousal. A third subgroup showed decreasing levels of pain and insomnia symptoms (Class 4, 12.5 %), and although the decrease in pain was modest, it is encouraging to find a subgroup of adolescents who show improvement from comorbid pain and insomnia over time. Earlier chronotype and less arousal-causing pre-sleep behaviors could predict these decreasing trajectories, compared to the high stable trajectories. One possibility that deserves further study is that early, proactive strategies that focus on late chronotypes and arousal-causing pre-sleep behaviors may help in preventing the concurrent development of pain and insomnia. For example, experimental studies may manipulate chronotype and pre-sleep behaviors and demonstrate their causal effect on pain and insomnia.

A subgroup of consistently high pain and insomnia symptoms was also identified (Class 2.4.9 %), constituting about 5 percent of the overall sample. Girls made up two thirds of this subgroup. Adolescents in this subgroup showed higher levels of symptoms on most of the baseline characteristics examined, including stress, depression, and anxiety. They also reported the shortest sleep times, the latest average chronotype, as well as the most problematic pre-sleep behaviors. Compared to Class 1 (low pain and insomnia), they reported a more than thirteenfold rate of generalized problematic pain. This indicates that the subpopulation of adolescents with comorbid pain and insomnia is associated with a particularly complex illness-profile, and indeed may benefit from specialized interventions. The current study explicitly proposes that adolescents with comorbid pain and insomnia constitute a distinct subpopulation but, as discussed before, did not reveal subgroups of adolescents with only pain or insomnia problems. Future studies should thoroughly explore potential differences between comorbid pain and insomnia, and on the other hand isolated pain or sleep conditions if observed.

The four classes identified in the current study correspond to previous studies on longitudinal pain trajectories in adults. Most commonly, four or five classes have been identified as the optimal solution in studies on pain, typically including one class with persistent low pain, one with persistent high pain, as well as two or three classes of fluctuating, increasing or decreasing pain [47]. Based on the few studies exploring pain trajectories in adolescents, they appear to follow similar patterns as in adults.[48]. Few studies have been done on insomnia trajectories in adolescents, but one study identified trajectories similar as those found in regard to pain [49]. Although the current study identified subgroups with concurrent pain and insomnia, the similarities of the trajectories with previously revealed pain or sleep trajectories add validity to the generalizability of the results.

Pre-sleep behaviors causing cognitive-emotional arousal were the most consistent predictor of change in both pain and insomnia symptoms. This is in line with previous research suggesting that cognitive-emotional arousal may delay sleep onset and lower sleep quality [12], and that worry, rumination and emotional distress are associated with the sleep-pain relationship [3,50]. Additionally, stress responses or arousal has been proposed to explain the sleep-pain relationship [5], as well as influencing melatonin secretion[26]. Pre-sleep behaviors causing arousal may have both a moderating and a mediating effect on comorbid pain and insomnia Moreover, the role of cognitive-emotional arousal in the sleep-pain relationship might be driven by trait negative affect [20], which is closely related to negative mood [51]. Negative mood is established as a mediator in the effect of sleep on pain [4] – and worry and rumination have a negative influence on mood [52]. This multiple impact of pre-sleep behaviors causing cognitive-emotional arousal would make it a particularly salient predictor of the simultaneous development of chronic pain and insomnia. We therefore encourage future studies to explore the efficacy of hybrid interventions for comorbid pain and insomnia that incorporate a more exclusive focus on pre-sleep behaviors causing cognitive-emotional arousal. Notably, sleep hygiene practices (including pre-sleep behaviors) often are the focus in insomnia-interventions for adolescents [7].

Unexpectedly, pre-sleep behaviors causing behavioral arousal did not consistently predict conjoint trajectories of pain and insomnia. However, pre-sleep behaviors (ASHS full scale score) and somatic pre-sleep arousal (according to the Pre-sleep Arousal Scale) have previously been associated with insomnia in adolescents suffering from chronic pain [12]. Plausible explanations for our null finding that require further investigation lie either in that this finding is specific to conjoint pain and insomnia symptoms, that the internal consistency of the behavioral arousal subscale was insufficient in the current study, ranging from .63 to .67, or that the items in this subscale are relatively positive in their valence.

Chronotype's association to the trajectories of pain and insomnia symptoms may help explain inconsistent results of non-pharmacological treatments for comorbid pain and insomnia [53,54]. It may be that social and behavioral factors related to adolescent sleep-wake patterns, which are not a target in psychological treatments, may impede or confound treatment effects. The influence of chronotype indicates that pharmacological, social or psychological interventions may be effective in treating the conjoint development of pain and insomnia, including melatonin [7], synchronizing adolescents' school time with their biological clock [55], and CBT [56]. Although we did not find a late chronotype to directly predict pain in the current study, melatonin used therapeutically has been shown to reduce both hyperalgesia and allodynia in different pain conditions [26]. One could speculate that the current results indicate that the effect of melatonin on pain is mediated through insomnia symptoms, practically meaning that advancing adolescents' sleep phase may lead to a reduction in insomnia symptoms, which, in turn, may reduce pain (but see evidence suggesting a direct effect of melatonin on pain [26]).

A strength of the current study is the large population sample of adolescents followed over four yearly measurement occasions. This large set of data allowed us to use class-invariant GMM and account for potential sub-distributions via the class-variable, as well as between-individual differences and within-individual temporal change via the growth factors. Accounting for within-class variance often decreases the risk of identifying spurious classes [16] and reduces the risk of bias in the trajectories [57]. To our knowledge, this is the first study to identify trajectories of pain and insomnia with a multidimensional GMM. The use of latent basis and unspecified growth curves is also a strength of the study, since it does not impose any restrictions to the shape of longitudinal change. It has been recommended over linear or polynomial models in studies within the social and behavioral sciences, since longitudinal change in humans rarely follow pure mathematical shapes [58]. Another strength is the commonly used and validated measures.

While the current study has many strengths, some limitations need to be considered. First, for current purposes, we summarized the experience of three common types of pain (musculoskeletal pain, headache and abdominal pain) in an average pain grade, taking into account the intensity, frequency, and interference of the experience. Although this composite measure captures covariance across different pain types with insomnia [5], future studies might want to focus on co-developmental patterns in specific pain types, which would also allow interpretation of the pain grades in terms of pain-related disability

only [17,59]. Indeed, the co-development of pain and insomnia might turn out to be different for specific pain types [60].

A second limitation is that only self-report measures of complex constructs were used. Since objective and subjective sleep measures appear to partly measure different aspects of sleep [9], future studies should include also objective sleep-related measures.

A third limitation is that diverging trajectories were not perfectly overlapping at baseline, which may (although unlikely) have confounded the multinomial analysis of diverging trajectories.

A fourth limitation is that although a class-invariant model, such as the current one, facilitates interpretation and communication of the results, it only allows for an overall within-individual analysis of predictive effects. An optimal model with class-varying variances would have allowed for even more optimized growth curve shapes (since each subgroup would have its own unique shape of longitudinal change) and for an exploration whether chronotype and arousal-causing pre-sleep behaviors had different predictive effects depending on subgroup. However, this would also increase the risk of overfitting the model to the specific sample and thereby impeding generalizability. We recommend future studies to explore such potential subgroup-differences via class-varying growth factors.

In conclusion, the current study brings novel insights into how pain and insomnia symptoms longitudinally co-develop in adolescents. We identified four unique subgroups, showing that longitudinal trajectories of pain and insomnia closely follow each other, and that chronotype and pre-sleep behaviors causing cognitive-emotional arousal could predict the trajectories. A considerable portion of adolescents have either high persistent or increasing levels of problematic pain and insomnia. Adolescence constitutes a melting pot of factors contributing to the development of both insomnia and pain [5], and therefore appears to be an important developmental stage for preventing these conditions from developing and becoming chronic sources of disability and suffering. A sleep-phase focus may be relevant in interventions for comorbid pain and insomnia in adolescents, and pre-sleep behaviors causing cognitive-emotional arousal seem to be of particular importance to focus on in psychological interventions.

Declarations

Acknowledgements

This study was made possible by access to data from the Three Cities Study, a longitudinal research program at the department of Law, Psychology and Social work at Örebro University, Sweden. The research program was supported by a grant from the Swedish research council for sustainable development (Formas), the Swedish research council for health, work life and welfare (Forte), The Swedish Research Council (VR) and Sweden's innovation agency (Vinnova) (grant number 2012-65). The program was approved by the regional ethics board of Uppsala (nr. 2013/384). All data collection was carried out in accordance with the ethical principles of the Declaration of Helsinki. Special thanks the

schools and adolescents who participated in the project. Additional thanks to Katja Boersma, PhD, project principal investigator, and Liesbet Goubert, PhD, for initial input on the study's focus. Additional thanks also to Brittany Evans, PhD, for input and help with methodological and statistical queries.

Author contributions

All authors made a substantial, direct, and intellectual contribution to the manuscript. TA conceived the idea behind the study. All authors contributed to the conceptual development of the study. TA & SB handled the raw dataset. Statistical analyses were performed by TA. All authors contributed to the interpretation of the results. TA wrote the manuscript and prepared figures and tables, with substantive input from MS, SB, MJF and JP. All authors reviewed the final manuscript.

Competing Interest Statements

The authors have no conflict of interests to declare.

Data availability

The syntax code and the variance-covariance matrix that the study's analyses are based on are provided in the Supplementary information, which allows for replication of the analyses. The raw dataset may not be publicly shared due to confidentiality concerns and a restriction that was included in the participation consent. For the purpose of evaluating the study's results, the raw dataset may be made available after permission from the Three Cities Study PI Katja Boersma (katja.boersma@oru.se).

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Figures

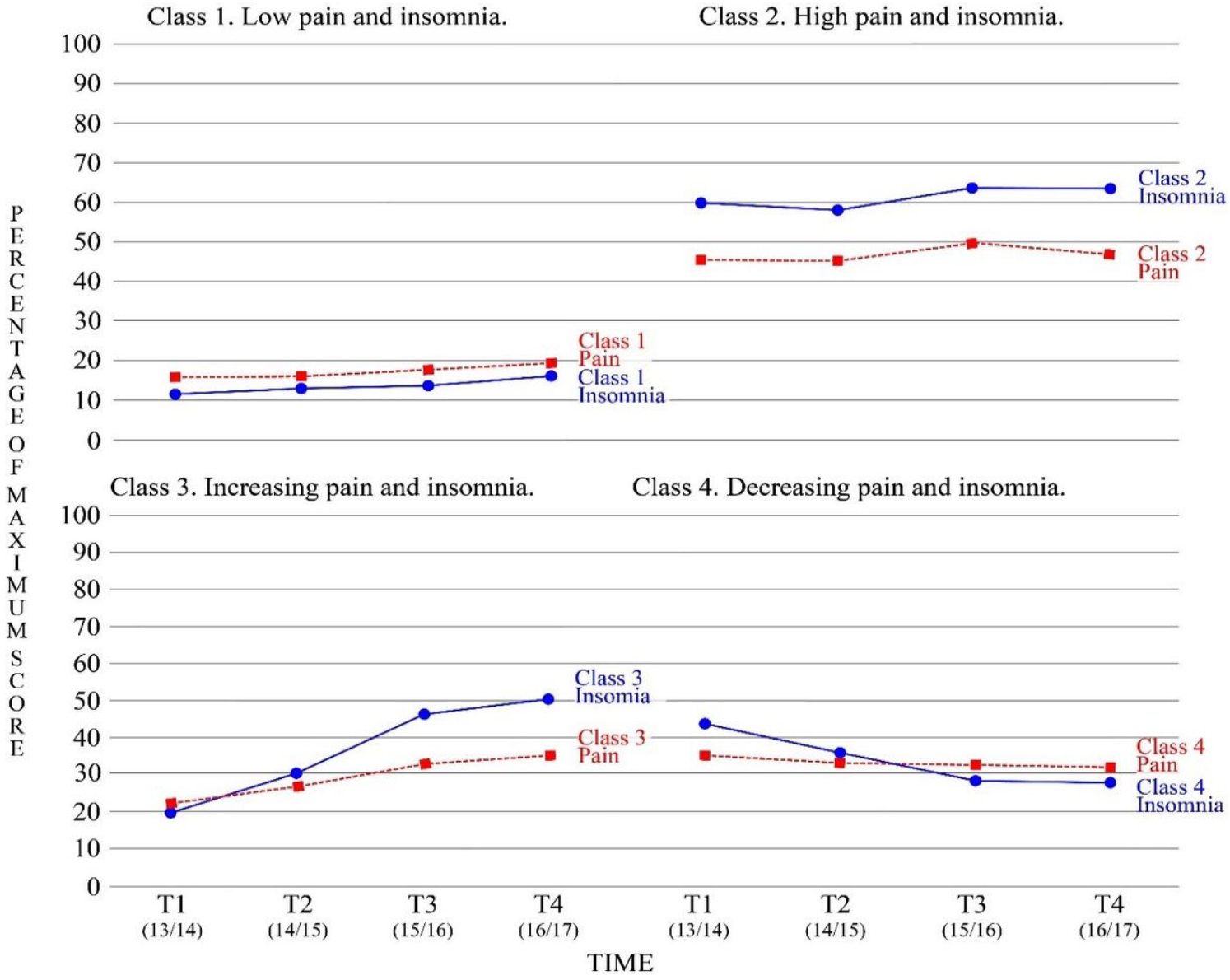

Figure 1

Longitudinal class solution of conjoint pain and insomnia development. The trajectories of pain are in red color (dotted line), and the trajectories of insomnia are in blue (solid line). The y-axis in the diagrams, which ranges from 0 to 100, represents percentage of maximum score of both insomnia symptoms and pain grade to facilitate comparisons of the trajectories. The x-axis represents measurement occasion, ranging from T1 to T4, and the numbers within parentheses are the age cohorts (in years) at each time point.

Supplementary Files

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