

Development of atopic disease and disturbed sleep in childhood and adolescence – a longitudinal population-based study

S. Jernelöv^{1*}, M. Lekander^{1,2,3*}, C. Almqvist^{4,5}, J. Axelsson^{1,2} and H. Larsson^{4,6}

¹Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden, ²Stress Research Institute, Stockholm University, Stockholm, Sweden,

³OsherCenter for Integrative Medicine, Karolinska Institutet, Stockholm, Sweden, ⁴Department of Medical Epidemiology and Biostatistics, Karolinska

Institutet, Stockholm, Sweden, ⁵Astrid Lindgren Children's Hospital, Karolinska University Hospital, Stockholm, Sweden and ⁶Karolinska Institutet center of Neurodevelopmental Disorders, Stockholm, Sweden

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Summary

Background Both atopic diseases and sleep disturbances have increased during recent decades, especially in children. Sleep is important for many aspects of immune regulation relevant in allergic diseases, and sleep disturbances are common in patients with such diseases. A connection between sleep disturbances and fatigue, and atopic disease is well established. However, the time course and putative causal relationships between these factors are obscure.

Objective We aimed at investigating the developmental relationships between subjectively reported sleep disturbances and symptoms of atopic disease, from childhood to adolescence.

Methods This longitudinal study used parent-report questionnaire data on symptoms of atopic disease, and sleep disturbances, from the Twin Study of Child and Adolescent Development (TCHAD). Overall, 1480 twin pairs born in Sweden were approached first when children were 8–9 years old, and again later at 13–14 years old. Response rates were 75% and 72%. Data from the TCHAD questionnaires were linked to the Swedish Medical Birth Register based on personal identification numbers.

Results Being overtired at age 8 increased the risk [OR; 95% CI (2.59; 1.31–5.11)] to develop rhinitis symptoms at age 13, even when controlling for gender, previous rhinitis, Socio-economic status, birth weight and other sleep disturbances at age 8. Likewise, symptoms of asthma at age 8 was an independent risk factor for being overtired at age 13 [OR; 95% CI (2.64; 1.44–4.84)], controlling for similar confounders.

Conclusion & Clinical Relevance The findings from this study are consonant with the proposition that atopic disease and disturbed sleep are more than passively interrelated. Future research needs to delineate whether causal relationships between these problems are at hand and, if so, at what periods in development this applies. These results point to a need for clinicians to investigate sleep difficulties and treat impaired sleep in paediatric patients with atopic disease.

Keywords atopic disease, epidemiology, longitudinal, paediatrics, sleep

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Correspondence:

Susanna Jernelöv, Karolinska Institutet, Department of Clinical Neuroscience, Section of Psychology, SE-171 77 Stockholm, Sweden.

E-mail: Susanna.jernelov@ki.se

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Introduction

Over the past decades, the prevalence of allergic diseases increased worldwide [1], especially in the highly developed Westernized societies and in younger ages [2]. Consonant with the fact that not only allergic dis-

ease but also stress and sleep disorders [3] have all increased in recent decades, a connection between these phenomena has received increased attention.

Everyday stress results in disturbed sleep in healthy individuals [4], and behavioural factors, such as sleep and stress, impact upon allergy severity and symptom control [5]. A recent meta-analysis of prospective cohort studies concludes that psychosocial factors are

*These authors contributed equally to this study.

significant predictors of both worsening of allergic symptoms, and new cases of atopy in both children and adults [6]. In addition, the same meta-analysis shows that atopy is a risk factor for developing mental health problems, that is, there is a reciprocal connection between psychosocial factors and atopy.

Sleep and fatigue are of particular interest in the perspective of atopic diseases. Sleep is central to re-establish homeostasis after demands [7], and disturbed sleep is related to a variety of long-term health outcomes [8]. Several studies of adult and child populations report elevated levels of sleep disturbances [9, 10] and fatigue [11, 12] in individuals with allergic disease. Even though the connection between sleep disturbances and fatigue on the one hand, and symptoms of atopic disease on the other, is well established, both the time courses and putative causal relationships between these factors are obscure.

Only two recent studies have investigated a longitudinal relationship between sleep and atopic disease, both being restricted to asthma [13, 14]. In these studies, disturbed sleep was found to be a risk factor for asthma onset. Despite the well-established cross-sectional relations described above, no longitudinal studies have investigated symptoms of atopic disease as a predictor of future sleep disturbances. Atopic diseases and asthma are common in early life [15], and their link to psycho-social factors is indicated to be strongest in children [6]. It is therefore particularly important to understand if sleep disturbances in childhood play a role in the development of atopic disease or onset of symptom expression, but also if atopic disease is a risk factor for future sleep disturbances.

Symptoms of atopic disease may cause sleep impairment, and several studies show the degree of sleep disturbances to be correlated with symptom severity e.g. [16, 17]. However, other studies suggest that a substantial proportion of asthmatic individuals with well-managed symptoms [18] and pollen-allergic patients out of pollen season with very low levels of allergic symptoms still have disturbed sleep [9]. Thus, as suggested by for instance Fang and colleagues [19], it is possible that mechanisms other than the actual symptoms could also be in operation. In line, recent studies suggest that disturbed sleep and atopic disorders can be connected through overlapping pathophysiological mechanisms. For instance, both a skew in the T-helper (Th) 1/Th2 balance towards Th2 dominance and increases in pro-inflammatory mediators, are central to airway hyperresponsiveness [20, 21] and associated with sleep disturbances [22, 23]. Dysregulated inflammatory processes could thus represent mechanisms that bi-directionally connect disturbed sleep and fatigue with atopic disease, both across and over time.

In summary, several observations suggest that sleep disturbances and atopic disease are interrelated, implying that either condition could be a risk factor for the development of the other. Such relations would be of special importance to delineate in children and adolescents during the years when atopic symptoms as well as sleep disturbances become manifest. In a population-based longitudinal study with parent-report information of sleep disturbances and symptoms of asthma, rhinitis and eczema at two time-points 5 years apart (age 8–9 and 13–14 respectively), we investigate whether disturbed sleep in childhood predicts development of disease symptoms in adolescence and *vice versa*; if presence of such symptoms in childhood increases the risk of developing sleep disturbances in adolescence.

Methods

Participants

This study was based on data from the Twin Study of Child and Adolescent Development (TCHAD) [24]. The target sample consisted of all the 1480 twin pairs born in Sweden between May 1985 and December 1986 who were alive and lived in Sweden. Data were collected in 1994 (age 8–9) and 1999 (age 13–14). The study was approved by the Ethics Committee at Karolinska Institutet (approval numbers: Dnr 94-277 and Dnr 98-486), and all participants consented to participate.

We used parent-reports of symptoms of asthma, rhinitis, eczema and sleep disturbances at wave 1 and wave 2, from which 1101 (75%) and 1063 (72%) of the parents responded respectively. Previous attrition analyses suggest no significant differences in gender ratio and family social economic index at wave 1 when comparing participants and non-participants at wave 2 [25]. Furthermore, results from a follow-back design revealed no significant differences in wave 2 data between participants and non-participants at wave 1 [25].

Data from the TCHAD questionnaires were linked to the Swedish Medical Birth Register based on personal identification numbers [26]. The parental reports of birth order and birth weight in TCHAD were used to ensure that the correct record in the Medical Birth Register was assigned to each twin.

Measures

Symptoms of asthma, rhinitis and eczema. As main outcomes, questions from the International Study of Asthma and Allergies in Childhood (ISAAC) were used, that is, 'Has your child ever had asthma' (yes/no) and 'Has your child ever had itchy eyes and runny nose' (rhinitis, yes/no) along with questions on recurrent

itchy rash on arms and legs, face and abdomen (eczema, yes/no) [27].

Sleep disturbances. Sleep disturbances were assessed by the four items from the Child Behaviour Checklist for Ages 6–18 (CBCL/6–18) relating to impaired sleep [28]. The CBCL/6–18 consists of 111 statements, rated on a 3-point scale (0 = not true; 1 = sometimes true; 2 = often true). The items used in this study were as follows: 'Has nightmares', 'Overtired', 'Sleeps less than other kids' and 'Trouble sleeping'. To increase power and reduce the number of tests, dichotomized variables were created for each of the four items, to compare participants for whom parents had responded 1 (sometimes true) or 2 (often true) with those who had not been given a score of 1 or 2.

Birth weight. Birth weight obtained from the Swedish Medical Birth Register was divided into categories of 500 grams from below 2,000 grams to above 3,500 grams.

Socio-economic status. Socio-economic status (SES) of the families was indicated by the occupational status of the parents; (I) Unskilled and semi-skilled workers, (II) Skilled workers/Assistant non-manual employees, (III) Intermediate non-manual collar workers and, (IV) Employed and self-employed professionals, higher civil servants and executives.

Data analysis

We used logistic regression models to investigate (1) the effect of different sleep disturbances at age 8 (i.e. having nightmares, being overtired, being a short sleeper and having trouble sleeping) on symptoms of asthma, rhinitis or eczema, respectively, at age 13 and

(2) the effect of symptoms of asthma, rhinitis or eczema at age 8 on the different sleep disturbances at age 13. A series of three increasingly complex models from bi-variate analyses (Model 1) to multivariate analyses were fitted to account for the confounding influences of pre-existing associations between the two assessments (i.e. the association between disease symptoms and sleep disturbances at age 8–9) and stability in the outcome measure – for example, the association between allergic symptoms assessed at age 8–9 and at 13–14 (Model 2). For example, when exploring the prediction of asthma symptoms at age 13 from nightmares at age 8, we added symptoms of asthma at age 8 into the model, to study the effect on incident asthmatic cases rather than on prevalent cases. Finally, in Model 3 we also added well-established covariates to the model, including birth weight and SES, and the other age 8–9 disease symptoms or sleep disturbances (see Tables 1 and 2). Odds ratios (OR) with 95% confidence intervals (CI) were estimated using generalized estimating equations models, which allow us to account for the dependent nature of the twin observations. All statistical analyses were performed in the SAS 9.1.3 using the GENMOD procedure (SAS Institute, Inc., Cary, NC, USA).

Results

Descriptive statistics

Table 1 shows rates of symptoms of asthma, rhinitis and eczema at age 8 and 13, which at age 8 was estimated as 5.9% (139 of 2357), 9.9% (232 of 2350) and 19.0% (447 of 2348) respectively. The corresponding estimates at age 13 were 7.5% (157 of 2086) for symptoms of asthma, 15.1% (325 of 2153) for symptoms of rhinitis and 23.5% (484 of 2063) for symptoms of eczema.

Table 1. Symptoms of Asthma, Rhinitis, Eczema; prevalence at ages 8–9 and 13–14

Age 8–9 years (W1)	Age 13–14 years (W2)		
	Asthma (<i>n</i> = 157)	No Asthma (<i>n</i> = 1929)	Info missing (<i>n</i> = 392)
Asthma (<i>n</i> = 139)	87	21	31
No Asthma (<i>n</i> = 2218)	60	1807	351
Info missing (<i>n</i> = 121)	10	101	10
Rhinitis (<i>n</i> = 232)	Rhinitis (<i>n</i> = 325)		Info missing (<i>n</i> = 381)
	139	No Rhinitis (<i>n</i> = 1772)	39
	166	54	331
No Rhinitis (<i>n</i> = 2118)	20	1621	11
Info missing (<i>n</i> = 128)	229	97	67
Eczema (<i>n</i> = 447)	Eczema (<i>n</i> = 484)		Info missing (<i>n</i> = 378)
	233	No Eczema (<i>n</i> = 1616)	67
	22	151	304
No Eczema (<i>n</i> = 1901)	233	1364	7
Info missing (<i>n</i> = 130)	22	101	

Symptoms of asthma, rhinitis and eczema were measured in two waves; wave 1 (W1) at age 8–9 and wave 2 (W2) at age 13–14. Total number of participants was 2478.

Table 2. Prevalence of sleep disturbances at ages 8–9 and 13–14.

	Age 13–14 years (W2)		
Age 8–9 years (W1)	Nightmares (<i>n</i> = 227)	No nightmares (<i>n</i> = 1884)	Info missing (<i>n</i> = 367)
Nightmares (<i>n</i> = 491)	95	307	89
No nightmares (<i>n</i> = 1680)	100	1311	269
Info missing (<i>n</i> = 307)	32	266	9
	Overtired (<i>n</i> = 131)	Not overtired (<i>n</i> = 1987)	Info missing (<i>n</i> = 360)
Overtired (<i>n</i> = 111)	21	74	16
Not overtired (<i>n</i> = 2064)	88	1641	335
Info missing (<i>n</i> = 303)	22	272	9
	Short sleeper (<i>n</i> = 101)	Not short sleeper (<i>n</i> = 1616)	Info missing (<i>n</i> = 362)
Short sleeper (<i>n</i> = 182)	43	103	36
Not short sleeper (<i>n</i> = 1990)	39	1633	318
Info missing (<i>n</i> = 306)	19	279	8
	Trouble sleeping (<i>n</i> = 67)	No trouble sleeping (<i>n</i> = 2043)	Info missing (<i>n</i> = 368)
Trouble sleeping (<i>n</i> = 111)	14	80	17
No trouble sleeping (<i>n</i> = 2066)	42	1688	336
Info missing (<i>n</i> = 301)	11	275	15

Sleep disturbances were measured in two waves; wave 1 (W1) at age 8–9 and wave 2 (W2) at age 13–14. Total number of participants was 2478.

Table 2 shows the past 6-month prevalence of sleep problems at age 8 and 13. The rate of nightmares, overtiredness, short sleep and sleep problems at age 8 was estimated as 22.6% (491 of 2171), 5.1% (111 of 2175), 8.4% (182 of 2172) and 5.1% (111 of 2177) respectively. The corresponding estimates of the rates at age 13 were 11.0% (227 of 2111) for nightmares, 6.2% (131 of 2118) for overtiredness, 4.8% (101 of 2116) for sleeplessness and 3.2% (67 of 2110) for trouble sleeping.

Prediction of asthma, rhinitis and eczema from sleep disturbances

Table 1 also provides information regarding incident cases of symptoms of asthma, rhinitis and eczema at age 13. Of the 157 children having asthma symptoms at age 13, 147 had responded at age 8. Of those children, 40.8% (60 of 147) had not reported asthma symptoms at age 8. In addition, about half of the children having symptoms of rhinitis (54.5%, 166 of 305) or eczema (50.4%, 233 of 462) at age 13, did not report such problems at age 8.

The impact of prior sleep disturbances on later developments of symptoms of asthma, rhinitis or eczema was explored. As can be seen in Table 3, being overtired at age 8 was associated with an increased risk for symptoms of asthma and rhinitis at age 13. The association between being overtired at age 8 and having asthma symptoms at age 13 disappeared after controlling for the stability in asthma symptoms (i.e. having symptoms of asthma already at age 8). In contrast, the association between being overtired at age 8 and having symptoms of rhinitis at age 13 remained significant (Model 3) even after controlling for rhinitis symptoms

at age 8, SES, birth weight and the other age 8–9 sleep disturbances. To test the robustness of this association, we excluded baseline cases of rhinitis. In this stratified analysis of children without rhinitis at age 8, the OR did not materially change (OR 3.00, 95% CI 1.56–5.78). Thus, being overtired was found to be an independent predictor of later development of rhinitis symptoms.

Prediction of sleep disturbances from asthma, rhinitis and eczema

Table 2 shows the number of children that developed sleep disturbances between the age of 8 and 13; that is, incident cases at age 13. Of the 227 children with nightmares at age 13, 195 had responded at age 8. Of those children, 51.3% (100 of 195) were not having nightmares at age 8. Most children who were overtired (80.7%, 88 of 109) or having trouble sleeping (75.0%, 42 of 56) at age 13 did not have such problems at age 8. Of the children who slept less than other kids at age 13, about half (48%, 39 of 82) had slept normally at age 8.

The impact of prior symptoms of asthma, rhinitis and eczema on later developments of sleep disturbances was explored. As can be seen in Table 4, having symptoms of asthma at age 8 was associated with an increased risk for being overtired, sleeping less than other kids and having trouble sleeping at age 13. The association between asthma symptoms and overtiredness remained significant even in Model 3. To test the robustness of this association, we excluded baseline cases of overtiredness. In this stratified analysis of children without overtiredness at age 8, the OR did not materially change (OR 2.08, 95% CI 0.97–4.44), although the association was no longer statistically significant. Thus, having

Table 3. 5-year prediction of symptoms of asthma, rhinitis and eczema from sleep disturbances

	Symptoms of asthma at age 13 OR (95% CI)	Symptoms of rhinitis at age 13 OR (95% CI)	Symptoms of eczema at age 13 OR (95% CI)
Nightmares at age 8			
Model 1	1.28 (0.86–1.91)	0.94 (0.69–1.29)	1.08 (0.82–1.44)
Model 2	–	–	–
Model 3	–	–	–
Overtired at age 8			
Model 1	3.16 (1.81–5.52)*	2.81 (1.74–4.55)*	1.34 (0.79–2.25)
Model 2	1.89 (0.74–4.79)	2.46 (1.25–4.82)*	–
Model 3	–	2.59 (1.31–5.11)*	–
Short sleeper at age 8			
Model 1	1.50 (0.86–2.62)	1.42 (0.90–2.24)	0.97 (0.65–1.47)
Model 2	–	–	–
Model 3	–	–	–
Trouble sleeping at age 8			
Model 1	1.38 (0.68–2.81)	1.61 (0.92–2.82)	1.11 (0.65–1.91)
Model 2	–	1.52 (0.79–2.89)	–
Model 3	–	–	–

* $P < 0.01$.

Model 1: ORs were adjusted for gender only.

Model 2: ORs were adjusted for gender and the stability in the atopic symptom being assessed (i.e. having the allergic problem already at age 8–9).

Model 3: ORs were adjusted for gender, the stability in the atopic symptom being assessed, socio-economic status, birth weight and the other age 8–9 sleep disturbances.

OR, Odds ratio; CI, Confidence interval.

Table 4. 5-year prediction of sleep disturbances from symptoms of asthma, rhinitis and eczema

	Nightmares at age 13 OR (95% CI)	Overtired at age 13 OR (95% CI)	Short sleeper at age 13 OR (95% CI)	Trouble sleeping at age 13 OR (95% CI)
Symptoms of asthma at age 8				
Model 1	1.40 (0.83–2.36)	2.74 (1.55–4.85)**	2.63 (1.34–5.18)**	2.33 (1.01–5.42)*
Model 2	–	2.28 (1.29–4.02)**	2.00 (0.94–4.24)	2.47 (0.97–6.26)
Model 3	–	2.64 (1.44–4.84)**	1.85 (0.71–4.83)	1.95 (0.75–5.09)
Symptoms of rhinitis at age 8				
Model 1	1.38 (0.93–2.06)	1.42 (0.84–2.39)	1.88 (0.98–3.61)	2.52 (1.26–5.03)**
Model 2	–	–	1.44 (0.68–3.61)	1.38 (0.58–3.31)
Model 3	–	–	–	–
Symptoms of eczema at age 8				
Model 1	1.01 (0.72–1.42)	1.01 (0.63–1.62)	1.85 (1.18–2.91)**	1.25 (0.68–2.29)
Model 2	–	–	1.55 (0.89–2.70)	–
Model 3	–	–	–	–

** $P < 0.01$; * $P < 0.05$.

Model 1: ORs were adjusted for gender only.

Model 2: ORs were adjusted for gender and the stability in the sleep disturbance being assessed (i.e. having the sleep disturbance already at age 8–9).

Model 3: ORs were adjusted for gender, the stability in the sleep disturbance being assessed, socio-economic status, birth weight and the other age 8–9 allergic symptoms.

OR, Odds ratio; CI, Confidence interval.

symptoms of asthma was found to be an independent predictor of later development of being overtired.

Symptoms of rhinitis at age 8 was significantly associated with having trouble sleeping at age 13, but the association disappeared when controlling for prior assessments of trouble sleeping. Symptoms of eczema

at age 8 significantly predicted sleeping less than other kids at age 13. However, this association disappeared after controlling for sleeping less than other kids at age 8. Thus, symptoms of rhinitis and eczema were not found to be independent predictors of later developments of trouble sleeping.

Discussion

Our study showed that overtired children ran a markedly increased risk of developing rhinitis symptoms in adolescence, and that having symptoms of asthma in childhood markedly increased the risk of being overtired in adolescence. These relations were significant when controlling for several well-known confounders including previous sleep disturbances or allergic symptoms, but the prospective association between asthma and overtiredness did not reach significance when excluding base-line cases of overtiredness. Other relations between atopic symptoms and sleep disturbances, or *vice versa*, were also shown, but were not stable when controlling for earlier problems and thus did not predict incident cases. Hence, these findings rather confirm previous observations of co-morbidity between atopic symptoms and sleep disturbances.

The proposition that sleep disturbances may act as risk factors for the development of symptoms of atopic disease is partially supported. Specifically, being overtired in childhood entailed a two- to threefold increased risk to carry rhinitis symptoms at adolescence. Earlier prospective studies have not investigated this relation, but the finding is consonant with earlier cross-sectional studies [11, 12]. The most stable connection was shown for future development of rhinitis symptoms but not for other symptoms of atopic disease. This could possibly be related to the natural course of development of allergy and the timing of our measurements, since rhinitis is often presented later in life as part of the 'allergic march' [29].

In addition, being overtired at 8–9 years was connected with an increased risk for asthma symptoms at 13–14 years. Although this relation was not significant when controlling for having had asthma symptoms earlier, the results are consonant with earlier studies, where frequent nocturnal awakenings during the first 3 years were associated with asthma at age 6 and 14 years [14], and sleep disturbances in 1990 were significantly more common among those participants who had developed asthma in 2003 [13]. It is reasonable that the general cross-sectional overlap between sleep disturbances and atopic disease partly reflects sleep disturbances due to disease symptoms, such as night-time exacerbations of asthma or eczema.

Also, having asthma symptoms in childhood was a predictor of becoming overtired in adolescence, which is in line with previously observed cross-sectional connections between symptoms of asthma and disturbed sleep or tiredness [30, 31], and fit with the proposition that asthma symptoms could play an aetiological and not only a prognostic part in tiredness [32]. However, the wide confidence interval and the non-significant association in the more conservative stratified analysis

(excluding base-line cases of overtiredness) indicate that this result should be interpreted with caution. Clearly, further research using a larger sample is needed to confirm a possible link between childhood asthma and disturbed sleep.

Overtiredness was more robustly related to disease symptoms than the other sleep related variables. Several lines of reasoning may explain this. For example, unlike some other sleep disturbances (e.g. nightmares), which may be most obvious to the person experiencing them, tiredness is accessible for observation by a parent during daytime. Tiredness could thus be more accurately reported and hence show up in the analyses. This could implicate that the other sleep disturbances were not measured in an optimal manner, but might have been under reported, yielding the negative results in this study. On the other hand, it is also possible that some of the cases of new incident rhinitis at follow-up have actually been present, at least in a less severe form, at baseline, but that measures were not sensitive enough to detect their presence. However, alternative explanations to explain the prospective relationship between tiredness and rhinitis can be considered. In line with the well-described connection between pro-inflammatory cytokines, sleep pressure and fatigue [33], the observed tiredness could result from inflammatory activity that will surface in manifest disease later during development. In addition, because disturbed sleep both increases levels of cytokines involved in inflammation as well as sleep regulation, and shifts the balance between Th1 and Th2 cytokines towards an allergy related (Th2) pattern [20–23], insufficient sleep may cause physiological responses that are not only involved in exacerbations but also in the development of atopic disease. Additional support for a relation between sleep and allergic disease was recently provided by Zhang et al. [34]. In a twin study exploring the relation between sleep time and sensitization to allergens, they found an increased risk of allergen sensitization in adolescents with the shortest sleep duration. If the relation between disturbed sleep and atopic disease would be confirmed to contain causal elements through inflammatory or other mechanisms, the high prevalence of sleep disorders among children and adolescents is alarming. For example, according to a Swedish survey there has been an increase in sleep problems the last ten years, with around 30% of adolescents reporting difficulties sleeping today [3], and in an Austrian sample, 88% of 11–15 year-old schoolchildren reported daily or occasional sleep problems [35].

Some limitations of the study should be kept in mind. First, we used a population-based sample of twins; hence, our results may not be extrapolated to clinical settings. However, population-based studies as opposed to clinic-referred samples do not introduce a

referral bias. Second, since data on sleep disturbances and atopic symptoms emanated from the same informant (i.e. parent-reports), we cannot rule out a possible bias in reporting and correlated measurement error. Third, although we used a large sample of twins, few incident cases of asthma symptoms were observed at age 13–14 ($n = 60$), which constrains the power to detect true associations in the adjusted models, as well as in the analyses of associations excluding base-line cases of over-tiredness. The results of these analyses therefore need to be interpreted with caution.

Conclusion

Data from this prospective population-based study add further support for the connection between atopic disease and sleep. Importantly, a relation between overtiredness in childhood and the development of rhinitis symptoms in adolescence is indicated. Similarly, the study suggests an impact of asthma symptoms on the later development of overtiredness. Thus, the study suggests but does not prove that common symptoms of ill-health in children and adolescents are prospectively related. Therefore, replication studies as well and investigations of potential mechanisms are urged, and future studies need to clarify if the relationships are causal, and if there are certain developmental periods where this may be more relevant.

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Authors Contributions

Susanna Jernelöv has made substantial contribution to the conception, design and interpretation of data, has drafted the article and revised it for important intellectual content and written (and approved) the final version to be published.

Mats Lekander has made substantial contribution to the conception, design and interpretation of data, has drafted the article and revised it for important intellectual content and approved the final version to be published.

Catarina Almqvist has made substantial contribution to the conception, design and interpretation of data, has revised the article for important intellectual content and approved the final version to be published.

John Axelsson has made substantial contribution to the design, interpretation of data, has revised the article for important intellectual content and approved the final version to be published.

Henrik Larsson has made substantial contribution to the conception, design, and data analysis and has drafted parts of the article and revised the article for important intellectual content, and approved the final version to be published.

Conflicts of interest

None of the authors has any conflicting interests regarding this article.

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