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Insufficient sleep during adolescence and risk of multiple sclerosis: results from a Swedish case-control study

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ABSTRACT

Background Shift work, which often results in sleep deprivation and circadian desynchrony, has been associated with increased risk of multiple sclerosis (MS). We aimed at studying the impact of sleep duration, circadian disruption and sleep quality on MS risk.

Methods We used a Swedish population-based case-control study (2075 cases, 3164 controls). Aspects of sleep were associated with MS risk by calculating OR with 95% CIs using logistic regression models.

Results Compared with sleeping 7–9 hours/night during adolescence, short sleep (<7 hours/night) was associated with increased risk of developing MS (OR 1.4, 95% OR 1.1–1.7). Similarly, subjective low sleep quality during adolescence increased the risk of subsequently developing MS (OR 1.5, 95% CI 1.3 to 1.9), whereas phase shift did not significantly influence the risk. Our findings remained similar when those who worked shifts were excluded.

Conclusions Insufficient sleep and low sleep quality during adolescence seem to increase the risk of subsequently developing MS. Sufficient restorative sleep at young age, needed for adequate immune functioning, may be a preventive factor against MS.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Shift work has been associated with increased multiple sclerosis (MS) risk, whereas the impact of sleep habits on the risk of MS has not previously been investigated.

WHAT THIS STUDY ADDS

⇒ Insufficient sleep and low sleep quality during adolescence dose-dependently increased the risk of MS.

⇒ A change in sleep timing between work/schooldays and weekends/free days did not influence the risk of the disease.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Educational interventions addressed to adolescents and their parents regarding the negative health consequences of insufficient sleep are of importance.

INTRODUCTION

Multiple sclerosis (MS) is an immune-mediated inflammatory and neurodegenerative disease, influenced by both genetic and environmental factors, including smoking, adolescent body mass index (BMI), Epstein-Barr virus infection, sun exposure and vitamin D. One factor that has not been extensively investigated as a contributor to MS is shift work. In Nordic studies, shift work has been associated with an increased risk of the disease,[1–3] predominantly when the exposure has taken place at young age.[1 2]

Irregular sleep-wake patterns and restricted sleep duration may be consequences of shift work but are also common during adolescence when sleep and circadian timing start to phase delay.[4] Sleep restriction and poor sleep quality affect immune pathways with increased proinflammatory signalling, which could increase the risk of inflammatory chronic diseases.[5 6] Circadian rhythms are also involved in regulating the immune response and disruption may result in disturbed melatonin secretion and immune dysfunction.[7]

Both human and experimental studies have suggested that insufficient sleep may contribute to the risk of inflammatory chronic diseases[8 9] and neurodegenerative processes,[10] although the possible association between sleep patterns and MS risk has not previously been investigated. The aim of this study was to investigate the influence of sleep duration, circadian disruption and sleep quality on MS risk.

METHOD

Design and study population

We used a population-based case-control study, the Epidemiological Investigation of Multiple Sclerosis (EIMS), comprising the Swedish general population aged 16–70 years. Incident cases were recruited from hospital-based and privately run neurology units. Cases were diagnosed according to the McDonald criteria by local neurologists.[11 12] For each case, two controls were randomly selected from the national population register, matched by age in 5-year age groups, sex and residential area. The general structure of the study has been described in detail elsewhere.[2 3]

Information on lifestyle factors and different exposures was collected using a standardised questionnaire. During the study period from April 2005 to March 2013, questionnaires were obtained from 2055 cases and 4518 controls (response rate 93% and 73%, respectively). In November 2013, complementary questions that were not part of

the original questionnaire, including questions regarding sleep habits, were sent to all participants who had answered the questionnaire during the above-mentioned period. Questionnaires that were not completely answered were complemented by phone or mail. The complementary questions were answered by 1686 cases (82%) and 2982 controls (66%).

In 2015, the EIMS questionnaire was updated to include the questions on sleeping habits, and during the study period from July 2015 to December 2018, the questionnaire was completed by another 724 cases and 795 controls. Cases and controls were recruited in the same way as in the previous study period.

Those with disease onset before the age of 20 (225 cases and 308 controls) and those who were unable to answer the questions regarding sleep habits were excluded (110 cases and 305 controls). Inability to answer the questions were due to difficulties remembering or having had irregular sleep patterns. The present study thus includes 2075 cases and 3164 controls (online supplemental figure 1).

Definition of exposure variables

Since shift work has primarily been associated with subsequent risk of MS if the exposure takes place at young age, and since altered sleep habits may be a consequence of MS, we focused on sleeping patterns and shift work during the age period 15–19 years. The questions regarding sleep were chosen from the Karolinska Sleep Questionnaire which has been validated.[13] The questions were slightly modified to cover sleep habits in different age periods (online supplemental table 1).

Sleep duration

Subjects were asked to estimate when they normally went to bed and when they woke up during workdays or schooldays, during different age periods. They also provided information regarding when they normally went to bed and when they woke up during weekends or free days. Habitual sleep duration during workdays or schooldays (15–19 years) were categorised into <7 hours/night (short sleep), 7–9 hours/night and 10 or more hours/night (long sleep).

Phase shift

The change in sleep timing between work/schooldays and weekend/free days was calculated. Phase shifts during the age period 15–19 years were categorised into <1 hour/night, 1–3 hours/night and >3 hours/night.

Sleep quality

Subjects were asked to estimate the quality of their sleep during different age periods using a 5-grade scale (very bad, rather bad, neither good nor bad, rather good, very good). Sleep quality (15–19 years) was categorised into high (rather good or very good) or low (neither good nor bad, rather bad, very bad).

The sleep-related exposure variables were also considered at the time of index, categorised in the same manner as above.

Statistical analysis

Correlations between habitual sleep duration, phase shift and sleep quality were assessed using Pearson correlation coefficients with 95% CIs. Different aspects of sleep were compared regarding MS occurrence by calculating ORs with 95% CI using logistic regression models. Trend tests for a dose-response relationship regarding each aspect of sleep and risk of MS were performed by using continuous variables in logistic regression models.

We performed the analysis overall as well as restricted to subjects without shift work. Shift work refers to permanent or alternating working hours other than ordinary day work and includes night work, day work (before 07:00) and evening work (after 21:00). Subjects were categorised into those who had or had not worked shifts before the age of 20 years.

All analyses were adjusted for age, sex, residential area, ancestry (Swedish or non-Swedish), smoking (ever or never), infectious mononucleosis (IM) history (yes, no, unknown) and sun exposure habits. Based on three questions regarding sun exposure where each answer alternative was given a number ranging from 1 (the lowest exposure) to 4 (the highest exposure), we constructed an index by adding the numbers together and thus acquired a value between 3 and 12. Sun exposure was then dichotomised into high or low exposure (index value more or less than 6). The rationale for adjusting for these factors was that they are both associated with sleep patterns and with risk of MS.

Since obesity may be a consequence of sleep-related aspects, we did not include BMI in our final analyses. We performed supplementary analyses further adjusted for BMI at age 20 years and for self-reported comorbidities (rheumatoid arthritis, systemic lupus erythematosus, psoriasis, thyroid disorders, type 1 diabetes and inflammatory bowel disease). We considered comorbidities at the time of 20 years and at index, respectively, in different models. We also made adjustments for smoking and IM status at the time of 20 years.

Short sleep during workdays or schooldays may be compensated for by sleeping longer during weekends/free days, and to study the influence of short sleep among those with adequate sleep during days off, we also studied the influence of short sleep among those who reported 7 or more hours of sleep/night during weekends/free days. In another supplementary analysis, we defined total sleep duration as the mean sleep duration/night during 1 week including both workdays or schooldays as well as days off. Total sleep duration was categorised in the same manner as habitual sleep duration. A sensitivity analysis was carried out defining short sleep as <6 hours hours/night, using the same reference group of 7–9 hours/night as in our main analyses. We also performed the analyses separately for those who were recruited to the study before and after the questions on sleep were included in the regular EIMS questionnaire. Finally, we considered sleep habits at index and conducted the analyses restricted to participants who reported similar sleep habits in adolescence and at index. All analyses were conducted using Statistical Analysis System (SAS) V.9.4.

RESULTS

The analyses of shift work and the risk for MS included 2075 cases and 3164 controls. The mean age at disease onset among cases was 34.8 years (SD 10.8). The characteristics of cases and controls in overall sample and by each aspect of sleep and shift work status at age 15–19 years are presented in online supplemental table 1 and in tables 1–3.

Sleep habits in adolescence

There was a correlation between sleep duration and sleep quality among both cases (r=0.32, 95% CI 0.28 to 0.36) and controls (r=0.28, 95% CI 0.28 to 0.32) that remained similar when the analysis was stratified by shift work. A change in sleep timing between work/schooldays and weekends/free days only correlated with sleep duration among shift workers (r=0.25 (95% CI 0.12 to 0.41) among cases and p=0.16 (95% CI 0.02

Table 1 Characteristics of cases and controls, by sleep duration (age period 15–19)

| | Sleep duration (hours/night) | | | | | |
| | <7 | | 7–9 | | 10– | |
	Cases	Controls	Cases	Controls	Cases	Controls
N	171	194	1752	2726	152	244
Women, n (%)	114 (67)	130 (67)	1269 (72)	2001 (73)	119 (78)	193 (79)
Swedish, n (%)	123 (71)	149 (77)	1396 (80)	2158 (79)	121 (80)	172 (70)
Phase shift, mean no. of hours (SD)	1.2 (1.5)	1.2 (1.4)	1.3 (1.1)	1.3 (1.1)	1.4 (1.2)	1.3 (1.2)
Sleep quality, mean (SD)	3.2 (1.4)	3.5 (1.3)	4.4 (0.8)	4.4 (0.8)	4.4 (0.8)	4.5 (0.8)
Smoking, n (%)	115 (67)	105 (54)	866 (49)	1128 (41)	71 (47)	88 (36)
Mean sun exposure (SD)	5.9 (1.9)	6.5 (1.9)	6.2 (1.8)	6.5 (1.8)	6.3 (1.7)	6.7 (2.0)
Mean adolescent BMI, kg/m (SD)	23.1 (4.1)	22.6 (3.7)	22.5 (3.9)	21.9 (3.2)	22.5 (3.9)	22.0 (4.3)
Infectious mononucleosis, n (%)	32 (19)	27 (14)	330 (19)	283 (10)	19 (13)	27 (11)
Age at disease onset (SD)	32.1 (11.2)		34.9 (10.6)		36.5 (10.8)	

Sleep quality was assessed on a 5-grade scale (1=lowest quality, 5=highest quality).
BMI, body mass index.

to 0.29) among controls). Regardless of shift work, there was no sign of correlation between phase shift and sleep quality.

Habitual sleep duration

Compared with a sleep duration of 7–9 hours/night, short sleep (<7 hours/night) was associated with increased risk of developing MS (OR 1.4, 95% OR 1.1–1.7), whereas long sleep (10 or more/night) was not associated with increased risk of the disease (table 4). The estimates remained significant when shift workers were excluded (table 4).

The association between short sleep duration during work/schooldays and subsequent MS risk also remained significant when the analysis was restricted to subjects who slept 7 or more hours during weekends or free days (OR 1.3, 95% CI 1.1 to 1.7).

Phase shift between work/schooldays and free days

Of those who reported phase shift exceeding 1 hour, 5 cases (0.6%) and 13 controls (1.1%) reported a negative phase shift. A change in sleep timing between work/schooldays and weekends/free days did not influence the risk of MS (table 5). No trend was observed between hours of phase shift and MS risk (p=0.5). The estimates remained similar when shift workers were excluded (table 5). There were also no signs of association between phase shift and MS risk when the analysis was stratified

by sleep duration (less than 7 hours or 7 or more hours) or sleep quality (1–3 or 4–5 on a 5-grade scale).

Sleep quality

Those who rated their sleep quality as low (3 or lower on a 5-grade scale) had a 50% higher risk of subsequently developing MS (table 6). There was a trend showing increasing MS risk with lower sleep quality (p<0.0001). This trend remained significant when the analysis was stratified into those who slept less than 7 hours/night (p for trend 0.01) or 7 hours/night or more (p for trend 0.005).

When sleep duration and sleep quality were put in the same model, both trends remained significant (OR 0.89, 95% CI 0.83 to 0.95 for sleep quality and OR 0.95, 95% CI 0.90 to 0.99 for sleep duration), indicating a lower risk of MS with increasing sleep duration and with higher sleep quality.

All results remained similar when the analyses were further adjusted for smoking, IM status and BMI at age 20 years and for comorbidities both at age 20 years and at onset, respectively (data not shown). They also remained similar when they were performed separately for those who were recruited to the study before and after the questions on sleep were included in the regular EIMS questionnaire (data not shown). When total sleep duration was considered (mean sleep duration/night during

Table 2 Characteristics of cases and controls, by phase shift (age period 15–19)

| | Phase shift between work/school and free days (hours) | | | | | |
| | <1 | | 1–3 | | >3 | |
	Cases	Controls	Cases	Controls	Cases	Controls
N	1263	1927	608	914	204	332
Women, n (%)	927 (73)	1433 (74)	436 (72)	661 (72)	139 (68)	230 (71)
Swedish, n (%)	1011 (80)	1502 (78)	472 (78)	732 (80)	157 (80)	245 (76)
Sleep duration, hours/night (SD)	8.0 (1.1)	8.1 (1.0)	8.1 (1.0)	8.2 (1.0)	8.0 (1.1)	8.1 (1.2)
Sleep quality, mean value (SD)	4.3 (0.9)	4.4 (0.8)	4.3 (0.9)	4.4 (0.8)	4.2 (1.0)	4.3 (0.9)
Smoking, n (%)	598 (47)	752 (39)	318 (52)	405 (44)	136 (67)	164 (51)
Mean sun exposure (SD)	6.1 (1.8)	6.5 (1.9)	6.5 (1.7)	6.6 (1.8)	6.2 (1.8)	6.6 (1.9)
Mean adolescent BMI, kg/m (SD)	22.5 (3.9)	21.9 (3.2)	22.7 (3.8)	21.9 (3.4)	22.8 (4.3)	22.4 (4.2)
Infectious mononucleosis, n (%)	220 (17)	193 (10)	114 (19)	95 (10)	47 (23)	49 (15)
Age at disease onset (SD)	36.0 (10.9)		32.7 (9.9)		33.9 (10)	

Sleep quality was assessed on a 5-grade scale (1=lowest quality, 5=highest quality).
BMI, body mass index.

Table 3 Characteristics of cases and controls, by sleep quality (age period 15–19)

| | Sleep quality (using a 5-grade scale) | | | |
| | Low sleep quality (1–3) | | High sleep quality (4–5) | |
	Cases	Controls	Cases	Controls
N	350	375	1725	2789
Women, n (%)	240 (69)	273 (73)	1262 (73)	2051 (74)
Swedish, n (%)	267 (76)	274 (73)	1373 (80)	2205 (79)
Phase shift, mean no. of hours (SD)	1.3 (1.4)	1.4 (1.3)	1.3 (1.1)	1.3 (1.1)
Sleep duration, hours/night (SD)	7.4 (1.4)	7.4 (1.4)	8.2 (0.9)	8.2 (0.9)
Smoking, n (%)	198 (56)	172 (46)	1725 (50)	1149 (41)
Mean sun exposure (SD)	5.9 (1.9)	6.6 (1.9)	6.3 (1.7)	6.5 (1.8)
Mean adolescent BMI, kg/m (SD)	23.0 (4.4)	22.6 (4.0)	22.5 (3.8)	21.8 (3.3)
Infectious mononucleosis, n (%)	70 (20)	42 (11)	311 (18)	295 (11)
Age at disease onset (SD)	32.1 (10.8)		35.3 (10.6)	

BMI, body mass index.

1 week including both workdays or schooldays and days off), the OR of MS among those with a sleep duration less than 7 hours/night was 1.4 (95% CI 1.1 to 1.8), with a significant trend showing increasing MS risk with decreasing total sleep duration (p=0.04) (not in table). Less than 5% of cases and controls reported a sleep duration less than 6 hours/night. When short sleep was defined as sleeping less than 6 hours/night, the OR was 1.5 (95% CI 1.2 to 2.0), compared with sleeping 7–9 hours/night (not in the table).

Sleep habits at index
When categorising the subjects based on sleep duration in adolescence and at index, short sleep at index was associated with increased risk of MS regardless of sleep duration in adolescence. The increased risk of MS associated with short sleep was most pronounced among those who reported short sleep duration both in adolescence and at index (OR 1.6, 95% CI 1.4 to 2.0), compared with those who consistently reported a sleep duration of 7 or more hours (online supplemental table 2).

Long sleep at index was also associated with MS risk (OR 1.7, 95% CI 1.1 to 2.6); however, when we restricted the analysis to those who reported similar sleep duration in adolescence and at index, short sleep remained associated with increased risk of MS (OR 1.5, 95% CI 1.1 to 2.0), but not long sleep (OR 1.0, 95% CI 0.5 to 2.0) (online supplemental table 3).

Poor sleep quality was associated with increased MS risk when it was reported at young age and when it occurred after adolescence, respectively, and was most pronounced among those who had reported poor sleep quality in adolescence and at index (online supplemental table 4).

DISCUSSION
Short sleep duration and low sleep quality seem to increase the risk of subsequently developing MS, whereas a shift in timing of sleep seems not to influence disease risk.

Insufficient sleep and poor sleep quality affects immune functions through multiple pathways, including increased production of proinflammatory markers, systemic inflammation and immune dysfunctions.[5][6] Sleep deprivation may also contribute to low-grade neuroinflammation, oxidative stress and disruption of the blood-brain barrier.[14–16] Furthermore, circulating levels of melatonin, a potent antioxidant involved in promoting neurogenesis, are reduced during sleep deprivation as a defence against the associated rise in oxidative stress.[17] Both human and experimental studies have suggested that insufficient sleep may contribute to the risk of inflammatory chronic diseases[7][8] and neurodegenerative processes.[9]

Table 4 OR of MS with 95% CI for subjects with different habitual sleep duration

Total				
Hours/night	ca/co*	OR (95% CI)†	OR (95% CI)‡	Trend
<7	171/194	1.4 (1.1 to 1.7)	1.4 (1.1 to 1.7)	
7–9	1752/2726	1.0 (reference)	1.0 (reference)	
10–	152/244	1.0 (0.8 to 1.2)	1.0 (0.8 to 1.2)	0.002
No shift work				
Hours/night	ca/co*	OR (95% CI)†	OR (95% CI)‡	Trend
<7	146/172	1.3 (1.1 to 1.7)	1.3 (1.0 to 1.7)	
7–9	1628/2560	1.0 (reference)	1.0 (reference)	
10–	141/233	1.0 (0.8 to 1.2)	1.0 (0.8 to 1.2)	0.003

*Number of exposed cases and controls.
†Adjusted for age, sex, residential area and ancestry.
‡Adjusted for age, sex, residential area, ancestry, smoking, IM history and sun exposure.
IM, infectious mononucleosis; MS, multiple sclerosis.

Table 5 OR of MS with 95% CI for subjects with different phase shift between work/school days and free days

Total				
Mean duration (hours)	ca/co*	OR (95% CI)†	OR (95% CI)‡	Trend
<1	1263/1927	1.0 (reference)	1.0 (reference)	
1–3	608/914	1.0 (0.9 to 1.1)	1.0 (0.9 to 1.2)	
>3	204/323	1.0 (0.8 to 1.2)	1.0 (0.8 to 1.2)	0.5
No shift work				
Mean duration (hours)	ca/co*	OR (95% CI)†	OR (95% CI)‡	Trend
<1	1174/1812	1.0 (reference)	1.0 (reference)	
1–3	559/851	1.0 (0.9 to 1.1)	1.0 (0.9 to 1.1)	
>3	182/302	0.9 (0.8 to 1.1)	1.0 (0.8 to 1.1)	0.3

*Number of exposed cases and controls.
†Adjusted for age, sex, residential area and ancestry.
‡Adjusted for age, sex, residential area, ancestry, smoking, IM history and sun exposure.
IM, infectious mononucleosis; MS, multiple sclerosis.

Table 6 OR of MS with 95% CI for subjects with different sleep quality (assessed on a 5-grade scale)

Total				
Value	**ca/co****	**OR (95% CI)†**	**OR (95% CI)‡**	**Trend**
5	1043/1710	1.0 (reference)	1.0 (reference)	
4	682/1079	1.0 (0.9 to 1.2)	1.0 (0.9 to 1.2)	
3	216/227	1.5 (1.2 to 1.8)	1.5 (1.3 to 1.9)	
1–2	134/148	1.5 (1.2 to 1.9)	1.5 (1.1 to 1.9)	<0.0001
No shift work				
Value	**ca/co****	**OR (95% CI)†**	**OR (95% CI)‡**	**Trend**
5	973/1607	1.0 (reference)	1.0 (reference)	
4	628/1014	1.0 (0.9 to 1.2)	1.0 (0.9 to 1.2)	
3	192/209	1.5 (1.2 to 1.8)	1.5 (1.2 to 1.9)	
1–2	122/135	1.5 (1.2 to 1.9)	1.5 (1.1 to 1.9)	0.0001

*Number of exposed cases and controls
†Adjusted for age, sex, residential area and ancestry.
‡Adjusted for age, sex, residential area, ancestry, smoking, IM history and sun exposure.
IM, infectious mononucleosis; MS, multiple sclerosis.

We observed that the association between short sleep duration during work/schooldays and subsequent MS risk persisted when the analysis was restricted to those who slept 7 hours or longer during weekends or free days. Similarly, when we considered the total amount of sleep per week, the association between low sleep duration and increased risk of MS persisted. Our finding is strengthened by previous studies indicating that extension of habitual short sleep does not counterbalance the immune consequences of sleep deprivation.[18 19] The increased production of proinflammatory cytokines due to sleep restriction remained elevated after two nights of recovery sleep.[20]

Since sleep restriction or altered sleep habits may be a consequence of neurodegeneration, we mainly focused on investigating the possible association between sleep habits during the age period 15–19 years and subsequent MS risk. Although our supplementary analyses indicated that short sleep and poor sleep quality may be important and possibly modifiable lifestyle factors for MS, these findings should be interpreted with caution due to the potential of reverse causation.

EIMS was designed as a population-based, case-control study and information regarding lifestyle factors was gathered retrospectively. Considering that sleep disorders are common among persons with MS and many patients suffer from fatigue,[21] there is a possibility that cases may recall previous sleep habits differently from controls. However, our findings remained similar when those who reported current low sleep duration (<7 hours/night) and those with current low sleep quality (<3 on a 5-grade scale) were excluded. They also remained similar when they were performed separately for those who were recruited to the study before and after the questions on sleep were included in the regular EIMS questionnaire. Further, sleep habits have not previously been investigated in relation to MS risk and no section of the regular or the follow-up questionnaire was given prime focus, optimising the chance of avoiding differences in the quality of the reported information between cases and controls. The previous association between shift work and MS risk[1–3] strengthens our findings of short sleep/low sleep quality as a risk factor for subsequently developing the disease, since the potential for memory error is probably relatively low when answering questions on shift work. However, we cannot completely rule out the existence of recall bias.

The questions regarding sleep habits that were sent out as a complementary questionnaire were answered by 82% of the cases and 66% of the controls. This could have resulted in selection bias. However, there was no difference with respect to age, sex or smoking habits between those who participated in EIMS complimentary questionnaire and those who did not. Similar findings were observed when we separately analysed those who filled out the complementary questionnaire in 2015 and those who were recruited later. The mean duration between disease onset and study inclusion was 0.6 years (SD 0.7) for those recruited after 2015 and the recall has probably not been affected to a large degree by the disease. The prevalence of lifestyle factors, such as smoking, among the controls was also consistent with that of the general population.[22] We thus believe that our findings are not affected by selection bias to a large extent.

Although we had the opportunity to adjust the analyses for a large number of potential confounding factors, we cannot completely rule out residual confounding. There may also exist characteristics linked to sleep patterns that we do not adjust for, such as stress and dietary habits.

Insufficient or disturbed sleep is common among adolescents, which partially can be explained by physiological, psychological and social changes that occur during this age period.[23] Associations have also been demonstrated between social media use and sleep patterns. Availability of technology and internet access at any time contributes to insufficient sleep among adolescents and represents an important public health issue.[24–29] Educational interventions addressed to adolescents and their parents regarding the negative health consequences of insufficient sleep are of importance.

In conclusion, insufficient sleep and low sleep quality during adolescence seem to increase the risk of subsequently developing MS. Sufficient restorative sleep, needed for adequate immune functioning, may thus be another preventive factor against MS.

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Supplemental material

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Supplementary table 1. Characteristics of cases and controls, overall sample.

	Cases	Controls
N	2075	3164
Women, n (%)	1502 (72)	2324 (73)
Swedish, n (%)	1640 (79)	2479 (78)
Sleep duration <7 hours/night 7-9 hours/night 10 or more hours/night	148 (8.3) 1520 (84.8) 125 (7.0)	167 (6.2) 2305 (86.0) 208 (7.8)
Phase shift <1 hour 1-3 hours More than 3 hours	1091 (60.9) 517 (28.8) 185 (10.3)	1640 (61.2) 758 (28.3) 282 (10.5)
Sleep quality Very bad, n (%) Rather bad, n (%) Neither good nor bad, n (%) Rather good, n (%) Very good, n (%)	36 (2.0) 80 (4.5) 181 (10.1) 590 (32.9) 906 (50.3)	43 (1.6) 89 (3.3) 194 (7.2) 892 (33.3) 1463 (54.6)
Smoking, n (%)	1052 (51)	1321 (42)
Mean sun exposure (SD)	6.2 (1.8)	6.5 (1.9)
Mean adolescent BMI, kg/m (SD)	23.3 (13.1)	22.0 (6.4)
Infectious mononucleosis, n (%) No Yes Don't know	1496 (72) 381 (18) 198 (10)	2538 (80) 377 (11) 289 (9)
Age at disease onset (SD)	35.1 (10.5)	

Supplementary table 2. OR of MS with 95% CI for subjects with different habitual sleep duration in adolescence and at index.

Hours/night		ca/co[a]	OR (95% C)[b]	OR (95% C)[c]
Age 15-19 years	At index			
7-	7-	980/1743	1.0 (reference)	1.0 (reference)
7-	<7	516/611	1.5 (1.3-1.7)	1.5 (1.3-1.8)
<7	7-	58/69	1.5 (1.0-2.1)	1.5 (1.0-2.1)
<7	<7	239/257	1.6 (1.3-1.9)	1.6 (1.4-2.0)

[a]number of exposed cases and controls; [b]adjusted for age, sex, residential area, and ancestry; [c]adjusted for age, sex, residential area, ancestry, smoking, IM history, and sun exposure.

Supplementary table 3. OR of MS with 95% CI for subjects with different habitual sleep duration at index.

Hours/night	ca/co[a]	Total		Similar sleep duration in adolescence and at index	
		OR (95% C)[b]	OR (95% C)[c]	OR (95% C)[d]	OR (95% C)[e]
<7	888/1179	1.3 (1.1-1.4)	1.3 (1.1-1.4)	1.3 (1.1-1.7)	1.5 (1.1-2.0)
7-9	863/1458	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
10-	42/43	1.6 (1.1-2.5)	1.7 (1.1-2.6)	0.9 (0.7-1.2)	1.0 (0.5-2.0)

[a]number of exposed cases and controls; [b]adjusted for age, sex, residential area, and ancestry; [c]adjusted for age, sex, residential area, ancestry, smoking, IM history, and sun exposure.

Supplementary table 4. OR of MS with 95% CI for subjects with different sleep quality in adolescence and at index (assessed on a 5-grade scale).

Sleep quality (value)		ca/co[a]	OR (95% C)[b]	OR (95% C)[c]
Age 15-19 years	At index			
4-5	4-5	1133/2058	1.0 (reference)	1.0 (reference)
4-5	1-3	592/731	1.5 (1.3-1.7)	1.5 (1.3-1.7)
1-3	4-5	68/80	1.5 (1.1-1.1)	1.5 (1.1-2.2)
1-3	1-3	282/295	1.7 (1.3-2.0)	1.7 (1.4-2.1)

[a]number of exposed cases and controls; [b]adjusted for age, sex, residential area, and ancestry; [c]adjusted for age, sex, residential area, ancestry, smoking, IM history, and sun exposure.

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Questions from EIMS

Sleep duration

At which time do you normally go to sleep during work or schooldays?

15-19 years	Clock time:
20-29 years	Clock time:
30-39 years	Clock time:
40 years or older	Clock time:

At which time do you normally wake up during work or schooldays?

15-19 years	Clock time:
20-29 years	Clock time:
30-39 years	Clock time:
40 years or older	Clock time:

At which time do you normally go to sleep during weekends or days off?

15-19 years	Clock time:
20-29 years	Clock time:
30-39 years	Clock time:
40 years or older	Clock time:

At which time do you normally wake up during weekends or days off?

15-19 years	Clock time:
20-29 years	Clock time:
30-39 years	Clock time:
40 years or older	Clock time:

Sleep quality

Generally, how would you describe your sleep?

very bad, rather bad, neither good nor bad, rather good, very good

Smoking

If you **do not smoke**, and **have never smoked**, put a cross in the box and proceed to the section

If you **smoke regularly**, or **have smoked regularly**, put a cross in the box.
Below, specify the time-period/time-periods and amount.

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Try to specify the average amount. Nb! The number is specified **per day**.

	From age	To age	Number of cigarettes per day
			Number of cigars/cheroots per day
			Number of pipe fills per day

If you **smoke non-regularly**, for example at parties, or **have smoked non-regularly**, put a cross in the box. Below, specify the time-period/time-periods and amount.

Try to specify the average amount. Nb! The number is specified **per week**.

	From age	To age	Number of cigarettes per week
			Number of cigars/cheroots per week
			Number of pipe fills per week

Sun exposure

If the weather is sunny, how often do you usually sunbathe?

| Never | A few times a month | A few times a week | Daily |

How often, during the last 5 years, have you visited a country that is sunnier than Sweden?

| Never | More seldom | Once a year | More than once a year |

How often, during the last 5 years, have you used a sunbed?

| Never | A few times a year | Once a month | Once a week |

Infectious mononucleosis

Infectious diseases that usually occur during childhood or youth

Have you had these infectious diseases?

| 1. Measles | No | Yes | Don't know | If "yes", specify at what age you think you had the disease: |

2. Mumps

3. Whooping cough

4. Chickenpox

5. Glandular fever

6. Other severe/long-lasting infection
If "yes", specify what infection