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Sleep Duration Affects Risk for Ulcerative Colitis: A Prospective Cohort Study

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Abstract

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Author Contributions

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Background & Aims—Sleep deprivation is associated with production of inflammatory cytokines. Disturbed sleep quality has been associated with increased risk of disease flare in patients with Crohn's disease (CD) or ulcerative colitis (UC). However, the association between sleep and risk of incident CD and UC has not been previously examined.

Methods—We conducted a prospective study of women who were enrolled in the Nurses' Health Study (NHS) I since 1976 and NHS II since 1989 and followed through detailed biennial questionnaires with > 90% follow up. We examined the association of sleep duration reported in 1986 in NHS I and 2001 in NHS II with incident CD and UC, diagnosed through 2010, in NHS I and 2009 in NHS II. Cox proportional hazards models adjusting for potential confounders were used to calculate hazard ratios (HR) and 95% confidence intervals (CI).

Results—Among 151,871 women, we confirmed 191 cases of CD (incidence 8/100,000 person-years [p-y]) and 230 cases of UC (incidence 10/100,000 p-y) over 2,292,849 p-y. Compared to women with reported usual sleep durations of 7–8 hrs/day (incidence 8/100,000 p-y), women with reported sleep duration < 6 hrs/day (11/100,000 p-y) or > 9 hrs/day (20/100,000 p-y) had a higher incidence of UC ($P<.05$). The multivariate HRs for UC were 1.51 (95% CI, 1.10–2.09) for sleep durations < 6 hrs/day and 2.05 (95% CI, 1.44–2.92) for sleep durations > 9 hrs/day, compared to sleep durations of 7–8 hrs/day. In contrast, sleep duration did not modify risk of CD. Duration of rotating night shift work was not associated with CD or UC.

Conclusions—Based on data from the NHS I and II, less than 6 hrs sleep/day and more than 9 hrs sleep/day are each associated with an increased risk of UC. Further studies are needed to evaluate sleep as a modifiable risk factor in the pathogenesis and progression of IBD.

Keywords

circadian clock; population; epidemiology; risk factor; inflammation

INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory bowel diseases (IBD) with a complex etiopathogenesis involving genetic risk, intestinal dysbiosis, and the external environment^{1, 2}. Despite significant advances in our understanding of the immunologic basis for these diseases, much of the variance remains unexplained by identified genetic risk variants^{2, 3}. Smoking remains the earliest and most consistently described environmental factor influencing the development of these diseases^{4–8}. Several other environmental influences have been described including hormone use, dietary, vitamin D, stress, non-steroidal anti-inflammatory drugs, and physical activity^{4, 7, 9–17}. Identification of environmental and behavioral risk factors is important because they provide a window into the pathogenesis of these diseases and the divergence in behavior of CD and UC despite substantial genetic overlap. Furthermore, by being amenable to modification, they offer attractive opportunities to modify risk of incident disease, achieve remission, or maintain quiescence.

Inadequate duration of sleep is common. Both short and long duration of sleep have important health implications and are associated with increased overall mortality, cardiovascular disease, and cancer^{18–30}. Specifically, both long and short sleep duration is

associated with increased risk of colorectal cancer^{26, 27, 30}. Considerable evidence supports a bidirectional association between sleep and immunologic diseases³¹⁻³⁶. Inflammatory cytokines including tumor necrosis factor- α (TNF), interleukin-1 (IL-1) and IL-6 affect sleep^{33,37,38}; antibodies to TNF- α improve sleep quality³⁹. Conversely, sleep deprivation increases susceptibility to dextran sodium sulfate (DSS) induced colitis in mice models³⁵. Impaired sleep quality is common in patients with IBD and is associated with an increased risk of relapse in those with impaired sleep quality at remission^{37, 40-42}. Additionally, some, but not all data show that rotating shift work, which is associated with impaired sleep, is associated with some adverse health outcomes⁴³⁻⁴⁸, and light cycle disruption influences Th17 pathway function and susceptibility to inflammatory diseases⁴⁹. To our knowledge, no prior studies have examined the effect of sleep duration or shift work on risk of incident CD or UC. Thus, within two large cohorts of women with detailed prospectively collected exposure and health information, we examined the association between duration of sleep and risk of CD and UC.

METHODS

Study Population

Our study included participants in the Nurses Health Study I (NHS I) and Nurses Health Study II (NHS II) cohorts which have been previously described⁸⁻¹⁶. In brief, the NHS I includes 121,700 female registered nurses between the ages of 30-55 years recruited in 1976 followed prospectively through biennial questionnaires ascertaining diet, lifestyle, and health information. The NHS II recruited female registered nurses between the ages of 25-42 years in 1989, similarly following them with biennial questionnaires. The rate of follow-up in both cohorts exceeds 90%. The present study includes women who completed the questions regarding sleep duration in 1986 (NHS I) or 2001 (NHS II). Women who had died, received a diagnosis of CD or UC, or had a diagnosis of cancer (except non-melanoma skin cancer) before this baseline questionnaire were excluded. Our study was approved by the Institutional Review Board of Brigham and Women's Hospital.

Assessment of Sleep Duration and Shift Work

Participants in NHS I were asked about "total hours of actual sleep in 24-hour period". The response categories were < 5, 6, 7, 8, 9, 10, or 11 hours or more. Participants in NHS II were asked the same question in 2001 with similar response categories. Self-reported sleep duration has been validated previously in these cohorts. In 2002, among women who completed the question on sleep duration in 2000, 480 were mailed a supplemental questionnaire and invited to keep a sleep diary for 1 week. There was strong correlation between self-reported sleep duration and the sleep diary (correlation co-efficient 0.79, p-value < 0.001). Furthermore, there was good reproducibility for sleep duration reported in 2000 and 2002 within a one hour deviation (correlation co-efficient 0.81)⁵⁰. Self-reported sleep duration also demonstrates moderate to strong correlation with sleep duration measured by polysomnography or actigraphy⁵¹⁻⁵³. Women who completed the sleep duration question were similar in age, body mass index, physical activity, alcohol consumption, and dietary factors to those who did not complete this question. Sleep duration was classified as 6 hours, 7-8 hours, and 9 hours consistent with prior analyses^{26,30,50}.

Shift work was assessed in 1988 in NHS I when participants were asked the question “What is the total number of years during which you worked rotating night shifts (at least 3 nights per month in addition to days or evenings in that month)?”. Response categories included never, 1-2, 3-5, 6-9, 10-14, 15-19, 20-29 and 30 years in NHS I while the top response category in NHS II was 20 years. Current shift work at the time of this baseline questionnaire was not assessed. Participants of NHS II were asked this question in 1989.

Ascertainment of cases

Our method for the ascertainment of CD and UC has been described in our previous publications⁹⁻¹⁶. In brief, with each biennial questionnaire, women were asked to self-report a diagnosis of CD and UC. Women with a self-reported diagnosis were sent a detailed supplemental questionnaire requesting further information on type of IBD, date of diagnosis, disease behavior and complications, and treatment as well as requesting permission to obtain relevant medical records from the treating physician. Among 2,427 women from NHS I and 1,011 women from NHS II who self-reported a diagnosis of CD or UC through 2010 in NHS I and 2009 in NHS II, 2,388 were still alive, did not have a diagnosis of IBD prior to the baseline questionnaire, and could be contacted. A total of 887 women subsequently denied the diagnosis based on a more detailed description of the disease on the supplementary questionnaire. Among the remaining 1,501 women, permission to review medical records was obtained from 983 and records were reviewed by 2 board-certified gastroenterologists blinded to exposure status. A diagnosis of UC or CD was made based on accepted clinical criteria incorporating history and duration of typical symptoms of abdominal pain, diarrhea, or rectal bleeding, and confirmatory endoscopic, histological, radiographic, and surgical findings⁵⁴⁻⁵⁶. Disagreements were infrequent and resolved through consensus. Among those with sufficient medical records, a diagnosis of IBD was rejected in 224, among which 167 were judged to have non-IBD chronic colitis. After excluding women with missing date of diagnosis or information on sleep duration, our final cohort for analysis of sleep duration included 191 incident cases of CD and 230 incident cases of UC.

Covariates

Information on smoking, menopausal status, and use of oral contraceptives, menopausal hormone therapy, aspirin, and non-steroidal anti-inflammatory drugs (NSAIDs) were obtained every 2 years. Dietary vitamin D and fiber were first assessed in 1986 in NHS I and 1991 in NHS II and updated every 4 years using a validated semi-quantitative food frequency questionnaire¹⁰¹². Physical activity was estimated in metabolic equivalents per hour (mets/hr) using a validated assessment administered every 2-4 years¹⁴. Depressive symptoms were assessed using the 5-item mental health index as described previously¹³. Consistent with prior analyses, we used time-varying covariates for our analyses to account for changes over follow-up with the exception of body mass index (BMI) (in kilograms per square meter) in which we used baseline values to minimize the modification of weight by symptoms related to disease.

Statistical Analysis

For analyses of sleep duration, participants contributed person-time from the date of return of the baseline questionnaire on sleep duration (1986 in NHS I and 2001 in NHS II) until the

diagnosis of CD or UC, death, or date of return of the last questionnaire, whichever came first. For analyses of shift work, participants began contributing person-time from the date of return of the baseline questionnaire on rotating shift work (1988 in NHS I and 1989 in NHS II). We regrouped response categories for sleep duration and duration of rotating night shift work in categories consistent with prior analyses from these cohorts⁵⁷. Cox proportional hazards models adjusting for potential confounders were used to determine the multivariate hazard ratios (HR) and 95% confidence intervals (CI). All models satisfied the proportionality of hazards assumption. There was no heterogeneity between the two cohorts in the association between sleep duration and CD or UC (P heterogeneity >0.30). Thus, we pooled data from both cohorts for the final analysis. We performed several sensitivity and subgroup analysis. In the cohort of women with self-reported mood status using the mental health index-5, we adjusted for depressive symptoms to establish if the association with sleep was independent of mood. To further reduce the likelihood of unmeasured confounder by comorbidities associated with sleep duration and disease risk, we additionally adjusted for a history of myocardial infarction to examine its effect on the association between sleep and CD or UC. Finally, we performed subgroup analysis stratifying by smoking status and body mass index. A two-sided p -value < 0.05 indicated independent statistical significance. All analyses were performed using SAS software 9.1 (SAS Institute, Cary, NC).

RESULTS

Baseline Characteristics

Our study included 151,871 women from NHS I and NHS II among whom we documented 191 incident cases of CD (incidence 8 per 100,000 person-years) and 230 incident cases of UC (incidence 10 per 100,000 person-years) over 24 years and 2,292,849 person-years of follow-up. **Table 1** presents the characteristics of the cohort according to reported sleep duration. Women who reported short sleep duration were more likely to be older, currently smoke, be overweight or obese, or regularly use aspirin compared to women with sleep duration of 7-8 hours. Intake of dietary fiber, vitamin D and physical activity were generally similar according to the three categories of sleep duration.

Sleep duration and risk of UC and CD

Compared to women with normal sleep duration, women with short sleep duration had an increased incidence of UC (incidence 11 per 100,000 vs. 8 per 100,000) (HR 1.50, 95% CI 1.09 – 2.07) (**Table 2**). Adjusting for potential confounders including smoking, BMI, and physical activity did not significantly alter the multivariate HR (1.51, 95% CI 1.10 – 2.09). Women who reported long sleep duration also had an increase in risk for UC (incidence 20 per 100,000, multivariate HR 2.05, 95% CI 1.44 – 2.92). We observed similar risks among overweight or obese women as those with normal BMI. In contrast, neither short (HR 0.90, 95% CI 0.63 – 1.28) nor long duration of sleep (HR 1.16, 95% CI 0.73 – 1.83) modified the risk of CD. Stratifying CD by area of involvement suggested a similar lack of association with either ileal or colonic disease ($p > 0.10$ for both short and long sleep duration).

In analyses according to history of smoking, the increase in risk of UC appeared more evident among ever smokers, with HR of 1.72 (95% CI 1.13 – 2.62) associated with short

sleep and 2.72 (95% CI 1.65 – 4.48) for long sleep duration (P interaction > 0.05). We also observed no interaction between smoking status, hormone use, or BMI and sleep duration in modifying risk of CD.

Shift work and risk of UC and CD

We explored the association between duration of rotating night shift work and risk of UC or CD (**Table 3**). Compared to women who reported no shift work, women with 1-5 years (HR 0.79, 95% CI 0.62 – 1.00) and 6 years of shift work reported similar risk of UC (0.82, 95% CI 0.58 – 1.14) ($P_{\text{trend}} = 0.11$). We also observed no association between number of years of night shift work and incidence of CD.

Sensitivity Analysis

We performed several sensitivity analyses. First, we excluded patients who were diagnosed with UC or CD within 2 years of the baseline questionnaire to exclude the possibility of subclinical symptoms of disease influencing duration of sleep. We observed no material change in our risk estimates. Given the previously reported association between depressive symptoms and risk of IBD¹³, and the known association between depression and sleep in IBD⁴¹, we also repeated our analysis adjusting for depressive symptoms assessed in 1992 in NHS I and 2001 in NHS II. The magnitude of association between short (HR 1.56, 95% CI 1.09 – 2.24) or long duration (HR 2.01, 95% CI 1.38 – 2.91) of sleep and UC remained unchanged. Similarly, the lack of association between sleep duration and risk of CD persisted.

DISCUSSION

Insufficient sleep is common in the general population and is associated with a spectrum of adverse health outcomes. Using two large prospective cohorts, we demonstrate that both short- and long-duration of sleep is associated with an increased risk of UC but not CD. These observed associations were independent of other known risk environmental risk factors.

Considerable evidence supports an association between sleep and the immune system^{31-35,373858}. Tang *et al.* demonstrated that both acute and chronically sleep-deprived mice were more susceptible to dextran sodium sulfate (DSS) induced colitis than mice that were not sleep-deprived³⁵. In particular, chronic sleep deprivation worsened histological and clinical severity of colitis. Sleep restriction also results in a reduction in circulating IL-2 and increases in TNF- α and monocyte chemoattractant protein-1, shifting the Th1/Th2 cytokine balance towards Th2³²³⁷⁵⁸⁵⁹. Such shifts can favor the development of UC given the more dominant role of the Th2 pathway in its pathogenesis. Even partial or short term sleep deprivation has been shown to increase concentrations of IL-6 and TNF- α ,³²³⁷⁵⁸⁶⁰ which influences intestinal permeability through alterations in circadian clock genes³⁴³⁷⁵⁸. Disturbed sleep can also induce activation of other inflammatory cells including natural killer cells and monocytes³⁴³⁷⁵⁸. Despite considerable sharing of risk loci between CD and UC, studies of environmental factors have revealed a differential effect for a number of them including smoking, appendectomy, dietary fiber, fat, and vitamin D. The reasons for this

divergence in effect are yet. Some pathways appear to be predominantly involved in the pathogenesis of Crohn's disease such as the innate immune response, while other pathways such as maintenance of barrier function is more important in ulcerative colitis. It is possible that factors such as sleep influence disease pathogenesis through an effect on maintenance of barrier integrity. However, this remains speculative and further experimental proof is needed if indeed the association is disease specific.

There are fewer data on the potential mechanistic basis by which long duration of sleep may influence risk of UC although the phenomenon of a "U-shaped" association with sleep has been described for other health outcomes including colorectal cancer and overall mortality²⁶²⁷³⁰⁵⁰⁶¹. It is possible that longer duration of sleep may be associated with poor sleep quality or fragmented sleep, which can promote a pro-inflammatory milieu. In an elegant study, Patel *et al.* found that that longer sleep duration was associated with an 8% increase in C-reactive protein levels and a 7% increase in interleukin-6 while shorter sleep duration was associated with an increase TNF- α levels, mechanistically supporting a pro-inflammatory effect for both long and short duration of sleep⁶².

Interestingly, we did not observe an association between duration of rotating night shift work was not associated with either UC or CD. There are a few possible explanations for this. First, a relatively small proportion of women reported prolonged duration of shift work. Given the relative rarity of CD and UC, we were unable to examine the effect of prolonged duration of shift work on disease risk, and indeed categories comprising a wider distribution of shift work may demonstrate an association. This is consistent with prior studies where associations with disease risk have been most apparent in the extreme categories of shift work⁴⁶⁴⁷⁵⁷. Secondly, number of years of shift work was assessed over the lifetime prior to completion of the questionnaire while sleep duration was specifically inquired about at the time of the baseline questionnaire. Thus, the apparent dichotomy between the effect of duration of shift work and sleep duration could also be due to differential effects of remote compared to recent exposure.

There have been few studies examining the effect of disturbed sleep in patients with established IBD⁴⁰⁻⁴²⁶³. In a large internet-based cohort study, we had previously reported a high frequency of impaired sleep quality even in IBD patients in clinical remission⁴¹. Furthermore, impaired sleep quality at baseline in those in clinical remission was associated with an increased likelihood of relapse at 6 months in CD. A second study by Ali *et al.* demonstrated an association between impaired sleep quality and histologic disease activity in 41 IBD patients undergoing ileocolonoscopy⁴⁰. Prior studies demonstrated a high prevalence of impaired sleep quality in those with IBD, more commonly in those with active disease than in remission³⁷⁴²⁶³.

There are several strengths to our study. The large size of the cohorts, prospective design, and prolonged duration of follow-up provide a unique opportunity to examine the association between sleep duration and incident disease with sufficient power to adjust for potential confounders. Second, all our cases were confirmed on chart review by two board certified gastroenterologists, limiting misclassification of outcomes with conditions associated that are often misreported as IBD, including functional bowel disease which has

also been associated with poor sleep^{64,65}. Last, the medical background of the participants also improved the accuracy of reported confounders and health information and facilitated our high follow-up rate.

We acknowledge several limitations to our study. First, our population consisted predominantly of Caucasian female nurses, and is thus not representative of the gender and ethnic distribution in the general population. However, the environmental associations previously identified in our cohorts were similar to those with from prior studies and the age-adjusted incidence of disease is consistent with those from other population based cohorts⁶⁶. Second, sleep duration was by self-report. However, in a validation study, subjective sleep duration correlated well with a 1 week sleep diary, and was stable between questionnaires administered 2 years apart⁵⁰. Third, there exists the possibility of reverse causality whereby women with symptoms prior to the diagnosis of their disease may experience disruption in sleep. However, our findings were robust on excluding women diagnosed within 2 years of the baseline questionnaire. As well, it is less likely that such subclinical symptoms would explain the association with both reduced and long duration of sleep. Fourth, the median age of diagnosis in our cohort is older than the expected age of onset for IBD. However, prior studies have not suggested a differential effect of environmental factors based on the age at diagnosis. Moreover, the associations described from our cohort such as an inverse association of CD with dietary fiber, fruits, and vegetables¹² is very similar to that observed in pediatric IBD⁶⁷, supporting the generalizability of our associations. Finally, as with all observational studies, we cannot exclude the possibility of unmeasured confounders although we adjusted for several key variables in our multivariate model.

In conclusion, we demonstrate a “U-shaped” relationship between sleep duration and risk of UC with both short and long-duration of sleep being associated with an increased risk of disease. These findings are consistent with studies demonstrating an association between sleep deprivation and a pro-inflammatory milieu in animal models and humans. Our findings suggest the possibility that modification of sleep habits may influence risk of subsequent disease among individuals at risk for UC or maintaining quiescence among those with established disease. Continued study of the mechanisms by which sleep may influence intestinal inflammation is warranted.

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Table 1Baseline[‡] characteristics of the study population according to self-reported sleep duration

	7-8 hours (n = 99,431)	6 hours (n=27,690)	> 9 hours (n = 24,750)
Mean age (in years) (standard deviation)	43.8(9.3)	48.8(8.3)	38.6(7.5)
White race (%)	98	96	98
Smoking status (%)			
Never Smoker	53	49	54
Past Smoker	31	30	31
Current Smoker	15	21	
Ever oral contraceptive use (%)	64	61	65
Pre-menopausal (%)	46	47	44
Post-menopausal hormone therapy (%)[‡]			
Never Users	24	28	23
Past Users	11	11	11
Current Users	18	15	20
Body Mass Index (%)			
< 20.0 kg/m ²	10	9	11
20.0 – 24.9 kg/m ²	53	49	52
25.0 – 29.9 kg/m ²	24	26	23
30.0 kg/m ²	12	17	13
Regular aspirin use[±] (%)	17	21	14
Regular NSAID use[±] (%)	16	13	17
Mean fiber intake (g/day) (SD)	18.7(5.5)	18.0(5.5)	18.8(5.8)
Mean vitamin D intake (IU/day) (SD)	367(244)	349(244)	381(252)
Mean physical activity (mets/hr) (SD)	40.5(156.1)	39.4(153.2)	43.2(165.4)

SD – standard deviation; NSAID – non-steroidal anti-inflammatory drugs; g/day – grams per day; IQR – interquartile range

[‡]Baseline characteristics according to the 1986 questionnaire for Nurses Health Study I and 2001 questionnaire for Nurses Health Study II.[±]regular use was defined as intake of 5 or more times per month

Table 2

Risk of Crohn's disease and ulcerative colitis according to self-reported sleep duration

	6 hours	7-8 Hours	9 hours
Person-years of follow-up	543,238	1,504,021	245,591
Crohn's disease			
Number of cases	42	125	24
Age-adjusted incidence #	8	8	10
Age-adjusted HR (95% CI)	0.92 (0.64 – 1.31)	1.0	1.18 (0.74 – 1.87)
Multivariate HR (95% CI) [†]	0.90 (0.63 – 1.28)	1.0	1.16 (0.73 – 1.83)
Ulcerative colitis			
Number of cases	59	121	50
Age-adjusted incidence #	11	8	20
Age-adjusted HR (95% CI)	1.50 (1.09 – 2.07)	1.0	2.09 (1.47 – 2.97)
Multivariate HR (95% CI) [†]	1.51 (1.10 – 2.09)	1.0	2.05 (1.44 – 2.92)

NSAID – non-steroidal anti-inflammatory drugs, HR – hazard ratio, CI – confidence interval, IQR – interquartile range

[†] Adjusted for age, cohort, smoking (never, past, current), body mass index (in kg/m²), oral contraceptive use (never, ever), use of post menopausal hormone therapy (premenopausal, postmenopausal hormone never user, ever user, regular use of NSAIDs (yes, no), regular use of aspirin (yes, no), dietary fiber intake (g/day), vitamin D intake (IU/day), physical activity (mets/hr)

per 100,000 person-years

Table 3

Risk of Crohn's disease and ulcerative colitis according to duration of shift work

	Never	1-5 years	6 years
Person-years of follow-up	1,353,116	1,516,221	514,149
Crohn's disease			
Number of cases	106	111	40
Age-adjusted incidence #	8	7	8
Age-adjusted HR (95% CI)	1.0	0.91 (0.70 – 1.20)	0.99 (0.69 – 1.43)
Multivariate HR (95% CI) †	1.0	0.92 (0.70 – 1.19)	0.95 (0.66 – 1.37)
Ulcerative colitis			
Number of cases	146	132	45
Age-adjusted incidence #	11	9	9
Age-adjusted HR (95% CI)	1.0	0.79 (0.62 – 1.00)	0.81 (0.58 – 1.14)
Multivariate HR (95% CI) †	1.0	0.79 (0.62 – 1.00)	0.82 (0.58 – 1.15)

The time period for analysis of shift work was from 1988-2010 in NHS I and 1991-2009 in NHS II. Over 3,393,486 person-years of follow-up, we identified 257 incident diagnoses of CD (incidence 8 per 100,000 person-years) and 303 incident diagnoses of UC (incidence 10 per 100,000 person-years).

NSAID – non-steroidal anti-inflammatory drugs, HR – hazard ratio, CI – confidence interval, IQR – interquartile range

† Adjusted for age, cohort, smoking (never, past, current), body mass index (in kg/m²), oral contraceptive use (never, ever), use of post menopausal hormone therapy (premenopausal, postmenopausal hormone never user, ever user, regular use of NSAIDs (yes, no), regular use of aspirin (yes, no), dietary fiber intake (g/day), vitamin D intake (IU/day), physical activity (mets/hr)

per 100,000 person-years