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Sleep during naturally occurring respiratory infections: A pilot study

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ABSTRACT

There is strong experimental support that infections increase the drive for sleep in animals, and it is widely believed that more sleep is part of an adaptive immune response. While respiratory infections (RI) are very prevalent in humans, there is a striking lack of systematic knowledge on how it affects sleep. We recruited 100 people, among whom 28 became sick with an RI during the study period (fulfilling criteria for influenza-like illness, ILI, or acute respiratory infection, ARI). We measured sick participants' sleep at home, both objectively (actigraphy) and subjectively (diary ratings), for one week as well as four weeks later when healthy. During the week with RI, people spent objectively longer time in bed and had a longer total sleep time compared to the healthy week. During the infection, participants also had more awakenings, but no significant differences in sleep latency or sleep efficiency. While sick, people also reported increased difficulties falling asleep, worse sleep quality, more restless sleep and more shallow sleep, while they did not report sleep to be less sufficient. Most problems occurred at the beginning of the sickness week, when symptoms were strong, and showed signs of recovery thereafter (as indicated by interactions between condition and day/night of data collection for all the 10 sleep outcomes). The degree of symptoms of RI was related to a worse sleep quality and more restless sleep, but not to any of the objective sleep outcomes or the other subjective sleep variables. Having a higher body temperature was not significantly related to any of the sleep variables. This study suggests that having a respiratory infection is associated with spending more time in bed and sleeping longer, but also with more disturbed sleep, both objectively and subjectively. This novel study should be seen as being of pilot character. There is a need for larger studies which classify pathogen type and include baseline predictors, or that manipulate sleep, in order to understand whether the sleep alterations seen during infections are adaptive and whether sleep interventions could be used to improve recovery from respiratory infections.

1. Introduction

Already the ancient Greeks claimed that sleep is altered during sickness, and many people believe that sleeping more may aid recovery from disease (Opp and Krueger, 2015). However, only recently the associations between sleep and immunity have rendered a more systematic interest (Irwin and Opp, 2017). Insufficient sleep alters immune functions (Irwin, 2015), and proper sleep is an important factor supporting a strong and efficient first line of defense against infections (Cohen et al., 2009; Prather and Leung, 2016). However, the relationships are bidirectional, sleep being altered in a number of infectious diseases (Opp and Krueger, 2015).

In animal studies (mainly in rodents and rabbits), bacterial or viral infections, at least in moderate doses, increase sleep duration and the amount of non-rapid eye movement (NREM) sleep, and reduce the time spent in REM sleep (Opp and Krueger, 2015). It has been hypothesized that these alterations support recovery and are adaptive responses to infection. Indeed, because cytokine-induced behavioral changes during sickness (i.e., "sickness behavior") are known to be adaptive and to contribute to an efficient host response against the pathogen (Dantzer, 2001), it is probable that the modifications to sleep during an infection also benefit immunity (Imeri and Opp, 2009). This is supported by animal models (in rodents, rabbits and drosophila), where less sleep reduces survival while more sleep improves survival from infections

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Table 1
Effects of having a respiratory infection (RI) and of days with infection on body temperature and symptoms of sickness. The left part concerns the effects of condition and weekdays, and the right part the effects of condition and days with infection/being healthy.

Fixed effects	Mixed effects ANOVA (Effect of condition and weekday)						Fixed effects	Mixed effects ANOVA (Effect of condition and days with infection/being healthy)					
	Body temperature			Symptoms				Body temperature			Symptoms		
	F	p-value		F	p-value			F	p-value		F	p-value	
Condition	1.4	0.248		102.04	< 0.001	***	Condition	1.29	0.267		106.11	< 0.001	***
Weekday	3.6	0.002	**	0.47	0.829		Days	1.85	0.093		21.16	< 0.001	***
Time of day	9.75	0.004	**	0.22	0.643		Time of day	8.41	0.007	**	0.17	0.680	
Condition: Weekday	0.62	0.713		1.35	0.232		Condition: Days	1.35	0.234		45.97	< 0.001	***
Condition: Time of day	0.46	0.500		1.04	0.308		Days: Time of day	0.51	0.804		0.38	0.890	
Weekday: Time of day	2.25	0.038	*	0.76	0.601		Condition: Time of day	0.97	0.326		2.78	0.096	
Condition: Weekday: Time of day	0.87	0.518		0.86	0.526		Condition: Days: Time of day	1.59	0.149		1.61	0.143	
Random effects	SD	N		SD	N		Random effects	SD	N		SD	N	
Condition: Subjects	0.165	54		1.776	54		Condition: Subjects	0.168	54		1.798	54	
Weekday: Subjects	0.063	196		0.802	196		Days: Subjects	0.059	196		0.841	196	
Time of day: Subjects	0.127	56		0.151	56		Time of day: Subjects	0.128	56		0.499	56	
Subjects	0.242	28		0.540	28		Subjects	0.241	28		0.523	28	
Residual	0.305	703		2.437	708		Residual	0.307	703		1.753	708	

The ANOVAs include the fixed effects of condition (period with RI vs healthy period), time of day (morning and evening), and weekday effects (in the left panel) and days with sickness or being healthy (in the right panel). The weekday effect is added as a factor to account for that subjects got sick at different days of the week. P-values have been calculated using Kenward-Roger adjusted denominator degrees of freedoms.

(Everson and Toth, 2000; Kuo and Williams, 2014; Toth et al., 1993).

Studies in humans show that an injection with bacterial endotoxin acutely promotes more NREM-sleep and suppresses REM-sleep, as in animal studies, but with no effects on sleep duration (Mullington et al., 2000; Trachsel et al., 1994). Two small studies where subjects were injected with virus (5 developed influenza like illness, ILI) after injection with Influenza B, and 5 developed ILI and 4 developed a common cold after injection with rhinovirus) showed longer self-reported sleep during the symptomatic period, but no effect on sleep quality or awakenings (Smith, 1992). An EEG study in subjects after a rhinovirus injection showed a shorter sleep duration during the symptomatic period, but no effects on the amount of REM or NREM sleep (Drake et al., 2000). A likely explanation for the inconsistencies is that human sleep seems more vulnerable to fever responses than animal sleep (Mullington et al., 2000). There is little support for an increased sleep duration in infected humans, which may be due to differences between humans and animals, but also due to study design limitations that have not allowed subjects to stay in bed for longer than 8 h (Drake et al., 2000; Mullington et al., 2000).

Acute respiratory infections are extremely prevalent and an estimated 17.8 billion upper respiratory infections occurred during 2016 alone (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017). Since sleep is believed to be part of an adaptive immune response and to aid recovery, it is surprising that no prior study has reported how naturally occurring respiratory infections (RI) affect objective sleep. The aim of the current study was to provide data regarding this issue by assessing subjective (diary ratings) and objective (actigraphy) sleep for one week during a naturally occurring acute respiratory infection. Enrolled people contacted us when suffering from symptoms fulfilling criteria for ILI (i.e., having at least one respiratory symptom such as cough, and one systemic symptom such as fever) or acute respiratory infection (ARI, i.e., having coryza with a systemic symptom), and were followed for one week, and subsequently followed again four weeks later if symptom free. Our hypotheses were that people would sleep longer during a respiratory infection but with reduced quality of sleep, with respect to both objective and subjective sleep. We believed that sleep alterations would be largest at the beginning of the week and then reduce as people recovered. Since people got sick on different days of the week (a factor affecting sleep), we also analyzed the influence of weekday on the outcomes.

2. Methods

2.1. Participants

One hundred subjects agreed to participate in the study and were assigned to the waiting list until they developed a respiratory infection. Based on the previous studies by Drake et al (2000), in which 7 individuals on a sample size of 21 developed cold symptoms after inoculation with a rhinovirus, we included 100 subjects so as to lead to the inclusion of 30–40 subjects becoming sick in a respiratory infection.

Inclusion criteria were 18–65 years of age, working/studying at least 32 h/week and being fluent in Swedish. Exclusion criteria were smoking or taking snuff/drugs, being a shift worker, having an autoimmune or mental disorder, or having had antibiotic treatment within the previous three months.

Subjects on the waiting list were instructed to contact the research team as soon as they started to feel sick, and had at least one of the following respiratory symptoms: cough, sore throat, shortness of breath, or coryza; as well as at least one of the following systemic symptoms: fever, headache, malaise or myalgia. When contacted, the research assistant inquired whether the symptoms occurred suddenly, at what time the subject had started to fulfill the symptom criteria necessary for contacting the research team, and what exact symptoms the subject was suffering from. If a subject fulfilled the criteria for influenza-like illness (ILI) or having coryza with a systemic symptoms (then fulfilling criteria for an ARI), they were immediately included in the data collection (ECDC, 2012), i.e. starting the same evening or the

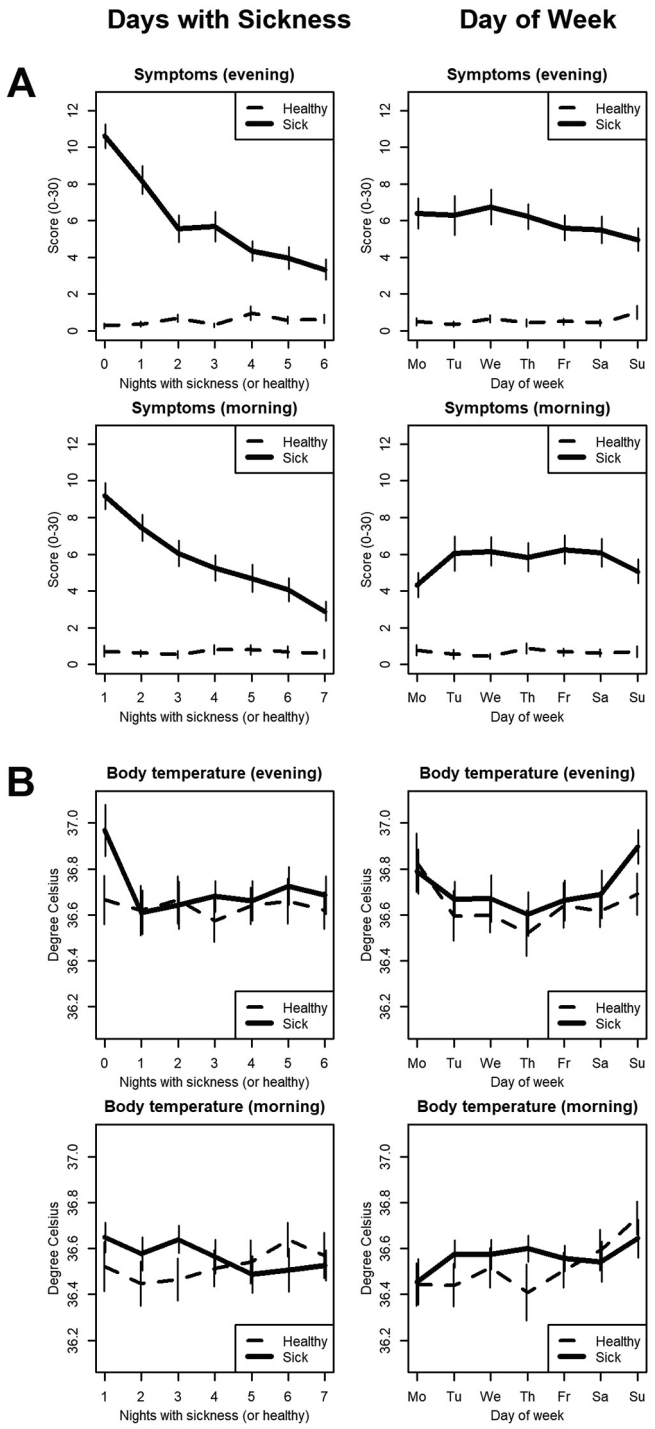

Fig. 1. Sickness symptoms and body temperature during a respiratory infection and when healthy. Observed means ± SEM, separately for evening and morning measures. Left panels show data plotted against number of nights with sickness (and matched with the same day of week for the healthy condition) and right panels show data plotted against day of week for A) sickness symptoms and B) body temperature. See Table 1 for detailed statistics.

next day when symptoms occurred late at night. Subjects were also instructed to avoid taking medication unless they felt it was absolutely necessary. Subjects on the waiting list were reminded to contact the research assistant as soon as feeling sick by email once per month during the study period. Twenty-nine subjects with a RI were included for participation (of these, 6 subjects had a body temperature higher than 37.5 °C including one higher than 38 °C). Of these 29 participants, one was excluded because of pregnancy. Twenty-eight participants (17 women; mean age: 33.4 ± 13.7 years, range 18–63) were therefore included in the present study. This study was carried out in accordance with the recommendations of the regional ethical review board in Stockholm. The protocol was approved by the regional ethical review board in Stockholm. All subjects gave written informed consent in accordance with the Declaration of Helsinki. Subjects who went through all study procedures were compensated with 1200 SEK.

2.2. Protocol

As soon as the subjects reported being sick, a research assistant visited them in their home. Subjects were given a study kit (including actigraph, ear thermometer (Thermoscan, Braun, city) and questionnaires) and received instructions on how to complete health and sleep diaries, record their body temperature at bedtime and directly after rising, and how to wear the actigraph. They filled out health and sleep diaries, took their body temperature and wore the actigraph for seven consecutive days and nights ("sickness" condition), after which a research assistant returned to the subject's home and collected the used materials kit. Approximately four weeks after their first registered sick day (depending on the participants' availability), the same subjects received a new study kit, and again completed the sleep diaries, took their body temperature, and wore the actigraph for seven consecutive days and nights ("healthy" condition). After completion, the kit was again collected at the subject's home. During both conditions, subjects were instructed not to take common over-the-counter medications for symptoms of an acute respiratory infection (such as ibuprofen and nasal sprays) unless absolutely necessary, and to avoid alcohol. They also registered any events that could have disturbed sleep (e.g., sick children, period cramps) in the sleep diary. The subjects were also wearing a t-shirt provided by us during the first 5 nights of each condition for analysis of sickness-related odor volatiles in a separate study.

2.3. Body temperature and sickness symptoms

In both conditions, participants were instructed to complete a health diary, measure body temperature and answer health-related questions, both in the evening and morning. Three measurements of body temperature were collected by the subjects using the ear thermometer they had received in the study kit, and the maximal value was selected for data analysis. Ten symptoms of infection (i.e., sneezing, sore throat, fever, headache, congested nose, runny nose, cough, nausea, muscle pain, dizziness) were rated on a 4-point scale ranging from 0 = "none" to 3 = "severe", providing a total score of sickness symptoms ranging from 0 to 30. Health-related questions were also answered, including coffee, alcohol and medicine consumption (if any).

2.4. Subjective sleep

The participants filled out the Karolinska Sleep Diary (Akerstedt et al., 1997) each morning. This sleep diary contains questions on sleep timing and quality, and the included items are rated on 5-point Likert scales, i.e., difficulties to fall asleep (1 "very difficult" to 5 "not at all"), sleep quality (1 "very poor" to 5 "very good"), restless sleep (1 "a lot" to 5 "not at all"), sleep duration (1 "not at all" to 5 "fully sufficient") and sleep depth (1 "very light" to 5 "very deep"). The score of difficulties to fall asleep and restless sleep were inverted so higher scores reflected increased difficulties to fall asleep and more restless sleep, respectively. Subjects also reported medication (see Table S1), and amount and duration of naps in an evening diary (see Fig. S1).

2.5. Objective sleep

Participants wore an actigraph (Camntech, AW4, CamNtech Ltd., Cambridge, UK) on the wrist for one week with the instruction to

Table 2
Effect of having a respiratory infection (RI) on subjective and objective sleep.

Outcome	Fixed effects								Random effects							
	Condition			Weekday			Condition: Weekday		Condition: Subjects		Weekday: Subjects		Subjects		Residual	
	F	p		F	p		F	p	SD	N	SD	N	SD	N	SD	N
Subjective sleep																
Difficulty falling asleep	4.53	0.043	*	3.78	0.002	**	1.08	0.375	0.00	54	0.12	195	0.41	28	0.97	351
Sleep quality	6.60	0.016	*	2.55	0.022	*	0.38	0.893	0.17	54	0.23	196	0.42	28	0.89	352
Restless sleep	9.06	0.006	**	2.18	0.048	*	1.66	0.129	0.16	54	0.42	196	0.43	28	0.80	352
Sufficient sleep	0.23	0.635		3.76	0.002	**	0.84	0.536	0.25	54	0.00	196	0.46	28	0.90	352
Sleep depth	6.55	0.017	*	1.84	0.094		0.51	0.802	0.00	54	0.27	196	0.39	28	0.68	353
Objective sleep																
Time in bed	9.21	0.006	**	3.25	0.005	**	0.62	0.711	0.21	49	0.00	182	0.65	28	1.21	294
Sleep latency	0.17	0.686		0.19	0.979		0.36	0.902	8.14	49	0.00	182	6.02	28	15.03	294
Awakening frequency	8.45	0.008	**	2.95	0.010	**	0.73	0.628	0.01	49	0.00	182	0.02	28	0.02	294
Total sleep time	7.93	0.010	*	3.24	0.005	**	0.59	0.742	0.00	49	0.00	182	0.44	28	1.13	294
Sleep efficiency	0.09	0.726		0.61	0.726		0.49	0.816	2.89	49	0.00	182	2.19	28	4.69	294

The ANOVAS include the fixed effects of condition (period with RI vs healthy period) and weekday effects. The weekday is added as a factor to account for that subjects got sick at different days of the week. P-values have been calculated using Kenward-Roger adjusted denominator degrees of freedoms. SD = Standard deviation. Sleep efficiency = total sleep time/time in bed.

remove it when bathing/showering, and to press an event button when turning off the lights when going to sleep and when rising in the morning. The following variables were selected for data analysis: time in bed (in hours), sleep latency (i.e., estimated time to fall asleep in minutes), awakenings (number of estimated waking bouts per hour asleep), total sleep time (estimated time when the subject is sleeping in hours), sleep efficiency [=(total sleep time/time in bed)*100, in %].

2.6. Missing data

Approximately 10% of the data were missing regarding body temperature, symptoms and subjective sleep, and these data points were mostly in the healthy condition. Data for 3 to 6 nights (1–3%) was missing for the sickness condition. During the healthy condition, 2 participants withdrew and 22 participants did not complete the diary regarding the last night (because of misinformation to subjects). Thus, data for 35–36 nights (18–20%) was missing for the healthy condition, mostly at the end of the week. In total, 351–353 observations were available for analyses.

Regarding objective sleep, 25% of the data were missing mainly due to technical issues or participants forgetting to wear the actigraph. In the sickness condition, 48 nights (24%) were unrecorded across 12 subjects, with the entire week missing for 4 subjects and only one night was recorded for 2 subjects. In the healthy condition, 49 nights (25%) were unrecorded across 19 participants, with the entire week missing for 1 subject, only one night recorded for 1 subject and 2 subjects withdrawing their participation. In total, 294 observations were available for analysis.

2.7. Statistics

The overall effect of sickness on body temperature, sickness symptoms, subjective sleep and objective sleep was estimated by mixed effects ANOVAs using condition (sickness versus healthy) as repeated factor. The effect of the day of the week was also included in the models because of potential differences between weekend and weekdays, as well as between weekdays. In addition, because body temperature and sickness symptoms were recorded in both the evening and morning, time of day was included in the models for these variables.

The mixed effect ANOVAs also fitted random effects to account for overall subject-specific effects, subject-specific day of week effects and subject-specific responses to sickness. The latter random effect was subsequently used to produce empirical Bayes' estimates of the subject-specific responses to sickness, for exploratory correlation analyses between all outcomes.

To explore whether modifications in sleep were related to sickness recovery, mixed effects ANOVAs with day/night of data collection (post-symptom onset/healthy control period) as repeated factors were used. Nights with sickness started from the first night in the sickness condition. This corresponded to the highest report of sickness symptoms in the evening for 24 (86%) participants. When feasible, data collection for the healthy condition began on the same day of the week as for the sickness condition. When this was not the case, the data from the 'healthy condition' after collection was aligned so that the weekdays matched with the sickness condition.

All analyses were performed in R (R Core Team), using lmer from the lme4 package (Bates et al., 2015) together with lmerTest (Kuznetsova et al., 2017) and pbkrtest (Halekoh and Hojsgaard, 2014) for Kenward-Roger approximations of p-values. P-values < 0.05 were deemed significant.

3. Results

3.1. Body temperature and sickness symptoms

Participants reported more sickness symptoms when having a RI compared to the healthy period (Table 1), and the analyses including the influence of possible weekday effects did not show a significant effect on symptoms (Fig. 1A, right panels). An interaction showed that the sickness symptoms developed differently across days in the week with RI as compared to the control week (Table 1). Fig. 1A (left panels) illustrates the recovery of symptoms across the period with an infection. Body temperature was influenced by time of day (higher in the evening than in the morning) and by weekday (higher degrees during the weekend), but not significantly increased by having a RI (Table 1, Fig. 1B).

3.2. Respiratory infections and subjective sleep

Table 2 and Fig. 2 (right panels) shows the overall effect of sickness on subjective sleep. During the sickness period, participants reported more difficulties falling asleep, reduced sleep quality, more restless sleep, and more shallow sleep (less deep), as compared to the control week (Fig. 2, right panels). However, there was no difference in how they rated their sleep sufficiency. Higher sickness symptom scores were significantly associated with more restless sleep and having a lower

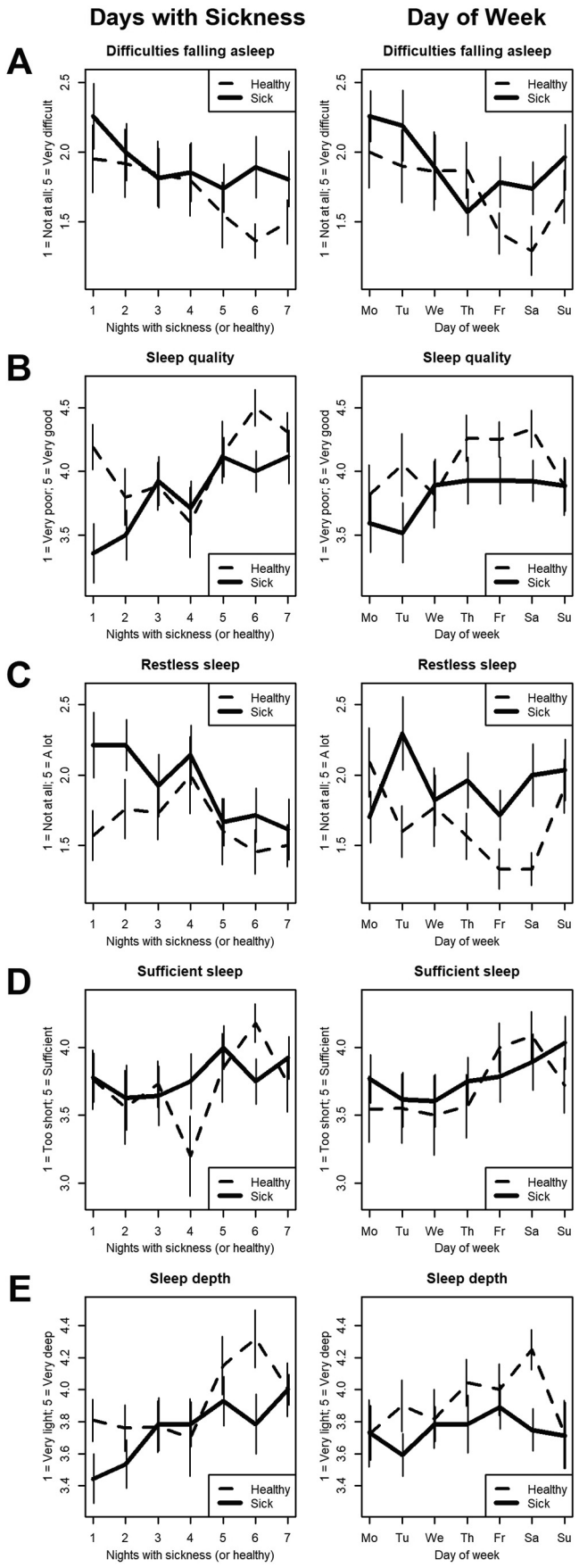

Fig. 2. Subjective sleep during a respiratory infection and when healthy. Observed means ± SEM. Left panels show data plotted against number of nights with sickness (and matched with the same day of week for the healthy condition) and right panels show data plotted against day of week for A) difficulties falling asleep, B) sleep quality, C) restless sleep, D) sufficient sleep, E) sleep depth. See Table 2 (for the right panels) and Table 4 (for the left panels) for detailed statistics.

sleep quality, but not to the other subjective sleep measures (Table 3).

3.3. Respiratory infections and objective sleep

The objective measurements of sleep showed that when suffering from a RI, individuals spent a longer time in bed and slept longer, but also had more awakenings compared to when being healthy (Table 2 and Fig. 3, right panels). Overall, sleep latency and sleep efficiency were not significantly different between the sickness condition and the healthy condition. Neither the degree of sickness symptoms nor body temperature were significantly associated with any of the objective sleep measurements (Table 3), although a trend was observed for people to spend more time in bed when sickness symptoms where higher ($p = 0.07$).

3.4. Subjective and objective sleep across the period with RI

The effects across days with a RI (compared to across the corresponding weekdays when healthy) are presented in Table 4 and revealed that all subjective sleep variables changed significantly across the period with sickness. As illustrated in Fig. 2 (left panels), subjective sleep was mostly affected during the first few days of the RI period (when symptoms peaked) and then improved across time, although some significant alterations were found at the end of the period when comparing with the healthy condition.

All objective sleep outcomes changed significantly across the week with RI, as indicated by interactions between condition and days with sickness (Table 4). While Fig. 3 (left panels) illustrates that time in bed, total sleep time and awakenings were higher at the beginning of the week with a RI, the interactions for sleep latency and sleep efficiency were less easy to interpret and could be due to changes occurring during the healthy week.

4. Discussion

This study showed that a naturally occurring RI affected both objective and subjective sleep in a number of ways: when sick, people spent objectively longer time in bed and slept longer, but also suffered from more awakenings, at least during the first days when symptoms were high. During sickness, people also reported having worse sleep quality, increased difficulties falling asleep, more restless sleep and less deep sleep. These findings are in agreement with two small previous studies of infections in humans that reported longer times in bed during the symptomatic period of an ARI or ILI induced by rhinovirus or influenza infection (Smith, 1992) and more awakenings during sleep (Drake et al., 2000). Critically, in the current study people slept objectively longer when having a RI, as well as suffered from a number of additional subjective sleep disturbances. Collectively, our findings indicate that the reduced sleep duration reported previously in response to an experimental rhinovirus infection (Drake et al., 2000) probably resulted from the study design (limiting time in bed to 8 h), and, that in a natural setting, individuals are likely to prioritize time in bed to increase their sleep duration when sickness symptoms are high. Despite subjects sleeping longer during a RI compared to when healthy, and in contrast to animal models (Toth, 1995), the data does not necessarily support an increased sleep need in response to the infection. It seems possible that the increased time in bed and total sleep duration could

Table 3
Correlations between specific responses to having a respiratory infection (RI).

	Variables	1	2	3	4	5	6	7	8	9	10
1	Symptoms	**1.00**									
2	Body temperature	0.10	**1.00**								
3	Sleep quality	**−0.44**	−0.03	**1.00**							
4	Restless sleep	**0.43**	0.23	**−0.50**	**1.00**						
5	Sufficient sleep	0.20	0.09	−0.03	0.30	**1.00**					
6	Sleep depth	−0.27	0.04	**0.48**	**−0.55**	−0.18	**1.00**				
7	Time in bed	0.40	0.09	0.08	0.17	**0.48**	−0.26	**1.00**			
8	Sleep latency	−0.10	−0.10	0.25	0.22	−0.12	−0.13	0.40	**1.00**		
9	Awakenings	0.08	0.33	**−0.44**	**0.58**	−0.01	−0.21	0.26	0.21	**1.00**	
10	Sleep efficiency	−0.10	−0.27	0.19	**−0.53**	0.05	0.25	−0.28	**−0.74**	**−0.60**	**1.00**

Subject-specific responses to RI are empirical bayes estimates of the condition: subjects random effect (Tables 1 and 2). Bold type face indicates $p < 0.05$. There were no observed subject specific responses for the variable "difficulties falling asleep" and "total sleep time", which were excluded from this analysis.

also result from people prioritizing sleep more when sick, compared to when healthy - many people often sleep slightly less than they should to be fully saturated (Axelsson and Vyazovskiy, 2015).

The participants reported more subjective sleep disturbances when suffering from a naturally occurring RI, which differs from earlier studies reporting no significant differences, or only trends for more disturbed sleep (Drake et al., 2000; Smith, 1992). In our study, sick individuals experienced more difficulties falling asleep, lower sleep quality, more restless sleep and lighter sleep compared to when they were healthy. Increased self-reported sickness symptoms were associated with stronger subjective sleep disturbances, namely lower sleep quality and restless sleep. Subjective sleep disturbances were worst when the symptoms peaked (at the beginning of the sickness period), then improved throughout the week as symptoms subsided, suggesting that subjective sleep disturbances can be driven by symptom intensity. Having a RI increased the number of awakenings compared to when healthy, in line with previously reported EEG measures during symptomatic rhinovirus infection (Drake et al., 2000), and this likely contributes to the subjective sleep disturbances we observed.

Notably, none of the objective sleep variables was significantly related to the degree of sickness symptoms or body temperature. This may be due to low power, large individual differences or different pathogens affecting sleep, temperature and symptoms in alternate ways. The fact that very few people were found to have fever may be due to differences in how people take their own temperature (despite clear instructions and three measures each time), and tympanic temperature not being a very reliable measure of core temperature (Moran et al., 2007). Furthermore, there was a clear weekend effect in temperature, most likely due to that subjects had different bedtimes and sampled their temperature later than during weekdays. Thus, data from the present study are not directly comparable to previous studies with better temperature measures, and where injections with bacterial endotoxin (e.g. LPS) causes systemic inflammation and stronger fever responses (Mullington et al., 2000). Overall, Mullington et al.'s findings indicated that limited pro-inflammatory responses increase the drive for sleep, while stronger immune challenges that also trigger endocrine and thermoregulatory host responses disturb sleep. Thus, the natural immune response to an infection can both increase the drive for sleep, and disturb sleep via host response mechanisms and other sickness symptoms. These findings also are consistent with the notion that inflammatory processes are involved in sleep disturbances (Irwin and Opp, 2017). Given that poor sleep quality and longer sleep latency are central symptoms in insomnia, and that they were observed during ARI, it is possible that immune processes contribute to pathological states of sleep disturbances.

There is strong support for sleep to supports the innate immune system and to be particularly important for the defense against infections (Irwin, 2002; Toth, 1995): naturally occurring short sleep, as well as sleep disturbances, increase the risk of developing a rhinovirus infection (Cohen et al., 2009; Prather and Leung, 2016). However, it remains unclear whether alterations in sleep patterns or architecture *during* infection are adaptive or whether they are predominantly side effects of an activated immune system. While more awakenings during sleep when the body fights an infection might have detrimental effects (Kuo and Williams, 2014; Lange et al., 2006), it may also be protective since it would also carry fever-promoting benefits (Imeri and Opp, 2009). On the other hand, the participants in this study clearly prioritized more time in bed, resulting in a longer total sleep time despite more frequent awakenings. This supports a reorganization of the infected host's behaviors to favor sleep, in line with animal studies (Toth, 1995). The increased time in bed during sickness could thus be an adaptive mechanism counteracting the detrimental effect of infection on sleep architecture, and possibly on immune function, by permitting the host to sleep as much as possible and increase sleep duration. Nevertheless, increased sleep duration was mainly apparent at the beginning of the sickness episode, when symptoms were greatest. It is possible that a longer sleep duration is no longer required in the second phase of an infection, when most of the pathogen has been eliminated, or when disturbed sleep no longer need to be compensated for by longer sleep time and time in bed. In this scenario, sleepiness and fatigue during the initial stages of infection (DellaGioia et al., 2013; Lasselin et al., 2017) would play an important role in promoting sleep and an effective host response. Alternatively, as symptoms subside, life-related obligations may simply regain higher priority at the expense of sleep. While the present literature show that sleep is altered during an acute infection, it is still unclear whether these alterations facilitate recovery.

It should be noted that sleep was not measured in the early asymptotic incubation phase in the present study due to the naturalistic design. The early studies by Smith found that subjective sleep was reduced during the incubation period of a respiratory infection (Smith, 1992), although this was not supported in polysomnography measured sleep in the study by Drake and colleagues (Drake et al., 2000). Future laboratory studies will have to determine how sleep during the incubation period can alter the course of infection. Furthermore, while the present study did not include a measure of depressive-like symptoms, an interesting aspect would be to analyze whether the relationships between infections and sleep disturbances are mediated by depression, as well as whether depression like symptoms are intensified as a consequence of the ARI-sleep relationships. Finally, although measuring sleep after recovery allowed to determine differences in sleep during ARI compared to when being healthy, measuring sleep at study entry (i.e., before the occurrence of ARI) would allow the analysis of how baseline sleep predicts susceptibility to infections.

Important limitations of the present study are that we did not confirm the infection by diagnostics and that subjects may have entered the study at slightly different phases of their infection. It would have been highly interesting to measure the impact of specific viral and bacterial infections on sleep, and it is probable that different causative agents were responsible for the RIs studied, also considering the fact that disease presented in the subjects between September and March

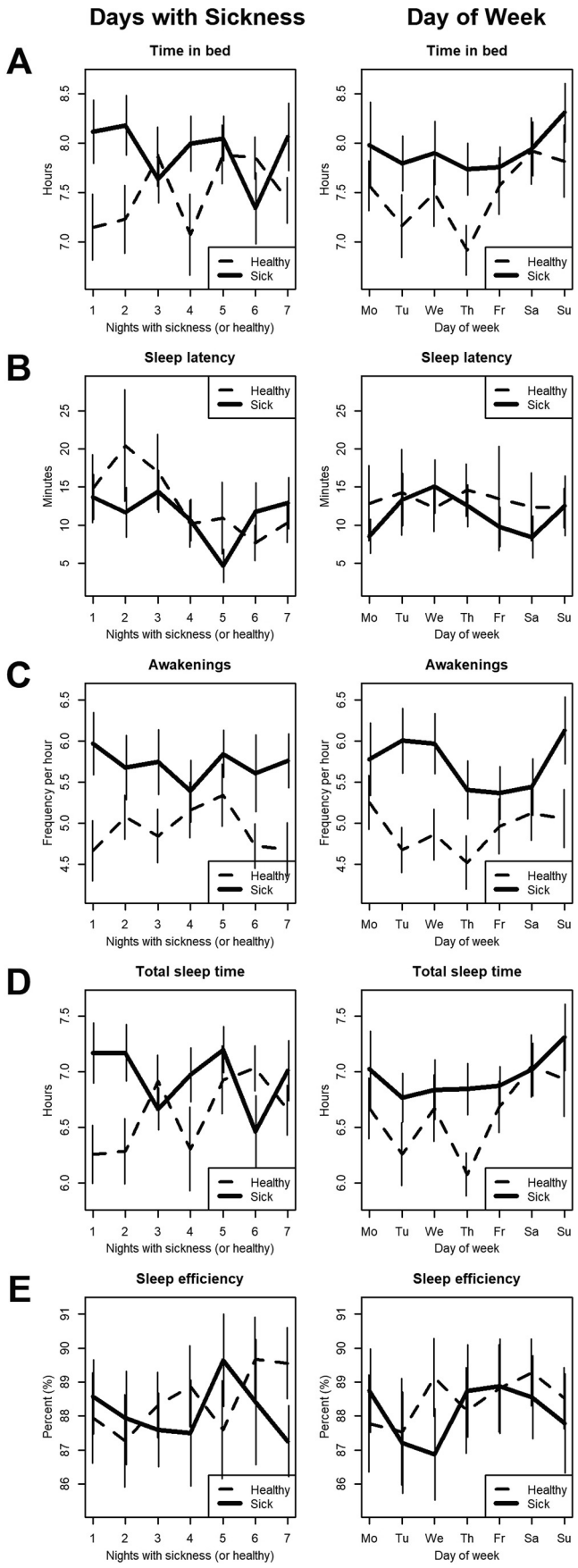

Fig. 3. Objective sleep during a respiratory infection and when healthy. Observed means ± SEM. Left panels show data plotted against number of nights with sickness (and matched with the same day of week for the healthy condition) and right panels show data plotted against day of week for A) time in bed, B) sleep latency, C) awakenings, D) total sleep time, E) sleep efficiency. See Table 2 (for the right panels) and Table 4 (for the left panels) for detailed statistics.

the following year. To assure the existence of an acute respiratory infection, we used the criteria for ILI, a nonspecific respiratory illness caused by a number of viruses (e.g., influenza virus, rhinovirus, coronavirus) and only included subjects with both systemic and respiratory symptoms (ECDC, 2012). Different respiratory viruses may have differential effects on sleep, particularly since some generate more severe symptoms than others, but symptom severity also varies greatly between individuals when suffering from the same virus. An additional limitation is that 13 of the subjects medicated at least once during the sickness week (e.g., 6 medicated against pain, 3 took antihistamines against allergies, and 4 took any of nasal spray, cough medicine or eye drops). While the medication is likely to have reduced some symptoms and possibly affected sleep, it was not feasible to make people avoid normal medication and symptom relief. The results should thus be seen as a description of how respiratory infections can affect sleep in a healthy normal population, where medication against symptoms is common, and that there is a need to further evaluate how medication influences the likely bidirectional relationships between symptoms and sleep.

Other limitations include the sample size (29 subjects out of 100 became sick), and a larger data loss than in experimental studies. Data loss was larger than expected, and there is a possibility that this caused a bias in the data, i.e., that subjects were less likely to wear the actigraph when sick. However, the fact that the data loss was similar between conditions indicates that this was not the case. Still, future home based studies would likely benefit from a more frequent contact with a research assistant encouraging and reminding subjects to adhere to the protocol. In addition, more regular temperature measurements by a trained person, measurements of blood cytokine concentrations, mucus production, and virus type, would give a better possibility to disentangle how different aspects of acute respiratory infections affects sleep. In future studies, it would also be highly interesting to know how specific symptoms relate to sleep (i.e., does a bunged up nose affect sleep differently than fever?). In line with this notion, better measurement of symptoms should be used, combining self-report symptoms with objective assessment of symptoms in a controlled manner. Another limitation with the present study is a possible order effect, where the subjects started with the RI week. It is possible that a first night effect caused a systematic bias in the results, although actigraphs do not disturb sleep as much as EEG and should be smaller when people sleep in their own home compared to than when sleeping in a laboratory. While actigraphy is a valid method for measuring sleep and some sleep disturbances, it can also underestimate wake time during sleep and it is a poor method for measuring naps (Sadeh, 2011). Thus, further studies that control for potential order effects and employ mobile EEG measurements are needed to increase our understanding of how sleep quality is affected. It is likely that nap duration may have been part of the sleep changes during sickness, but since this is difficult to measure accurately in the field, this should preferably be measured in laboratory conditions.

The major strength of this study is that participants' subjective and objective sleep was assessed at home during naturally occurring infection and when healthy. The majority of previous studies have assessed the effect of naturally occurring or experimentally induced infection on sleep in laboratory settings (Drake et al., 2000; Mullington et al., 2000; Trachsel et al., 1994), where the participants had to reorganize their life so as to be available for the study. Here, the effect of

Table 4
Effect of days having a respiratory infection (RI) on subjective and objective sleep.

Outcomes	Fixed effects									Random effects							
	Days			Condition			Condition: Days			Days: Subjects		Condition: Subjects		Subjects		Residual	
	F	p		F	p		F	p		SD	N	SD	N	SD	N	SD	N
Subjective sleep																	
Difficulty falling asleep	1.39	0.221		4.73	0.039	*	2.13	0.048	*	0.16	195	0.00	54	0.41	28	0.98	351
Sleep quality	3.86	0.001	**	5.39	0.028	*	5.32	< 0.001	***	0.19	196	0.17	54	0.42	28	0.87	352
Restless sleep	2.24	0.042	*	9.03	0.006	**	3.17	0.005	**	0.38	196	0.10	54	0.44	28	0.82	352
Sufficient sleep	1.97	0.073		0.31	0.584		4.59	< 0.001	***	0.00	196	0.25	54	0.46	28	0.90	352
Sleep depth	3.03	0.008	**	6.25	0.019	*	5.43	< 0.001	***	0.26	196	0.00	54	0.39	28	0.67	353
Objective sleep																	
Time in bed	0.80	0.570		9.16	0.006	***	8.29	< 0.001	***	0.00	182	0.19	49	0.65	28	1.20	294
Sleep latency	1.62	0.145		0.08	0.779		2.95	0.008	**	0.00	182	7.97	49	6.12	28	14.70	294
Awakening frequency	0.62	0.711		6.79	0.016	*	3.46	0.002	**	0.00	182	0.01	49	0.02	28	0.02	294
Total sleep time	0.82	0.558		6.89	0.016	*	8.02	< 0.001	***	0.00	182	0.00	49	0.45	28	1.12	294
Sleep efficiency	0.37	0.897		0.27	0.609		2.26	0.037	*	0.00	182	2.94	49	2.08	28	4.68	294

The ANOVAS include the fixed effects of condition (sickness period vs. healthy period) and days with sickness or being healthy. P-values have been calculated using Kenward-Roger adjusted denominator degrees of freedoms. SD = Standard deviation. Sleep efficiency = total sleep time/time in bed.

an acute respiratory infection on sleep was evaluated when sleep had to compete with other life-related obligations and rewarding activities. In spite of its high ecological validity, the present study should be viewed as a pilot study and future studies need to examine the stability of the results.

In conclusion, having an acute respiratory infection was associated with subjects spending more time in bed, sleeping longer and having more disturbed sleep as compared to a healthy week. Larger studies and classification of virus type and influences of medication are needed if we are to describe the relationship between naturally occurring infections and sleep patterns in more detail. While this ecological field study suggests that people prioritize and sleep more when acutely sick, further studies should investigate whether this is a replicable finding, and whether the sleep alterations can positively impact recovery from respiratory infections.

Conflict of interest statement

The authors declare not conflict of interest.

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Availability of data

Data and code are available at: https://osf.io/wbdmj/.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2019.02.006.

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