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Do sleep, stress, and illness explain daily variations in fatigue? A prospective study ☆

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ABSTRACT

Objective: Fatigue is related to a number of serious diseases, as well as to general well-being. It is also a major cause of sickness absence and use of health facilities. Still, the determinants of variations in fatigue are little investigated. The purpose of present study was to investigate the relationships between the daily variations of fatigue with sleep during the previous night, stress or disease symptoms during the same day — across 42 consecutive days of normal life.
Methods: 50 individuals participated and gave diary reports and used an actigraph across the 42 days. The data was analyzed using a multilevel approach with mixed model regression.
Results: The analyses showed that the day-to-day variation in fatigue was related to (poor) sleep quality ($p < .001$) and (reduced) sleep duration ($p < .01$) the previous night, as well as to higher stress ($p < .05$), and to the occurrence of a cold or fever ($p < .001$) during the same day as the fatigue rating. Fatigue was also strongly related to poorer subjective health ($p < .001$) and sleepiness ($p < .001$) during the same day.
Conclusion: The results indicate that prior sleep (and sleepiness) as well as stress and illness are consistently connected to how fatigue is experienced during normal living conditions.

Introduction

Fatigue is a common medical symptom in a wide range of diseases [1,2], and a central characteristic in the chronic fatigue syndrome [3], burnout [4], depression [5], and insomnia [6]. Fatigue is also an integral part of sickness behavior in relation to a number of inflammatory states [7]. For example, administration of a (typhoid) vaccine that causes an increase in interleukin (IL-6) levels is paralleled by increased fatigue [8]. Along the same line, observational studies show that poor subjective health, which is closely associated with fatigue, is related to both low-grade inflammation [9,10] and short sleep [11–13].

Because of its inhibitory and negative subjective quality, and its central role in many diseases, fatigue is also an important predictor of consumption of medical resources [14], lack of self-care ability [15], sickness absence [16–18], as well as of lack of return to work after long term sickness absence [17,18].

Outside the clinical area, fatigue is associated with high work demands, heavy work, long hours, female gender and low age [19–22]. Fatigue is also associated with stress, sleep problems [23–25] and experimental sleep deprivation [13,26]. The prevalence of fatigue varies greatly depending on how it is measured, but, as an example, the prevalence of "often being fatigued during the last two weeks" was 32.8% in a national representative sample of 58,000 Swedes [21].

Despite its apparent importance, the fatigue construct is not clearly defined, although it often refers to a state of energy depletion [27–29]. No physiological indicators exist, only questionnaires and rating scales. These include typical items like "fatigued", "tired", and "exhausted" [30] and the most used fatigue scale is probably "The fatigue severity scale" (FSS) [31]. However, most items in this scale describe effects of fatigue *when fatigue is actually present*, not how often it is present. It is, hence, not possible to estimate an amount or severity of fatigue in general.

Sleepiness, while highly related to fatigue, is usually not included among types of fatigue since it is conceptually different [32,33]. Thus, sleepiness reflects a drive to fall asleep [34], rather than a state of energy depletion. The relation between the two concepts has been a topic for repeated discussions [27,28] but empirical studies of their relation are rare.

Available studies on fatigue have mainly been of a cross-sectional nature although some of the studies above have been longitudinal and spanned long time periods. However, it is a common experience that fatigue varies between days although documentation seems to be lacking. If established, it seems reasonable to believe that a day-to-day variation may be linked to variations in stress or disease the same day or to the

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adequacy of the immediately preceding sleep episode. No previous studies exist, however. A better understanding of such links may give important insights into the day-to-day variations in work performance, well-being, health care consumption, quality of life, and other phenomena. An investigation of how the daily variations of fatigue relate to sleep/health/stress would require daily measures across a longer period of time. Such an approach has been used for investigating the effect of the daily variation of sleep on the daily variation of mood across two weeks [35]. Such a longitudinal approach requires multilevel modeling to handle the longitudinal covariation involved.

The aim of the present study was to investigate how fatigue during the day (rated at the end of the day) would be related to: sleep during the prior night (measured with actigraphy and a sleep diary in the morning), stress and illness (fever, cold) and subjective health during the same day and across a period of 42 days. We believe that the results of such a study would contribute.

Methods

A total of 50 subjects participated. The participants were recruited through advertisements and personal contacts. The intention was to obtain a normal, healthy sample. Exclusion was based on questions on whether the participant suffered from depression, anxiety disorders, insomnia, cardiovascular disease, hypersomnia, diabetes, and diseases requiring regular medication. The response alternatives were: no/yes/yes but more than a year ago. This was complemented by a short anamnestic screening by a physician, but no subject was excluded on medical grounds, probably because the health requirements were carefully explained in the invitation to participate.

The participants received an economic compensation of approximately $180. The ethical committee of the Karolinska Institute approved the study. All participants gave written informed consent and the study was carried out according to the principles of the Declaration of Helsinki.

The study covered one entire year and for each individual data was collected daily over a period of 6 weeks. At the start a background questionnaire was filled out. Each morning a sleep diary with sleep quality ratings were filled out and during the day sleepiness and stress were rated every 3 h during wakefulness. Every evening during the study the participants filled out a diary reporting on health symptoms, including fatigue, subjective health, having had a fever, and having had a cold during the day. During the entire measurement period, the subjects wore an actigraph for sleep recording.

Measurements

The questionnaire included questions about age, gender, marriage status (cohabitation/single, number of children <7 years old living at home, housing (own house/apartment — 1/0), education (university/high school/less than high school), employment (employed/unemployed/student), white collar/blue collar work, work hours (day work/shift work (roster) with nights, shift work (roster) without nights/permanent morning work, permanent evening work/other), smoking (yes/no), alcohol consumption (never/occasional/2–4 times per month/2–3 times per week/4 days per week or more, exercise (nothing/seldom/light exercise 1–2 times per week/>2 times per week and becomes sweaty/serious exercise – almost competition level), pain killers (never/occasionally/once per week, 2–3 times per week/almost every day). Depression and anxiety were measured through the Hospital Anxiety and Depression Scale [36,37].

For fatigue measurement once a day the fatigue severity scale was unsuited due to its more trait-like items. It is also relatively long for use every day. Instead, we used a scale that quantified the amount of fatigue during the present day using the items: persevering fatigue, full of energy (reverse coded), mentally exhausted, and physically exhausted [38,39]. Cronbach's alpha in that study was 0.86 and fatigue fell markedly from high levels at the start of the study after being sick-listed for long-term exposure to stress [39]. The score ranged from 1 (not at all) to 5 (to a high degree) and the Cronbach alpha of the scale in the present study was 0.83. The participants were instructed to fill out this scale each evening before bedtime. At the same time they reported their self-rated health (SRH) (How would you rate your state of health for the day? 1–7; very poor–excellent) [9], as well as occurrence of fever and/or a cold (scale 1–5, "not at all" to "to a large extent"). The latter constituted the "illness score".

Stress and sleepiness were rated every third hour during the time awake on nine-graded Likert scales. The stress scale, ranged from 1 (no stress at all) to 9 (maximum stress imaginable) [40] and has been used in a previous study of daily stress [41]. Sleepiness was rated on the Karolinska Sleepiness Scale [42]. This scale ranges from 1 (very alert) to 9 (very sleepy, fighting sleep, an effort to keep awake). In the present study a mean was calculated for each day based on the interval between 8 and 22 h.

The Karolinska sleep diary (KSD) [43], was filled out in the morning and included: bedtime (h), time of awakening (h), sleep latency (h), sleep quality (how did you sleep?, very well 5–very poorly 1), feeling refreshed after awakening (completely 5–not at all 1), calm sleep (very calm 5–very restless 1), did you get enough sleep? (definitely enough 5–definitely too little 1), ease of waking up (very easy 5–very difficult 1), and ease of falling asleep (very easy 5–very difficult 1). Four items formed a sleep quality index (SQI): sleep quality, calmness of sleep, ease of falling asleep, and sleep throughout the allotted time. Using bedtime, time of awakening and sleep latency, a measure of diary total sleep time (TST) was derived for each day.

Actigraphy was measured using the Cambridge Actiwatch® actigraph. It was attached to the non-dominant wrist and emptied and reloaded every three weeks. The actigraph is essentially a piezoelectric crystal that senses acceleration in three dimensions and has a threshold over which "activity" is scored. No or little activity is scored as sleep using a proprietary algorithm that takes into account not only the activity but also the pattern of activity. Actigraphs in general have a reasonable validity and reliability [44] and the actigraphy in this study has a correlation of $r = 0.70$ with polysomnographical recording of total sleep time (TST) [45]. Also bedtime and time of rising were obtained through the actigraph. The subjects were instructed to use the event marker at lights out and at rise time.

Statistical analysis

The design of the present study involved an analysis of the longitudinal covariation between variables. One may envision the analysis as a traditional regression analysis for one individual. Thus, for day one there is a pair of data with, for example, a sleep quality for the elapsed night in one column and fatigue reported in the evening later the same day. This is then repeated for day 2 in the next row, for day 3 in the row after that, up to day 42. Sleep quality is then regressed on fatigue for that individual and a regression coefficient is obtained representing the change in the dependent variable as a function of the change in the independent variable (Fig. 1). When the regression coefficient is averaged across all individuals a mean regression coefficient (with standard errors) is obtained that can be tested for significance. However, since there will be serial dependencies across the 42 measurement points as well as collinearity between some independent variables, and a second level of analysis (between groups) is added, another approach than classical regression is necessary. For this purpose a multilevel analysis was used [46]. This kind of approach has been used to, for example, demonstrate the daily covariation of mood and sleep across two weeks [35].

All statistical analyses were performed with the statistical package Stata 11 (StataCorp, College Station, USA) [47]. Linear mixed effect